Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV

Web supplement

Annex 2 Evidence to decision-making tables and supporting evidence

WHO/HIV/2015.36

Contents

This document is a supplement to the guideline which is available at http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/

Annex 2.1.1 Evidence to decision making framework A1.1 When to start in asymptomatic HIV+ adults and adolescents

In adults and adolescents living with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?

In adults, adolescents and children living with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?	
Population	Adults, adolescents and children living with HIV (WHO clinical stage 1 or 2)
Intervention	ART initiated > CD4 500 cells/mm^3
Comparator	ART initiated ≤CD4 500 cells/mm^3
Outcome(s)	Death, AIDS, tuberculosis, non-AIDS events[1], uptake, adherence, retention, viral suppression, severe treatment-related adverse events (harm) HIV transmission, HCV transmission (for HIV and HCV coinfected population), HBV transmission (for HIV and HBV coinfected population) Children: immunological recovery, HIV drug resistance, adherence, retention, TB incidence and neurodevelopment
Sub-analyses	Age: Adolescents 15–19 years All adults >19 years Adults >19–50 years Adults >50 years Populations: Pregnant and postpartum women People who inject drugs Men who have sex with men Transgender people Sex workers HIV and HCV coinfected individuals HIV and HBV coinfected individuals HIV-positive partners of women on option B+

Background:

2013 ARV guidelines recommendations

- **As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4), and individuals with CD4 count ≤350 cells/mm^3 should start ART as a priority (strong recommendation, moderate-quality evidence).**

- **ART should be initiated in all individuals living with HIV with a CD4 count >350 cells and ≤500 cells/mm^3, regardless of WHO clinical stage (strong recommendation, moderate-quality evidence).**

ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 count in the following situations:

- **individuals with HIV and active TB disease (strong recommendation, low-quality evidence);**

– **individuals coinfected with HIV and HBV with evidence of severe chronic liver disease (strong recommendation, low-quality evidence);**
– **partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence); and**
– **pregnant and breastfeeding women with HIV.**

- **All pregnant and breastfeeding women with HIV should initiate triple ARV drugs (ART), which should be maintained at least for the duration of mother to child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (strong recommendation, moderate-quality evidence).**
- **For programmatic and operational reasons, particularly in generalized epidemics, all pregnant women and breastfeeding**

[1] Non-AIDS events include non-AIDS cancer, cardiovascular disease, diabetes mellitus, renal disease, nervous system disease and liver disease.

Setting: Primarily for low- and middle-income countries with high prevalence, low prevalence or concentrated HIV epidemics.
Perspective: Public health approach rather an individualized approach.

Subgroup considerations*:* Important subgroups to consider include adolescents as well as populations at increased risk, such as people who inject drugs, men who have sex with men, transgender individuals and sex workers. Pregnant and breastfeeding women are also a key subgroup, but there is already a recommendation for immediate ART initiation regardless of CD4 cell count or WHO clinical stage, and this will be further reviewed as a separate PICO question.

women with HIV should initiate ART as lifelong treatment (conditional recommendation, low-quality evidence).

- **In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother to child transmission risk has ceased (conditional recommendation, low-quality evidence).**

	Criteria	Judgements	Research evidence	Additional considerations
PROBLEM	**Is the problem a priority?**	**Yes**	• Since 2010, randomized controlled trials and observational studies are showing that early ART initiation reduces HIV mortality, HIV morbidity, disease progression, hospitalization and HIV transmission. Moreover, it also reduces TB incidence and facilitates decentralization and task shifting. Current evidence strongly supports initiation at a CD4 count threshold of 500 cells/mm^3, with a stronger gradient of effect towards lower CD4 cell count values. • Modelling projections and ecological studies also suggest that very early ART initiation (regardless of or above 500 cells/mm^3 CD4 cell count threshold) can influence HIV incidence over time, if testing, ART coverage and retention at the population level are very high. • Current estimates of global coverage of HIV testing and ART coverage are still not satisfactory (40–50%) and late diagnosis and treatment initiation is very common, even in high-income settings (25–40%). Several studies suggest that retention decreases over time on ART (from 80–85% to 60–65% over 5 years). • Concerns about long-term safety, drug resistance and the affordability and sustainability of immediate ART initiation has been discussed in recent years, and how early ART should be initiated is still an open question.	• UNAIDS has proposed global 90–90–90 targets, calling for 90% of all people with HIV to know their status, 90% of these to be linked to ART and 90% of those who are receiving ART to have suppressed viral loads by 2020. These targets aim to reduce the number of people dying from AIDS-related causes to 500 000 per year and the number of people newly infected with HIV to to 500 000 per year. • Current WHO guidelines already recommend initiation of treatment regardless CD4 cell count in several situations such as active TB, HBV with severe liver disease, pregnant women (option B+) and HIV-serodiscordant couples. • Some high-income and upper-middle-income settings are recommending ART initiation regardless of CD4 cell count.

	Criteria	Judgements	Research evidence	Additional considerations
QUALITY OF EVIDENCE	**How substantial are the desirable anticipated effects?** **How substantial are the undesirable anticipated effects?** **What is the overall certainty of the evidence of effects?**	***Moderate quality evidence***	• A 2015 WHO systematic review and meta-analysis identified 18 eligible studies, of which **17 were observational studies**, including data from large multicohort collaborations (NA-ACCORD, EUROSIDA, ICONA, CASCADE, HIV-CAUSAL) and **one was a randomized controlled trial** (TEMPRANO-ANRS 12136). **Six observational studies reported results from single cohorts** that did not appear in other studies, while the remaining 11 observational studies had overlapping study populations. • The evaluated outcomes were: **mortality, severe HIV disease or malignancy, clinical progression, AIDS events, non-AIDS events, tuberculosis, severe treatment-related adverse events and HIV transmission**. We also examined **combined outcomes**, such **as mortality and severe HIV disease or malignancy**. Data were pooled across studies separately for randomized controlled trials and cohorts and estimated summary effect sizes. • The studies evaluated in this systematic review detected **risk reduction**, but **without statistical significance** for mortality (1 randomized controlled trial: RR=0.91, 95% CI 0.27–3.08; 3 cohorts: RR=0.68, 95% CI 0.39–1.21), severe HIV disease or incident malignancies (1 randomized controlled trial: RR=0.60, 95% CI 0.30–1.22), non-AIDS events (1 randomized controlled trial: RR=0.99, 95% CI 0.20–4.89), AIDS events or death (2 cohorts: RR=0.63, 95% CI 0.16–2.49), malignancies (1 randomized controlled trial: RR=0.91, 95% CI 0.06–14.38), invasive bacterial infections (1 randomized controlled trial: RR= 0.6, 95% CI 0.1–3.58) and tuberculosis (1 randomized controlled trial: RR=0.52, 95% CI 0.22–1.21). Two cohort studies did not find reduced risk of HIV transmission (RR=1.17, 95% CI 0.46–2.98). The quality of evidence for all these outcomes was rated as **low or very low**. • **Moderate-quality** evidence indicates that ART initiation in adults living with HIV at CD4 count ≥500 cells/mm^3 in the absence of other treatment indications leads to less "severe HIV morbidity" (**death, severe HIV disease or malignancy as a combined outcome**) than patients who deferred treatment (1 randomized controlled trial, HR=0.56; 95% CI 0.33–0.94) • **Moderate-quality** evidence indicates that ART initiation in HIV-infected adults at CD4 count ≥500 cells/mm^3 in the absence of other treatment indications **may not be associated with an increased risk of grade 3 or 4 adverse events** (1 randomized controlled trial, HR=0.58; 95% 0.30–1.11), and	• The literature for beginning ART at CD4 counts ≥500 CD4 cells/mm^3 is far less robust than the evidence outlined in the previous systematic review (beginning ART at CD4 counts between 350 and 500 cells/mm^3). • Considerations for universal ART in pregnant women were largely based on programme feasibility rather than data suggesting that option B+ is better for mothers and prevention of transmission than option B. • The 2013 WHO systematic review found evidence suggesting that early ART initiation (at CD4 count between 350 and 500 cells/mm^3) may reduce the risk of HIV disease progression or death, reduce the risk of being diagnosed with a non-AIDS defining illness and may increase the likelihood of immune recovery. Further, this previous review found that grade 3 or 4 laboratory abnormalities are more often found in people who initiate ART early rather than defer their treatment to CD4 counts <350 cells/ mm^3). • The generalizability of the results of this systematic review is limited, since the bulk of the identified literature comes from high-income settings with few studies contributing data from Africa and Asia. • In the majority of clinical trials and cohorts that have evaluated the optimal CD4 threshold for ART initiation, the comparisons were done with the

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			there was **very-low-quality** evidence of **increased risk of any severe laboratory adverse event** (1 cohort, RR=1.43; 95% CI 1.13–1.81) **and hepatic adverse events** (1 cohort, RR=1.45, 95% CI 1.03–2.04). • **Very-low-quality** evidence indicates that ART initiation in HIV-infected adults at CD4 count ≥500 cells/mm^3 in the absence of other treatment indications is associated with a **lower risk of HIV disease progressio**n (1 cohort , HR=0.20; 95% CI 0.10–0.42) **and transmitting HIV to unifected partners** (1 randomized controlled trial, RR=0.11; 95% CI 0.06–0.19). • Aside from HIV serodiscordant couples, there is **no particular breakdown of outcomes by age** (children, adolescents, older adults), **coinfections** (hepatitis B, hepatitis C), **pregnancy status or key populations** (injecting drug users, sex workers, transgender people, men who have sex with men) in the reviewed studies. • The **TEMPRANO study** (ANRS 12136), a randomized controlled trial conducted in 9 urban sites in Côte d'Ivoire, showed that in settings with high prevalence of bacterial infections and TB, immediate ART initiation plus 6 months of isoniazid preventive therapy significantly and independently reduced the occurrence of severe HIV morbidity (defined as a combined outcome of invasive bacterial diseases, TB, AIDS events and non-AIDS malignancies) by 44% compared with the standard of care, with no increased risk of severe adverse events (Danel et al., 2015). • **The START Study,** which enrolled 4685 people at 215 sites in 35 countries (27% of the participants were women, and approximately half were gay men) looked at rates of AIDS and serious AIDS-defining illness or death in people who were randomized to receive early or immediate ARV treatment versus deferring ARV treatment until their CD4 dropped below CD4 count <350 cells/mm^3). 86 events (death, AIDS, serious non-AIDS) occurred among those in which treatment was initiated later, while only 41 events occurred in those started on ART immediately – representing a 53% reduction in negative outcomes among those treated early. This effect was consistent across countries of different income and geographical regions. • **The HIV CAUSAL study**, a multicountry cohort study from the United States and Europe compared the effectiveness of immediate ART initiation in adults with HIV living in high-income counties and showed that immediate initiation	standard of care, which changed over time (for example: <200, <250, <350 and <500 CD4 cells/mm^3) and can influence the analysis and impact in the power and size effect of these studies. • The long-term duration of HIV infection and presence of several biases in observational and ecological studies (such as confounders and lead time bias) can be misleading for the decision on how early ART should start based solely on this type of study. • The consequences of chronic inflammation associated with HIV disease is still unknown and can be affected by some ARV drugs used for treatment. • There are no definitive, randomized, clinical trial data showing that treatment should be initiated in people whose CD4 counts are above 500 cells/mm^3. Despite evidence of impact of ART on HIV transmission at individual level (HPTN 052), there is insufficient information from randomized controlled trials on the preventive benefits of very early ART at the population level. The final results of ongoing HIV clinical (START) and incidence studies (PopART, SEARCH, BCCP, TasP-KZN) are expected only after 2016. • Recent studies on very early treatment of people living with HIV during acute infection and some HIV cure studies are showing a significant reduction on the size of HIV reservoirs, reduction of inflammation-associated markers and a

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			increases survival and AIDS-free survival, although the size effect of the benefit is small (RR = 1.02, 95% CI 1.01–1.02). Compared with immediate initiation, the mean survival time at 7 years under initiation at **CD4 <500 cells/mm^3 and at CD4 <350 cells/mm^3 was 2 and 5 days** shorter, respectively. Seven years after HIV diagnosis, 100%, 99% and 93% of individuals would have been in need of combined ART, and 87%, 87% and 84% would have HIV-RNA <50 copies/ml, under immediate initiation, initiation at CD4 <500 and <350 cells/mm^3, respectively. Earlier combined ART initiation might help increase the proportion of individuals with suppressed viral replication as long as resources exist to sustain the corresponding increase in the number of patients in need of cART (Lodi et al, 2015, in press). • **The HIV-CAUSAL** cohort also evaluated the impact of immediate ART initiation in HIV-positive individuals aged >50 years and showed a reduction in all cause and non-AIDS-related mortality, but the benefit is small compared with deferring therapy until CD4 count drops to below 500 cells/mm^3 [RR=1.03, 95% CI 1.02–1.05] or 350 cells/mm^3 [RR=1.10 , 95% CI 1.07–1.12) (Lodi et al-, 2015, IWHOD 2015, abstract 18). • Preliminary safety and efficacy data from **SEARCH** (24 weeks, unpublished data): – CD4 subgroup analysis showed with no statistically significant differences in terms of treatment retention, incidence of serious adverse effects or discontinuation because of ART toxicity among people who initiated ART with CD4 >500 (*n*=914) compared with those who initiated ART with CD4 between 350 and 500 (*n*=299). – high retention in care (>90%) and viral load suppression rates (92 %), including for people living with HIV with CD4 > 500 cells/mm^3.	better immune restoration profile compared with those treated with chronic established infection.

	Criteria	Judgements	Research evidence	Additional considerations

<table>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?</td><td>No major variability</td><td>
<table>
<tr><th>Ranking outcomes</th><th>Mean</th><th>Rating</th></tr>
<tr><td>Viral suppression</td><td>8</td><td>Critical</td></tr>
<tr><td>Uptake of treatment</td><td>8</td><td>Critical</td></tr>
<tr><td>Adherence</td><td>8</td><td>Critical</td></tr>
<tr><td>Retention</td><td>8</td><td>Critical</td></tr>
<tr><td>Death</td><td>7</td><td>Critical</td></tr>
<tr><td>Progression to AIDS</td><td>7</td><td>Critical</td></tr>
<tr><td>TB and other opportunistic infections</td><td>7</td><td>Critical</td></tr>
<tr><td>Severe treatment-related adverse events (harm)</td><td>7</td><td>Critical</td></tr>
<tr><td>Non-AIDS-related events (bacterial infections, cancer, cardiovascular disease, diabetes, renal disease, nervous system disease and liver disease)</td><td>7</td><td>Critical</td></tr>
<tr><td>HIV transmission</td><td>7</td><td>Critical</td></tr>
<tr><td>Immune recovery</td><td>6</td><td>Important</td></tr>
<tr><td>HCV transmission (for people HIV and HCV coinfected)</td><td>5</td><td>Important</td></tr>
<tr><td>HBV transmission (for people HIV and HCV coinfected)</td><td>5</td><td>Important</td></tr>
</table>
</td><td>• No important variability was observed for the ranking of these outcomes.</td></tr>
<tr><td>Benefits and harms of the options</td><td>Does the balance between desirable effects and undesirable effects favour the option or the comparison ?</td><td>Adults: benefits > > harm
Adolescents: benefits probably > harm</td><td>• Benefits (desirable effects):
– Modelling projections showed that earlier ART initiation (assuming the excellent linkage to and retention in pre-ART care) is expected to lead to substantial numbers of HIV infections averted (UNAIDS Fast-Track report, 2014).
– Evidence from clinical studies shows reduction in severe HIV morbidity and risk of disease progression with earlier ART initiation, without increase in the occurrence of severe adverse events associated with ART (TEMPRANO study).
– Programmatic data from several countries that are offering immediate ART to all HIV-positive individuals.. Brazilian AIDS programme established an ART test and offer policy at the end of 2013, and preliminary analysis shows significant increase in ART uptake and reduction in the time between HIV diagnosis and ART initiation irrespective of baseline CD4 cell count (Brazilian Ministry of Health, 2014). However, a slight reduction in treatment retention was observed at 18 months</td><td>• According to several studies conducted in adolescents in Africa and Asia, young people are at high risk of loss to follow-up, with those 15–19 years old and those 20–24 years old at particular risk. Higher rates of loss to follow-up were seen pre- and post-ART initiation as well as in those attending PMTCT services.</td></tr>
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	Criteria	Judgements	Research evidence	Additional considerations
			compared with those who initiated ART at CD4 <500 (Brazilian Ministry of Health, unpublished data). In Rwanda, an observational study conducted by the Ministry of Health showed that ART initiation at CD4 ≥500 cells/mm^3 was associated with increase in linkage to care and survival in adults with HIV at CD4 ≥500 cells/mm^3 (Nsanzimana et al., unpublished data). In Viet Nam, the preliminary results of a small pilot project on immediate ART initiation in people who inject drugs with HIV (V-HEART project) suggest a high uptake, care retention, adherence to ART and viral suppression irrespective of CD4 cell count at 6-month follow-up (*n*=146). However, late presentation to care remains a critical problem (Viet Nam Ministry of Health, unpublished data; Brazilian Ministry of Health, unpublished data). Preliminary data from another pilot study on the test-and-treat strategy in men who have sex with men and transgender people in Thailand (*n*=800) showed high uptake of ART without significant difference in treatment-related adverse events compared with the baseline CD4 count (<350, 350–500 and >500 cells/mm^3). CD4 cell count gains and viral suppression rates were also similar among all treatment groups (Brazil Ministry of Health and Thailand Ministry of Health, 2015). – Universal immediate treatment is projected to increase the number of eligible people by 30–35% compared with 2013 criteria (CD4 <500). Some modelling projections using Kenya, Malawi and South Africa suggest that immediate ART initiation in all people living with HIV linking to care could prevent 6–14% of overall HIV-related deaths over the next decade compared with the current guidelines with initiation at CD4 ≤500. The vast majority of that impact is due to a reduction in loss to follow-up and deaths during pre-ART care rather any direct therapeutic or prevention benefits conferred by a change in eligibility from the current guidelines. However, the limited and already overstretched infrastructure and financial capacity of the majority of countries with a high burden of HIV, associated with the flat line in the global funding framework are important challenges for further expansion of the eligibility criteria above 500 CD4 (HIV Modelling Consortium, 2015). – In some resource-limited settings with a high burden of TB and bacterial diseases, early ART can decrease the burden of these diseases in people living with HIV (TEMPRANO and several population modelling studies).	

	Criteria	Judgements	Research evidence	Additional considerations
			– Potential further decreased risk of death or disease progression (including non-AIDS events). – Decreased risk of HIV sexual transmission (randomized controlled trial in HIV-infected serodiscordant couples and population-based modelling studies). . – A more permissive CD4 count threshold may provoke a change in treatment-seeking behaviour, with a reduction of late presentation. • ***Risks and harm (undesirable effects):*** – Immediate ART initiation increases the proportion of people needing treatment. – The median CD4 cell count at presentation to care and ART initiation has being increasing slowly in the majority of resource-limited settings and seems not be strongly driven by the changes in eligibility criteria established in normative guidelines. Early testing and better linkage to care seem to be the main factors that can accelerate it. – Despite progressive improvement on treatment regimens, concerns about the long-term consequences of chronic exposure to current available ARV drugs at the individual level (long-term toxicity, risk of emerging drug resistance, negative impact in lifestyle of lifelong therapy) are common. – Concerns about additional ART toxicity (known and unknown side effects) due to earlier start and longer exposure to ARV drugs. However, the median additional time of exposure to ART in immediate ART in recently infected people compared with the 500 CD4 threshold criteria is only 1–2 years. – Increase in CD4 threshold or additional other CD4-independent situations (such as HCV, age >50 years, key populations) will not necessarily increase the ART	

	Criteria	Judgements	Research evidence	Additional considerations
			coverage, since many individuals living with HIV are presenting late for testing and treatment even in high-income settings (median CD4 count at initiation is usually below 250 cells/mm^3 in low- and middle-income countries and still below 350 cells/mm^3 in most high-income settings). – Unclear whether people will test or enrol early enough and/or accept care and ART. Concerns related to increase in stigma, lifestyle changes, discrimination and disclosure problems. – Unclear effect on long-term adherence, retention and drug resistance development. – Concern has been voiced that treatment may result in some people who urgently need treatment being displaced by people for whom treatment would be beneficial (but no clear evidence of this happening so far).	

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RESOURCE USE	**How large are the resource requirements (costs)?**	***More resource intensive***	• There is an enormous gap between aspiration to provide ART to all people living with HIV according to eligibility criteria and the actual numbers of people living with HIV attaining viral suppression through consistent and effective treatment. • WHO/UNAIDS estimates that there are approximately 35 million people living with HIV worldwide and almost 14 million were receiving ART (June 2014), which represents approximately 40% of the eligible people according to the 2013 WHO guidelines (approximately 26 million people). The change in the eligibility criteria from CD4 ≤500 to CD4 >500 or regardless of CD4 cell count would increase the current global treatment gap from 12 million to approximately 21 million people. • Treating all 26 million people living with HIV currently eligible for ART according 2013 WHO guidelines could cost US$ 16 billion annually, and extending treatment to all regardless of CD4 cell count could cost US$ 20 billion annually, about triple the current US$ 6 billion that is being spent on treatment globally (UNAIDS Fast-Track report, 2014).	• The number of people on ART will continue to grow, projected to be 1.5 million per year. By 2018, approximately 55% global coverage of those eligible according to the 2013 WHO ART guidelines (ARV Forecasting Technical Working Group, 2015).
	What is the certainty of the evidence of		• Ministries and donors may feel under pressure to address immediate increased cost and service demand.	• UNAIDS estimated that global HIV funding available from all sources – domestic public and

	Criteria	Judgements	Research evidence	Additional considerations
	resource requirements?		• The funding of ART programmes in the majority of low- and middle-income countries is heavily dependent on external funding despite growing domestic HIV spending observed in recent years. • Donor funding has plateaued since the onset of the global economic turndown in 2008 and does not show signs of increasing. In addition, there remains a gap between available resources and estimated need.	private spending, donor government bilateral assistance, multilateral organizations and private philanthropic aid disbursements – totalled US$ 18.9 billion in 2012, of which 53% was provided by domestic resources (Keiser-UNAIDS report, 2013). • Despite this increase, total resources available in 2012 were well below the UNAIDS estimate of US $22 billion to US$ 24 billion in annual funding that will be needed by 2015 to address the impacts of HIV (Keiser-UNAIDS report, 2013).
	Does the cost–effectiveness of the option favour the option or the comparison?		• According to UNAIDS projections, in the long term, expanding ART to all people living with HIV (assuming an excellent linkage to care and retention) is projected to avert 21 million AIDS-related deaths and 28 million new infections by 2030 (UNAIDS Fast-Track report, 2014). • According to a modelling study in South Africa, expanding ART to all people living with HIV is projected to avert 3.5 million new infections and save almost US$ 30 billion through 2050 (Granich et al., 2012). • Another South Africa modelling study estimated that immediate ART initiation in all people living with HIV costs US$ 8400 per HIV infection, considered as cost-effective according to the WHO threshold of 3 times the country's per capita GDP. However, a combination of a high coverage rate of voluntary male circumcision (more cost-effective – US$ 1100 per HIV infection) and ART among people with CD4 <350 cells/mm^3 was estimated to be US$ 5 billion less expensive than immediate ART initiation in all people living with HIV from 2009 to 2020 (Bärnighausen et al., 2012).	

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EQUITY	**What would be the impact on health equity?**	***More equitable***	• The principles of utility, efficiency and fairness should be used in guiding the efforts to select the people who will receive ART on a priority basis and to determine where and how programmes will be conducted. • Equity concerns that, in a context of limited resources, very early treatment may result in some people in urgent need of treatment being displaced by people for whom treatment would be beneficial but not yet definitively proved. • If starting ART in HIV-infected asymptomatic individuals with CD4 count ≥500 cells/mm^3 or regardless of CD4 count is considered, it may need to be conditional on: – human rights– or demand-based model of care (practitioners explain health and prevention benefits and allow people to decide whether they would like to initiate ART without coercion); – the burden of disease (ART likely to have stronger protective effects on individual health in areas with a high burden of AIDS and some comorbidities such as bacterial diseases and TB); and – high ART coverage in the country. • However, there are strong concerns from communities on a mandatory or coercive approach in high-risk marginalized populations (such as people who inject drugs and sex workers) and issues on legal framework and equitable access, particularly in countries with a concentrated epidemic and low ART coverage.	• A recommendation of ART initiation regardless of CD4 cell count will reduce the apparent disparity between the ART recommendations of high-income settings and low- and middle-income countries. • Risk of inequity in ART access, particularly for people with symptomatic HIV disease.
ACCEPTABILITY	**Is the option acceptable to key stakeholders ?**	***Adults: acceptable with minor variability*** ***Adolescents: acceptable with major variability***	A **community-led global consultation** of people living with HIV (206) and service providers (74) was undertaken to determine the acceptability, challenges and facilitators of **earlier initiation of ART** and viral load monitoring. • **Twenty-four workshops** engaging groups in focus discussions were carried out in **eight countries**[2] targeting different populations (adults, key populations, adolescents, parents and caregivers and service providers). • **Eighty percent of the participants were receiving ART**, with 7% starting ART regardless of CD4 count or at CD4 <500. Access to a viral load test varied greatly by region: more than 90% of the participants from Europe and Latin America had received a least one viral load test versus 55% of African and 64% of Asian participants. **Key findings:** • Overall for community participants living with HIV (people living with HIV) and service providers, **early initiation of treatment is acceptable** and the health benefits	

[2] Kenya, India, Indonesia, Peru, Portugal, Ukraine, Zambia and Zimbabwe.

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			are well understood. • It was uniformly noted that a **collaborative decision** between service provider and client or caregiver is optimal. The **right to decide when to start treatment** must rest with the client, and the ultimate decision must be client-driven. • Treatment initiation at any time must **include comprehensive and accurate information** and the **right to informed choice** about starting treatment and staying in care. • **Full understanding and readiness** of clients initiated on ARV drugs is required; otherwise they **are likely to default** – this was uniformly noted. • **Motivation to initiate treatment** was often described as being driven by the **desire to regain and maintain health** and a strong will to live. For those **initiating treatment early**, this motivation may be less strong. **Other challenges**, such as stigma, lack of disclosure and confronting side effects, **may be harder to overcome** when illness is not driving the choice to initiate treatment. • While motivating people living with HIV to **start treatment may be relatively easy** to do, **staying on and adhering to treatment over the long term is challenging**. • **Stigma and discrimination** were uniformly raised as **fundamental concerns** constraining treatment access, affecting the quality of services and infringing on the ability of clients to adhere to and stay on treatment. **Regardless of subgroup, the majority of participants described experiences** of discrimination and stigmatization when accessing services. • To **promote ongoing engagement in care and adherence**, it is critical that clients have: access to adequate and consistent **supplies of free or affordable ARV drugs**; a facility that is easily **accessible and convenient**; concern and support from **providers who are trained and are sensitive** to the needs of people living with HIV (including key population groups); provider and/or community **adherence support**; facilities that actively work to **enhance adherence**; national programmes and facilities **reduce structural barriers**; facilities that **specifically serve or are dedicated** to people living with HIV and/or key populations and that are built in systems and spaces that help **ensure privacy and confidentiality**. • Ideas on the terms test and treat versus test and offer were mixed across population groups and regions. – **Test and treat** (a) implied **lack of choice**; (b) focused primarily on biomedical aspects of health without paying attention to other considerations (c) is sometimes **associated with coercion** or forced treatment; (d) and primarily focuses on prevention among those who are not infected **rather than protecting people living with HIV**. – **Test and offer**: (a) was seen as too soft by providers and people living with HIV (especially advocates); (b) that it would not encourage early treatment initiation	

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			and (c) would **lose information on the benefits or urgency to start treatment**. While **test and offer was seen as more palpable** by some participants and in some cases conveyed the message that clients' right to choose was respected. Regional and subgroup differences • The main regional difference was **treatment access**. For those in sub-Saharan Africa, this was a major concern. Moving towards treating everyone was welcomed as an **advocacy platform for increasing treatment access** across the region. • Women, especially pregnant women, felt that they **had limited control over decisions** to start treatment. • Women were particularly concerned about **loss of confidentiality** when starting treatment. • Key populations living with HIV experience **double stigma and discrimination.** • Key populations require **specialized services and support** that are responsive to their needs that can help alleviate or change social norms that negatively impact on the health and their rights. • Adolescents and young people voiced **being left out of decision about treatment altogether**, often without their knowledge of their own status or what the treatment is for. This was highlighted as **a major barrier to adherence**. • **Supportive and sensitive health providers, peer support** and sharing experiences, especially during transition to adult services, are critical for adherence for adolescents. • Parents and caregivers felt that facilities had **insufficient numbers of trained staff members** to adequately provide care and support the treatment needs of their children. • **Psychosocial support for parents and caregivers** is required, especially around disclosure to the child. • Service providers face **particular challenges** when initiating and maintaining treatment among certain populations. • For service providers to effectively support people living with HIV to engage with care, initiate and maintain treatment, they require: (a) **national guidelines** that support the strategic use of ART while also supporting the right of people living with HIV to decide when and how to begin treatment; (b) consistent **training** and capacity-building; (c) consistent **supplies of drugs** and commodities and (d) the decentralization of services. **A review of published and grey qualitative literature was carried out to explore acceptability on the timing of ART initiation.** Twenty-two publications from 2006 to 2015 were identified; published studies, grey literature reports and conference abstracts. No	

	Criteria	Judgements	Research evidence	Additional considerations
			publication reported specifically the views of those <19 years of age; 9 publications included key populations and 11 service providers. Key findings identified: • For people living with HIV, the acceptability for earlier treatment is **greater with the knowledge that treatment reduces mortality risk**. When people are well, earlier treatment and adherence is harder to accept. • The main motivations of people living with HIV for earlier treatment were to **delay or avoid illnesses and prolong life**. Service providers mainly acknowledged the preventive benefits of earlier ART. • For service providers, there was general acceptance and support of earlier ART initiation ≤500 cells/mm^3 for asymptomatic people. There was **greater acceptance for clients with comorbidities or conditions associated with a higher risk of HIV transmission** such as for pregnant women. • Service providers described the cautious optimism of a clear message that one size fits all strategy is not appropriate, and **considering the individual primarily** and manage their side effects, with some **preferring improving HIV testing** over earlier treatment. • For people living with HIV, **concerns about initiating and maintaining** included: adhering to ART; anxiety about side effects and potential resistance; the sustainability of ART access; the impact of inconvenience in normal life; disclosure; the cost of services and ART; and fear of criminalization of key populations. • For service providers, long-term toxicity, reduced efficacy of ART, adherence, disinhibition around sexual risk-taking, fears of coercion and clients' early treatment acceptance were all concerns. • For earlier treatment to be acceptable, people living with HIV highlighted the **requirement for** (a) a human rights approach, (b) shared decision-making, (c) the benefit of treatment to be focused on the individual rather than prevention and (d) improved literacy related to the use of ARV drugs. • For key populations, **eliminating stigma associated around "being infectious"** was seen as a key motivation. • For adolescents, providers were concern about **adolescents' poor adherence and**	

	Criteria	Judgements	Research evidence	Additional considerations
			resistance. The acceptability for early initiation was dependent on certain conditions such as **readiness, engagement in care and stable life circumstances**. However, some felt the preventive benefits outweighed the potential harm.	
FEASIBILITY	**Is the option feasible to implement?**	***Adults: yes, probably feasible*** ***Adolescents: yes***	• In high-coverage and high-burden scenarios, it will likely be easier to shift to earlier treatment sooner, but the large absolute numbers will be a challenge. In low-coverage and high-burden settings, setting priorities is suggested based on the setting, intervention and patient groups. In settings with low coverage and concentrated epidemics, enabling the environment and focusing on legal framework and human rights issues are important first steps. • According to a 2014 WHO survey in 144 countries, 51% had adopted the 500 CD4 threshold to initiate ART, 26% were still using 350 CD4 threshold and only 7% were recommending ART regardless of CD4 value (GARPR 2015). However, the median CD4 at the start of ART has been below 350 in almost all settings, including high-income countries. • Current global ART coverage is around 40 % of all people living with HIV, according to a 2014 UNAIDS/WHO report, but still very heterogeneous when distributed by region and target populations. • These recommendations probably need to be phased in, since they may not be currently feasible in many high-burden settings with less-developed health systems, low rates of testing, poor pre-ART care, insufficient human resources, limited laboratory capacity, finite budgets and competing health priorities. • Universal ART for pregnant and breastfeeding women (option B+) has been successfully rolled out in many high-burden settings and has been officially adopted by almost all countries in sub-Saharan Africa and high-burden countries in Asia. So it is potentially more feasible for countries to take this type of approach. At the same time, significant challenges with retention, especially postpartum, have emerged. Lessons learned from this experience suggest that programmes will need to pay very close attention to adherence and retention and will need to develop carefully thought out systems to ensure that people who start ART are adequately prepared for lifelong treatment. • High level of uncertainty of the feasibility of the recommendation for ART initiation at CD4 >500 for all people living with HIV (low to moderate in some specific situations as countries with high ART coverage in people living with HIV with CD4 ≤500 or low HIV prevalence).	• There are several ongoing implementation trials evaluating the feasibility, acceptability, clinical efficacy and impact of immediate treatment for all people living with HIV regardless of CD4 cell count at population level (SEARCH, MaxART), but their results are expected only in 2017–2018. • Criminalization and stigma or discrimination against people living with HIV and key populations commonly affected by HIV (men who have sex with men, transgender people, sex workers, people who inject drugs, migrants) are critical barriers to early presentation and treatment initiation.

	Criteria	Judgements	Research evidence	Additional considerations
			• According to a preliminary evaluation of country concept notes submitted to the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2014, among 28 HIV high-burden countries in Africa, only 6% have adopted and fully implemented the CD4 threshold for ART initiation, 29% adopted but are still in the initial implementing stage and 65% are still adopting the 350 CD4 threshold. Among these countries, 17 showed significant programmatic gaps in terms of ART needs and what can be covered with the resources (Global Fund to Fight AIDS, Tuberculosis and Malaria concept notes, 2015).	

Conclusions

Type of recommendation or decision	We recommend against the intervention or for the comparison	Conditional recommendation not to use the intervention or to use the comparison	We suggest using either the intervention or the comparison	Conditional recommendation to use the intervention **Adolescents**	We recommend the intervention **Adults**
	☐	☐	☐	☒	☒

Recommendation or decision

ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count *(strong recommendation, moderate-quality evidence).*

ART should be initiated among all adolescents living with HIV regardless of WHO clinical stage and at any CD4 cell count *(conditional recommendation, low-quality evidence).*

Research priorities

- Implementation science on interventions to improve timely uptake and retention along the ART cascade.
- More evidence on the clinical impact and size effect of benefits for ART use among people with CD4 >500 cells/mm^3.
- Public domain reporting of serious harm for initial combined ART studies is limited. Insufficient data exist to determine whether particular ART drugs or regimens are associated with the most serious types of harm.
- The implications of earlier ART initiation in terms of adherence and retention in care need to be better understood.
- The impact of earlier initiation on health services in the context of decentralization and task-shifting needs to be monitored and documented.
- Use of other markers (albumin, CD4/CD8, CD8) as predictors of AIDS and non-AIDS-related morbidity and mortality.
- WHO needs to prepare tools to assist countries in the decision on setting prioritied and phased implementation of these recommendations considering clinical, epidemiological and programmatic parameters.

Author(s): Anglemyer, Andrew
Date: 18 May 2015
Question: Should ART in eligible patients with CD4 >500 cells/mm^3 versus CD4 <500 cells/mm^3 be used for HIV treatment?
Settings: Africa, Asia, Australia, Europe and North America
Bibliography: CASCADE 2003, CASCADE 2011, Danel (TEMPRANO) 2015, Donnell 2010, Garcia 2004, Gras 2007, He 2013, HIV CAUSAL 2010, HIV CAUSAL 2011, Jean 2013, Jean 2014, Jia 2012, Jose 2014, Kitahata 2009, Le 2013, Merito 2006, Okulicz 2015, Palella 2003, Schneider 2013, Sterne 2009

Quality assessment							Number of people		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ART in eligible patients with CD4 >500 cells/mm^3	CD4 <500 cells/mm^3	Relative (95% CI)	Absolute		
Mortality												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	5/222 (2.3%)	5/201 (2.5%)	RR 0.91 (0.27 to 3.08)	5 fewer per 1000 (from 15 fewer to 17 more)	⊕⊕○○ LOW	CRITICAL
Mortality (clean)												
3	observational studies	serious[2]	serious[3]	serious[4]	not serious	none	351/7572 (4.6%)	895/18 952 (4.7%)	RR 0.68 (0.39 to 1.21)	15 fewer per 1000 (from 10 more to 29 fewer)	⊕○○○ VERY LOW	CRITICAL
Mortality (overlap)												
6	observational studies	very serious[5]	serious	very serious[6]	not serious	none	918/86 832 (1.1%)	7901/335 225 (2.4%)	RR 0.64 (0.51 to 0.81)	8 fewer per 1000 (from 4 fewer to 12 fewer)	⊕○○○ VERY LOW	CRITICAL
Death, severe HIV infection or malignancy												
1	randomized trials	not serious	not serious	not serious	serious[11]	none	23/212 (10.8%)	38/201 (18.9%)	HR 0.56 (0.33 to 0.94)	83 fewer per 1000 (from 11 fewer to 127 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
AIDS or death												
2	observational studies	serious[7]	not serious	not serious	not serious	none	698/5252 (13.3%)	2058/12 491 (16.5%)	RR 0.63 (0.16 to 2.49)	61 fewer per 1000 (from 138 fewer to 245 more)	⊕○○○ VERY LOW	CRITICAL

AIDS or death (overlap)												
4	observational studies	serious[5,7]	serious[9]	not serious	not serious	none	926/14 251 (6.5%)	3830/45 102 (8.5%)	RR 0.77 (0.49 to 1.21)	20 fewer per 1000 (from 18 more to 43 fewer)	⊕○○○ VERY LOW	CRITICAL
Severe HIV infection or malignancy[12]												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	12/222 (5.4%)	18/201 (9.0%)	RR 0.6 (0.3 to 1.22)	36 fewer per 1000 (from 20 more to 63 fewer)	⊕⊕○○ LOW	CRITICAL
HIV disease progression												
1	observational studies	serious[7]	not serious	serious[8]	not serious	none	98/257 (38.1%)	295/398 (74.1%)	HR 0.2 (0.10 to 0.42)	504 fewer per 1000 (from 308 fewer to 615 fewer)	⊕○○○ VERY LOW	CRTICAL
Invasive bacterial infection												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	2/222 (0.9%)	3/201 (1.5%)	RR 0.6 (0.1 to 3.58)	6 fewer per 1000 (from 13 fewer to 39 more)	⊕⊕○○ LOW	CRITICAL
Malignancies (AIDS and non-AIDS)												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	1/222 (0.5%)	1/201 (0.5%)	RR 0.91 (0.06 to 14.38)	0 fewer per 1000 (from 5 fewer to 67 more)	⊕⊕○○ LOW	CRITICAL
TB (pulmonary or disseminated)												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	8/222 (3.6%)	20/201 (10.0%)	RR 0.52 (0.22 to 1.21)	48 fewer per 1000 (from 21 more to 78 fewer)	⊕⊕○○ LOW	CRITICAL
HIV transmission												
1	randomized trials	not serious	not serious	serious[10]	very serious[1]	none	2/100 000 (0.0%)	20/100 000 (0.0%)	RR 0.11 (0.06 to 0.19)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
HIV transmission												
2	observational studies	serious[7]	not serious	not serious	very serious[1]	none	6/366 (1.6%)	12/912 (1.3%)	RR 1.17 (0.46 to 2.98)	2 more per 1000 (from 7 fewer to 26 more)	⊕○○○ VERY LOW	CRITICAL

Any serious adverse effects												
1	observational studies	not serious	not serious	not serious	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.43 (1.13 to 1.81)	59 more per 1000 (from 18 more to 107 more)	⊕⊕○○ LOW	CRITICAL
Grade 3 or 4 laboratory abnormalities (other than neutropaenia)												
1	randomized trials	not serious	not serious	not serious	serious[11]	none	15/212 (7.1%)	25/201 (12.4%)	HR 0.58 (0.30 to 1.11)	52 fewer per 1000 (from 14 more to 87 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Liver serious adverse effects												
1	observational studies	not serious	not serious	not serious	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.45 (1.03 to 2.04)	61 more per 1000 (from 4 more to 135 more)	⊕⊕○○ LOW	CRITICAL
Liver serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	4/436 (0.9%)	5/413 (1.2%)	RR 0.76 (0.2 to 2.85)	3 fewer per 1000 (from 10 fewer to 22 more)	⊕⊕○○ LOW	CRITICAL
Renal serious adverse effects												
1	observational studies	not serious	not serious	not serious	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 0.9 (0.4 to 2.01)	14 fewer per 1000 (from 89 fewer to 131 more)	⊕⊕○○ LOW	CRITICAL
Renal serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	0/436 (0.0%)	5/413 (1.2%)	RR 0.09 (0.01 to 1.54)	11 fewer per 1000 (from 7 more to 12 fewer)	⊕⊕○○ LOW	CRITICAL
Blood serious adverse effects												
1	observational studies	not serious	not serious	not serious	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.4 (0.87 to 2.26)	61 more per 1000 (from 20 fewer to 193 more)	⊕⊕○○ LOW	CRITICAL
Neurology serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	3/436 (0.7%)	2/413 (0.5%)	RR 1.42 (0.24 to 8.46)	2 more per 1000 (from 4 fewer to 36 more)	⊕⊕○○ LOW	CRITICAL
Cardiovascular serious adverse effects (randomized controlled trials)												

1	randomized trials	not serious	not serious	not serious	very serious[1]	none	0/436 (0.0%)	1/413 (0.2%)	RR 0.32 (0.01 to 7.73)	2 fewer per 1000 (from 2 fewer to 16 more)	⊕⊕○○ LOW	CRITICAL
Other serious adverse effects												
1	observational studies	not serious	not serious	not serious	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.4 (0.94 to 2.08)	61 more per 1000 (from 9 fewer to 166 more)	⊕⊕○○ LOW	IMPORTANT
Other non-AIDS events												
1	randomized trials	not serious	not serious	not serious	very serious[1]	none	3/515 (0.6%)	3/511 (0.6%)	RR 0.99 (0.2 to 4.89)	0 fewer per 1000 (from 5 fewer to 23 more)	⊕⊕○○ LOW	IMPORTANT

1. Fewer than 50 events
2. One of three point estimates suggested a reduced risk.
3. One of three studies did not provided adjusted estimates.
4. One study compared 500 versus 350–499 cells/mm^3. Two studies compared 500 versus <500 cells/mm^3.
5. There is large overlap of populations between the cohorts.
6. Two studies did not make comparisons between ≥500 and <500 cells/mm^3 directly.
7. Unadjusted estimates.
8. Study did not make direct comparisons between ≥500 and <500 cells/mm^3 (such as early versus deferred).
9. One study's results suggested an increased risk.
10. Comparison is <350 cells/mm^3.
11. From 50 to 199 events.
12. Severe HIV infection or malignancy.

Author(s): Anglemyer, Andrew
Date: 18 May 2015
Question: Should ART in eligible patients with CD4 >500 mm^3 versus CD4 <500 mm^3 be used for HIV treatment for adolescents?
Settings: Africa, Asia, Australia, Europe and North America
Bibliography: CASCADE 2003, CASCADE 2011, Danel (TEMPRANO) 2015, Donnell 2010, Garcia 2004, Gras 2007, He 2013, HIV CAUSAL 2010, HIV CAUSAL 2011, Jean 2013, Jean 2014, Jia 2012, Jose 2014, Kitahata 2009, Le 2013, Merito 2006, Okulicz 2015, Palella 2003, Schneider 2013, Sterne 2009

Quality assessment							Number of people		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ART in eligible patients with CD4 >500 cells/mm^3	CD4 <500 cells/mm^3	Relative (95% CI)	Absolute		
Mortality												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	5/222 (2.3%)	5/201 (2.5%)	RR 0.91 (0.27 to 3.08)	5 fewer per 1000 (from 15 fewer to 17 more)	⊕○○○ VERY LOW	CRITICAL
Mortality (clean)												
3	observational studies	Serious[3]	Serious[4]	Serious[5,1]	not serious	none	351/7572 (4.6%)	895/18 952 (4.7%)	RR 0.68 (0.39 to 1.21)	15 fewer per 1000 (from 10 more to 29 fewer)	⊕○○○ VERY LOW	CRITICAL
Mortality (overlap)												
6	observational studies	very serious[6]	serious	very serious[1,7]	not serious	none	918/86 832 (1.1%)	7901/335 225 (2.4%)	RR 0.64 (0.51 to 0.81)	8 fewer per 1000 (from 4 fewer to 12 fewer)	⊕○○○ VERY LOW	CRITICAL
Death, severe HIV infection or malignancy												
1	randomized trials	not serious	not serious	Serious[1]	Serious[12]	none	23/212 (10.8%)	38/201 (18.9%)	HR 0.56 (0.33 to 0.94)	83 fewer per 1000 (from 11 fewer to 127 fewer)	⊕⊕○○ LOW	CRITICAL
AIDS or death												
2	observational studies	Serious[8]	not serious	Serious[1]	not serious	none	698/5252 (13.3%)	2058/12 491 (16.5%)	RR 0.63 (0.16 to 2.49)	61 fewer per 1000 (from 138 fewer to 245 more)	⊕○○○ VERY LOW	CRITICAL

AIDS or death (overlap)												
4	observational studies	Serious[6,8]	Serious[10]	Serious[1]	not serious	none	926/14251 (6.5%)	3830/45102 (8.5%)	RR 0.77 (0.49 to 1.21)	20 fewer per 1000 (from 18 more to 43 fewer)	⊕○○○ VERY LOW	CRITICAL
Severe HIV infection or malignancy[13]												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	12/222 (5.4%)	18/201 (9.0%)	RR 0.6 (0.3 to 1.22)	36 fewer per 1000 (from 20 more to 63 fewer)	⊕○○○ VERY LOW	CRITICAL
HIV disease progression												
1	observational studies	Serious[8]	not serious	Serious[1,9]	not serious	none	98/257 (38.1%)	295/398 (74.1%)	HR 0.2 (0.10 to 0.42)	504 fewer per 1000 (from 308 fewer to 615 fewer)	⊕○○○ VERY LOW	CRTICAL
Invasive bacterial infection												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	2/222 (0.9%)	3/201 (1.5%)	RR 0.6 (0.1 to 3.58)	6 fewer per 1000 (from 13 fewer to 39 more)	⊕○○○ VERY LOW	CRITICAL
Malignancies (AIDS and non-AIDS)												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	1/222 (0.5%)	1/201 (0.5%)	RR 0.91 (0.06 to 14.38)	0 fewer per 1000 (from 5 fewer to 67 more)	⊕○○○ VERY LOW	CRITICAL
TB (pulmonary or disseminated)												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	8/222 (3.6%)	20/201 (10.0%)	RR 0.52 (0.22 to 1.21)	48 fewer per 1000 (from 21 more to 78 fewer)	⊕○○○ VERY LOW	CRITICAL
HIV transmission												
1	randomized trials	not serious	not serious	Serious [1,11]	very serious[2]	none	2/100000 (0.0%)	20/100000 (0.0%)	RR 0.11 (0.06 to 0.19)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	CRITICAL
HIV transmission												
2	observational studies	Serious[8]	not serious	Serious[1]	very serious[2]	none	6/366 (1.6%)	12/912 (1.3%)	RR 1.17 (0.46 to 2.98)	2 more per 1000 (from 7 fewer to 26 more)	⊕○○○ VERY LOW	CRITICAL

Any serious adverse effects												
1	observational studies	not serious	not serious	Serious[1]	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.43 (1.13 to 1.81)	59 more per 1000 (from 18 more to 107 more)	⊕○○○ VERY LOW	CRITICAL
Grade 3 or 4 laboratory abnormalities (other than neutropaenia)												
1	randomized trials	not serious	not serious	Serious[1]	serious[12]	none	15/212 (7.1%)	25/201 (12.4%)	HR 0.58 (0.30 to 1.11)	52 fewer per 1000 (from 14 more to 87 fewer)	⊕⊕○○ LOW	CRITICAL
Liver serious adverse effects												
1	observational studies	not serious	not serious	Serious[1]	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.45 (1.03 to 2.04)	61 more per 1000 (from 4 more to 135 more)	⊕○○○ VERY LOW	CRITICAL
Liver serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	4/436 (0.9%)	5/413 (1.2%)	RR 0.76 (0.2 to 2.85)	3 fewer per 1000 (from 10 fewer to 22 more)	⊕○○○ VERY LOW	CRITICAL
Renal serious adverse effects												
1	observational studies	not serious	not serious	Serious[1]	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 0.9 (0.4 to 2.01)	14 fewer per 1000 (from 89 fewer to 131 more)	⊕○○○ VERY LOW	CRITICAL
Renal serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	0/436 (0.0%)	5/413 (1.2%)	RR 0.09 (0.01 to 1.54)	11 fewer per 1000 (from 7 more to 12 fewer)	⊕○○○ VERY LOW	CRITICAL
Blood serious adverse effects												
1	observational studies	not serious	not serious	Serious[1]	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.4 (0.87 to 2.26)	61 more per 1000 (from 20 fewer to 193 more)	⊕○○○ VERY LOW	CRITICAL
Neurology serious adverse effects (randomized controlled trials)												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	3/436 (0.7%)	2/413 (0.5%)	RR 1.42 (0.24 to 8.46)	2 more per 1000 (from 4 fewer to 36 more)	⊕○○○ VERY LOW	CRITICAL
Cardiovascular serious adverse effects (randomized controlled trials)												

1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	0/436 (0.0%)	1/413 (0.2%)	RR 0.32 (0.01 to 7.73)	2 fewer per 1000 (from 2 fewer to 16 more)	⊕○○○ VERY LOW	CRITICAL
Other serious adverse effects												
1	observational studies	not serious	not serious	Serious[1]	not serious	none	76/447 (17.0%)	1207/7860 (15.4%)	RR 1.4 (0.94 to 2.08)	61 more per 1000 (from 9 fewer to 166 more)	⊕○○○ VERY LOW	IMPORTANT
Other Non-AIDS Events												
1	randomized trials	not serious	not serious	Serious[1]	very serious[2]	none	3/515 (0.6%)	3/511 (0.6%)	RR 0.99 (0.2 to 4.89)	0 fewer per 1000 (from 5 fewer to 23 more)	⊕○○○ VERY LOW	IMPORTANT

1. Adolescents were very poorly represented in this studies, and uncertainty remains on the degree of generalizability of these findings to the adolescent population.
2. Fewer than 50 events.
3. One of three point estimates suggested a reduced risk.
4. One of three studies did not provided adjusted estimates.
5. One study compared 500 versus 350–499 cells/mm^3. Two studies compared 500 versus <500 cells/mm^3.
6. There is large overlap of populations between the cohorts.
7. Two studies did not make comparisons between ≥500 and <500 cells/mm^3 directly.
8. Unadjusted estimates.
9. Study did not make direct comparisons between ≥500 and <500 cells/mm^3 (such as early versus deferred)
10. One study's results suggested an increased risk.
11. Comparison is <350 cells/mm^3.
12. From 50 to 199 events.
13. Severe HIV infection or malignancy.

Annex 2.1.2 Evidence to decision making framework A1.3 Duration of ART Option B+ (pregnant and breastfeeding women)

Should pregnant and breastfeeding women living with HIV started on triple ARV drugs continue on lifelong ART regardless of the eligibility criteria?

Should pregnant and breastfeeding women with HIV started on triple ARV drugs continue on lifelong ART regardless of the eligibility criteria?	
Population	HIV-positive pregnant and breastfeeding women
Intervention	Continue lifelong ART beyond cessation of breastfeeding (or after delivery if no breastfeeding) regardless of eligibility criteria for treatment (such as CD4 ≤500 cells/mm^3)
Comparator	Stop ART at cessation of breastfeeding (or after delivery if not breastfeeding) if not otherwise eligible for ART (such as CD4 >500 cells/mm^3)
Outcome(s)	Maternal mortality, morbidity, adverse events, adherence, mother-to-child transmission, HIV horizontal transmission, HIV drug resistance, retention, stopping and restarting ART (option B), TB incidence, programmatic feasibility and advantages
Subgroup analyses	Prevalence setting Fertility rate Key populations: Adolescents People who inject drugs Sex workers

Setting: Resource-limited settings of high and low HIV prevalence where either breastfeeding or replacement feeding is national policy for mothers living with HIV.

Perspective: A simplified public health approach that takes into account limited access to laboratory and human resources.

Subgroup considerations: The evidence from the reviews was examined according to settings of low or high HIV prevalence, background fertility rate and issues in key populations including adolescents, sex workers and people who inject drugs.

Background: The 2013 WHO guidelines recommended that all pregnant and breastfeeding women start triple ART immediately at diagnosis and then either continue until the end of the exposure period (option

Background:

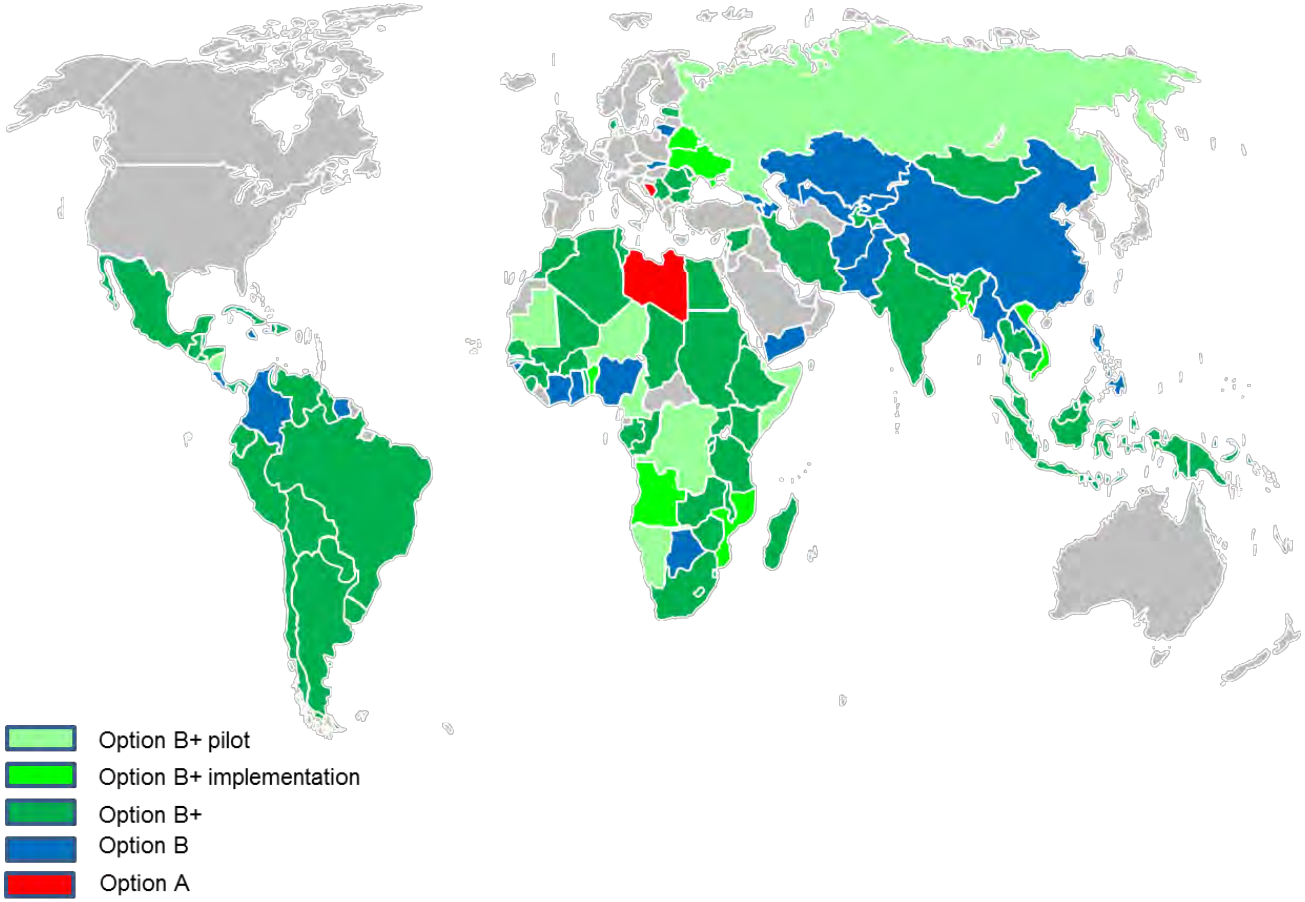
2013 ARV guidelines recommendations

ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 count in the following situations:

- **individuals with HIV and active TB disease (strong recommendation, low-quality evidence);**
- **individuals coinfected with HIV and HBV with evidence of severe chronic liver disease (strong recommendation, low-quality evidence);**
- **partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (strong recommendation, high-quality evidence); and**
- **pregnant and breastfeeding women with HIV.**

- **All pregnant and breastfeeding women with HIV should initiate triple ARV drugs (ART), which should be maintained at least for the duration of mother to child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (strong recommendation, moderate-quality evidence).**
- **For programmatic and operational reasons, particularly in generalized epidemics, all pregnant women and breastfeeding women with HIV should initiate ART as lifelong treatment (conditional recommendation, low-quality evidence).**
- **In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother to child transmission risk has ceased (conditional recommendation, low-quality evidence).**

B) or remain on lifelong ART (option B+). This was the first WHO recommendation for a universal treatment approach, but some countries had already begun to implement this concept. Malawi was the first national programme to adopt option B+, and since then many others have followed suit. All the high-burden high-priority countries in the Global Plan (21 in sub-Saharan Africa plus India) and are now implementing either option B or option B+. The map below shows a preliminary analysis of the global status around PMTCT guideline adoption. Most countries are either piloting, rolling out or already fully implementing option B+. Based on available data on the burden of disease, this means **that 83% of pregnant women living with HIV worldwide are in countries where option B+ forms part of the policy framework**.


Option B+ pilot
Option B+ implementation
Option B+
Option B
Option A

	Criteria	Judgements	Research evidence	Additional considerations

PROBLEM	**Is the problem a priority?**	***Yes***	• Although most countries have adopted option B+, there are still important considerations around the risks and benefits of lifelong therapy for all.
			• In countries with high prevalence and a high fertility rate, there are public health benefits to option B+ for prevention of vertical and horizontal transmission, but individual benefits remain unclear, and as a result some countries continue to advocate option B.
			• For some subpopulations of pregnant women, such as adolescents, people who inject drugs and sex workers, there may be particular concerns about the balance between the risks and benefits of option B versus option B+ that might influence decision-making.
			• Pregnant adolescents living with HIV in particular face unique challenges with regards to PMTCT that may influence the appropriate prevention strategy.
			  ○ **MTCT:** A study in South Africa found that MTCT risk is higher among infants of adolescent mothers living with HIV compared with adult mothers living with HIV (10.8% versus 6.1%, OR 1.7).[1]
			  ○ **Loss to follow-up:** Age has been shown to be independently associated with loss to follow-up among pregnant women. One study reported that younger women <25 years had a 2.2-fold greater risk of being loss to follow-up than women >35 years.[2] Similarly in Malawi, loss to follow-up was higher in women who were aged 13–24 years when initiating ART than those older than 25 years (adjusted RR 1.29).[3]
			  ○ **Unintended pregnancy**: In a study of HIV-positive adolescents in Kenya, 50% of 800 adolescents surveyed had been pregnant, 25% had multiple pregnancies and 75% of all pregnancies were unplanned.[4]	

	Criteria	Judgements	Research evidence	Additional considerations

	Criteria	Judgements	Research evidence	Additional considerations

QUALITY OF EVIDENCE	**How substantial are the desirable anticipated effects?**
	How substantial are the undesirable anticipated effects?
	What is the overall certainty of the evidence of effects?
		Moderate quality evidence based on the same rating as for adults	A systematic review was conducted on option B versus option B+. 27 studies were reviewed, of which 18 were on option B (including 2 randomized controlled trials, 1 single-arm and 12 cohort studies all in sub-Saharan Africa) and 9 on option B+ (1 randomized controlled trial and 8 cohorts). The review highlighted that there is insufficient evidence from studies to answer the question of whether option B+ is the optimal PMTCT strategy. No randomized controlled trials or observational studies were identified that compare option B and B+ and **no GRADE table has been developed** for this review. The results are summarized below, grouped under some of the key outcomes.
			
			Option B studies
			
			Maternal mortality: Maternal mortality was reported in 8 studies and ranged from 0% to 1.6%.[5,6,7,8,9,10,11,12] Two studies reported progression to severe disease after stopping ART, but the rates of progression were low, with an average of 1.5% (0.47–2.53%) of mothers advancing to WHO stage IV.[13,14] A total of four studies reported immune failure once ART stopped.[15,16,17,18] The risk of falling below a CD4 threshold of 350 cells/mm^3 increased with time. Six months after stopping ART, only 1.5% of women reached eligibility, whereas by 24 months 36% of women were treatment eligible. Viral suppression was reported in 3 studies. On average, 89% of mothers on B+ were virally suppressed at 6 months postpartum.[19,20,21]
			
			Adherence: Women were largely adherent, with more than 80% of women reported to be more than 95% adherent during pregnancy and 6 months postpartum.[22,23]
				To supplement the sytematic review, we underook a literature seach to examine the clinical and operational impact of stopping ART in people living with HIV, with a focus on pregnant women. 26 studies were examined. Most used older criteria for treatment eligibility (CD4 <350). Key findings are summarized below:
				CD4$^+$ decline
				• Postpartum women who discontinue ART commonly experience CD4 decline, but there is heterogeneity within the results.
				• Studies have looked at CD4 at baseline and at stopping ART as predictors of how soon women reach treatment thresholds.
				• For baseline CD4
				  ○ In general, CD4 <500 resulted in 6–20% of women reaching treatment threshold within 6 months of stopping.[46,47,48]
				  ○ By contrast, if CD4 was

	Criteria	Judgements	Research evidence	Additional considerations

			Resistance: One study reported drug resistance, with 12 (63%) of women who had not suppressed viral replication to have resistance markers.[24]
			
			Retention: Loss to follow-up varied, with one study reporting loss to follow-up 31.9% before delivery[25] and others reported lower rates of 8.8% and 19.4% at 6 and 12 months, respectively.
			
			MTCT and child survival: Option B works well for prevention. MTCT rates were not significantly different from 6 weeks[26,27,28] to 24 months.[29,30] with studies reporting rates below 5%. Child mortality ranged between 5.2% and 7.2% in three studies.[31,32,33] HFS was analysed in a number of studies and ranged from 93.2% at 3 months to 85.8% at 12 months.[34, 35, 36]
			
			<u>Option B+ studies:</u>
			
			Maternal mortality: Maternal mortality was reported in 4 studies and averaged 0.7% at 6–12 months post enrolment.[37,38,39,40] Viral supression was 96% at 6 months.[41]
			
			Adherence: The adherence reported across studies was high: 94.3% at 6–12 monhts after enrolment.[42,43]
			
			Retention: Many studies reported findings on retention, which ranged from 70.6% at 6 months[44] to 90.5% at 3 months after enrolment.[45]
			
			No studies on either option B or B+ reported HIV tranmsission rates to sexual partners.
			
			The review did not identify any evidence on option B or B+ outcomes among key populations and adolesccents. This remains a critical area of needed research.
				>500, only 1.5% of women reached the threshold 6 months after stopping.[48]
				• For CD4 at ART stop
				  ○ CD4>550 was associated with 7% of women reaching threshold 18 months later.
				  ○ Whereas, for CD4 <550, anywhere from 27% to 50% of women reached threshold at 18 months.[49,50]
				• In the Kesho Bora study, at 18 months after discontinuation, 30% of women with CD4 >350 at baseline had crossed the treatment threshold.[51]
				<u>Immune activation</u>
				• Treatment stop is associated with increased immune activation, characterized by a slower decline in inflammatory markers than in women on ART.[52,53]
				<u>Disease progression</u>
				• A report from Brazil showed that women who stopped with lower baseline CD4 (<500) had a 2.5-fold higher risk of WHO stage 2 or 3 clinical events than those with a baseline CD4 >500 cells/mm^3.[54]
				<u>Drug resistance</u>
				• Very limited data on drug resistance in postpartum women who stop ARV at the end of transmission risk. Suggests that, provided women were adherent while taking

	Criteria	Judgements	Research evidence	Additional considerations

In summary, although there are benefits to continuous ART in terms of CD4 decline and disease progfression, there is no definitive evidence that option B+ is superior to option B.

Summary of option B and option B+ outcomes

Outcome	Option B		Option B+	
	n/N	% (95% CI)	*n/N*	% (95% CI)
Maternal mortality	122/13 802	0.9% (0.85–0.95%)	165/23 117	0.7% (0.59–0.81%)
Viral suppression at 6 months	1 119/1 254	89.2% (87.4–90.9%)	1 141/1 189	96.0% (94.9–97.1%)
Adherence at 6–12 months	366/434	84.3% (80.9-87.7%)	1 300/1 379	94.3% (93.0–95.4%)
Retention at 4–6 months	7 779/8 530	91.2% (90.6–91.8%)	12 414/16 405	75.7% (75.0–76.4%)

ARV drugs, treatment stop does not result in signigificant rates of resistance.[55]

Retention

- One of the important programmatic otucomes of stopping ART in postpartum women is poor retention,[56,57,58] with one study reporting that women who were not yet eligible for ART had a 10-fold higher risk of loss to follow-up than those who were eligible.[59]
- Good follow-up after treatment stop is a problem in both resource-rich and resource-limited settings. In the United Kingdom, 2 of 3 women who presented at antenatal care for a second pregnancy having had start and stop of ART, had a CD4 below 350.[60]

Summary of stopping ART

The available evidence around stopping ART in pregnant women, although limited, highlights some of the negative impacts on a variety of clinical and operational outcomes, particularly for women with lower CD4 counts, suggesting that, where feasible, lifelong ART for pregnant women should be considered. In settings unable to implement option B+, evaluating CD4 at ART initiation or at 6 months postpartum can be useful in

	Criteria	Judgements	Research evidence	Additional considerations
				identifying the pregnant women who would benefit most from continuing on lifelong ART rather than stopping. Although there are documented downsides to stopping, it is noteworthy that resistance does not appear to be a significant issue, especially where women have been adherent to ARV drugs during pregnancy.

	Criteria	Judgements	Research evidence	Additional considerations
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	***No major variability***	**WHO outcomes ranking survey** **A1.3 Should pregnant and breastfeeding women with HIV started on triple ARV drugs continue on lifelong ART regardless of eligibility criteria?** **Population: pregnant and breastfeeding women living with HIV** **Intervention: any intervention for pregnant and/or breastfeeding women with HIV infection who are on option B+ and continue with lifelong ART** **Comparator: any intervention for pregnant and/or breastfeeding women with HIV infection who begin combination ART and discontinue after cessation of breastfeeding (or after delivery if no breastfeeding)**	.

Answer options	Mean	Rating
Maternal mortality	8	Critical
Maternal morbidity	8	Critical
Mother-to-child transmission or infant HIV infection	8	Critical
Maternal viral load	8	Critical
Adherence to ART (as measured by investigators)	8	Critical
Retention in treatment	8	Critical
Acceptability to women	8	Critical
HIV transmission to sexual partners	7	Critical
Development of antiretroviral resistance	7	Critical
TB incidence	7	Critical
Adverse events	7	Critical
Sustainability of service delivery	7	Critical
Maternal CD4 or clinical staging (when initiated option B+)	6	Important
Fertility rate	6	Important

	Criteria	Judgements	Research evidence	Additional considerations
BENEFITS & HARMS OF THE OPTIONS	**Does the balance between desirable effects and undesirable effects favour the option or the comparison?**	***Benefits > harm***	Summary of the key benefits and risks of implementing option B+ over option B.[61] **Benefits** • Preventing transmission in future pregnancies • Reduced transmission to uninfected partners (hypothesized) • Avoids repeated cycles of stopping and starting ART for women with multiple pregnancies • Avoid potential downsides of stopping ART and restarting • Simplification of service delivery, since there is no need to establish eligibility before initiating ART. Practically much easier to implement this than deciding when to do CD4 • Rapid ART initiation without potential delays due to CD4 testing and thereby reducing risk of MTCT • Reduced risk of developing TB • Some data suggest improved maternal mortality and slower disease progression in women who receive continuous ART verus interrupted ARV drugs • Reduces the need for and cost of diagnosis of disease progression if women are to remain on lifelong treatment regardless of eligibility for treatment • Women might be less likely to drop out of HIV care after the end of the transmission risk period when option B is stopped • Large numbers of women will be eligible anyway **Risks** • Additional potential risk of toxicity because of additional time on treatment • Newly diagnosed pregnant women may feel unprepared for ART. Particular challenges associated with loss to follow-up in adolescents • Uncertain acceptability of lifelong ART among pregnant women • It has been suggested that women may seek pregnancy as a means to access	

	Criteria	Judgements	Research evidence	Additional considerations
			lifelong treatment • Increased net cost	

	Criteria	Judgements	Research evidence	Additional considerations
RESOURCE USE	**How large are the resource requirements (costs)?**		• The total cost of option B+ was US$ 2069 per women over 5 years regardless of CD4+ count, breastfeeding status or duration. For breastfeeding women with a **CD4 count between 350 and 500 cells/mm^3**, the incremental cost per women of option B+ versus B was **US$ 255**; and for non-breastfeeding women this was **US$ 154**. For breastfeeding women with a **higher CD4 count >500 cells/mm^3,** the incremental cost per women of option B+ versus B ranged from **US$ 606 to US$ 808** (depending on the duration of breastfeeding). Among non-breastfeeding women with a high CD4 count, the incremental cost of option B+ relative to option B was **US$ 100**.[62]	
	What is the certainty of the evidence of resource requirements?			
	Does the cost–effectiveness of the option favour the option or the comparison?	***More resource-intensive but probably cost-effective***	Since the early 2000s, several model-based analyses have supported the cost–effectiveness of PMTCT strategies. Early studies examined the impact of single-dose nevirapine compared with no intervention and found that single-dose nevirapine was either cost-saving or very cost-effective, with incremental cost–effectiveness ratios (incremental cost–effectiveness ratios) less than US$ 100 per year of life saved. Such economic benefits were due not only to the very low cost of single-dose nevirapine, but also to the substantial savings that occur when a single child is prevented from acquiring HIV infection. (In the pre-ART era, these savings occurred because very costly opportunistic infections, hospitalizations and deaths in health-care facilities were avoided.) In more recent years, cost-effectiveness analyses have examined the potential value of more intensive ARV regimens for PMTCT. Despite the higher medication and program costs of maternal ART, such studies have generally found **option B or B+ to be cost-saving or very cost-effective, compared with option A.** These findings relate again to the cost-savings from averting HIV infection among children, now including the costs of lifelong ART. **When outcomes beyond the MTCT risk in the index pregnancy are included** (for example, maternal health benefits, PMTCT in subsequent pregnancies or preventing transmission to sexual partners of HIV-infected	

	Criteria	Judgements	Research evidence	Additional considerations
			women), **option B+ has also been found to be cost-saving or very cost-effective compared with option B.** Cost–effectiveness studies comparing options B and B+ are summarized below. • **Fasawe et al., 2013 (Malawi)**[63]: option B+ not only prevents infant infections but it improved 10-year survival in mothers by more than 4-fold compared with current practice in 2010. Option B+ also had an incremental cost–effectiveness ratio of US$ 455 per life-year gained over current practice, which is considered favourable. • **VanDeusen et al., 2015 (Ghana)**[64]: option B+ costs US$ 785 per QALY gained, which is considered very cost-effective by WHO benchmarks and substantially reduces MTCT in future pregnancies, with an estimated 668 HIV infections prevented in children annually. • **Ciaranello et al., 2013 (Zimbabwe)**[65]: Replacing option B with option B+ improved combined maternal and infant life expectancy from 38.32 to 39.05 years. Option B+ had an incremental cost–effectiveness ratio of US$ 1370 per year of life saved compared with option B, which is similar to many current HIV-related health interventions. • **Gopalappa et al., 2014 (multi-country)**[66]: Data from Kenya, South Africa, Viet Nam and Zambia show that option B+ was the most cost-effective strategy when compared to options A and B, with an incremental cost–effectiveness ratio of between US$ 6000–23 000 per infection averted (varying by country). Option B+ averted more child infections and prevented more adult sexual transmission than option B. • **Ishikawa et al., 2014 (Zambia)**[67]: Option B and B+ were considered more cost-effective than option A. Calculation of the cost–effectiveness based on costs of PMTCT programme and benefits in terms of infant and partner infections indicated a incremental cost–effectiveness ratio of US$ 75 per QALY gained for option B and US$ 132 per QALY gained for option B+ compared with option A. • **Adesina & Alkenbrack, 2015 (Nigeria)**[68]: Option B+ averted an estimated 78 000 vertical infections, while option B+ averted 65 000. With an incremental cost of US$ 0.5 billion for option B+ (US$ 4.5 billion versus US$ 4 billion), the cost per vertical infection averted was US$ 83 000 for option B and US$ 65 000 for option B+. **Table 1. Summary of cost–effectiveness outcomes of studies** **Study** | **Comparator** | **Cost–effectiveness** | **Cost–effectiveness** | **Cost–effectiveness**	

	Criteria	Judgements	Research evidence	Additional considerations

		(DALY/QALY)	(cost per infection averted)	(life expectancy)
Fasawe et al., 2013 (Malawi)	Options A and B	US$ 60 per DALY averted (B) US$ 57 per DALY averted (B+)	US$ 1331 (B) US$ 1265 (B+)	US$ 338 per life-year gained (B) US$ 455 per life-year gained (B+)
VanDeusen, et al. (Ghana)	Option B	US$ 785 per QALY gained		US$ 618 per life-year gained
Ciaranello et al., 2013 (Zimbabwe)	Option B			US$ 1370 per life-year gained
Gopalappa et al., 2014 (multicountry)	Option A		US$ 6000–23 000	
Ishikawa, et al., 2014 (Zambia)	Options A and B	US$ 74 per QALY gained (B) US$ 132 per QALY gained (B+)	US$ 1023 (B) US$ 1254 (B+)	
Adesina & Alkenbrack, 2015 (Nigeria)	Option B (average cost–effectiveness, includes all associated costs)		US$ 83 000 (B) US$ 65 000 (B+)	

	Criteria	Judgements	Research evidence	Additional considerations
EQUITY	**What would be the impact on health equity?**	***More equitable***	• There are no known major equity concerns. • All pregnant women must be given ART as a priority to minimize infections among children. • Unclear what impact B+ rollout has had on ART access for other populations, but possibly positive?	

	Criteria	Judgements	Research evidence	Additional considerations
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	***Acceptable with no major variability***	**A review of published and grey qualitative literature was carried out to explore the acceptability of lifelong ART among pregnant and breastfeeding women and health-care workers.** Nine published studies conducted between 2012 and 2014 and 1 report from a global survey conducted in 2014 including 94 countries were included. Only 2 studies included health-care workers views. Key findings identified: • **Acceptability:** Although most studies found general acceptability of option B+,[69] there were concerns among women about accepting lifelong ART and fear of drug side effects for their children.[70,71] • **Perceived benefit for infants**: Participants in general valued the protection that option B+ offered in terms of vertical transmission, along with the ability to breastfeed for longer and the associated health improvements for the child.[72] • **Perceived benefit for women:** Other benefits described included the possibility of having more children, enabling natural childbirth and the protection of partners. Mothers reported feeling healthier because they are on treatment and that it encourages disclosure, testing and ARV uptake. Many acknowledged that option B+ provided access to treatment that would prolong their own lives.[73] • **Challenges of lifelong treatment:** Challenges to treatment reported include; disclosure (to partner, employer and others),[74] stigma and discrimination, costs and transportation, male involvement[75], lack of support[76] and side effects, toxicity[77] and resistance.[78,79,80] Additionally the belief that HIV care for the mother's own health is unimportant once the infant is born, especially if the child was HIV negative.[81] Negative treatment and attitudes from health-care workers were also raised in multiple studies[82,83,84,85] and the right of potential coercion.[86] Although option B+ aims to deliver ART within antenatal care services, 45% of eligible women reported that they were referred to separate ART services, suggesting challenges with integrating these services.[87]	Many of the benefits and challenges described by the community would actually apply equally to option B as well as to option B+. However, some issues are unique to option B+. Benefits include the protection of partners and feeling healthier in themselves. The risks include lack of support for lifelong treatment and operationally the challenge of linkage between maternal and child health services and ART.
FEASIBILITY	**Is the option feasible to implement?**	***Yes***	• See country presentations reflecting decision-making processes around feasibility • Operational considerations regarding whether integration or co-location of maternal, newborn and child health services with ART versus referral of services is better for women and improves retention and adherence to ART. • Need for strengthened data systems to track medication adherence and patient follow-up, especially across multiple service delivery sites – such as antenatal care, maternal, newborn and child health services and ART centres. • The existing evidence on option B+ highlights challenges associated with the adherence and retention of pregnant and especially postpartum women. Why is this the case? ○ Long-term success of option B+ will require targeted interventions to	

	Criteria	Judgements	Research evidence	Additional considerations
			improve adherence and retention in care, including greater education and counselling on the maternal health benefits of option B+ to improve patient acceptability and support women in coming to terms with lifelong treatment as they are rapidly initiated on ART. o Could same-day start be part of the problem? Too much too soon? o Additional support, whether community or peer support may also benefit pregnant women, particularly adolescents who have greater loss to follow-up than older women.	

Conclusions

Type of recommendation or decision	We recommend against the intervention or for the comparison	Conditional recommendation not to use the intervention or to use the comparison	We suggest using either the intervention or the comparison	Conditional recommendation to use the intervention	We recommend the intervention
	☐	☐	☐	☐	☒

Recommendation or decision

ART should be initiated among all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

Research priorities

- Randomized controlled trials of option B and option B+
- Implementation research evaluating the real-world effectiveness of option B+
- Comparing co-location and integration of ART within maternal, newborn and child health services services versus referral of women to ART programmes. Which is better for women a What is the right time after delivery to make that referral?
- Health benefits for women resulting from starting treatment for life on high CD4 counts, especially for younger women
- Health implications for women stopping and starting treatment with each pregnancy (on high CD4 counts), especially for younger women
- Implications for nutrition and mortality through allowing breastfeeding for one year instead of six months
- Barriers to uptake of option B+ and solutions
- Studies in key populations and pregnant adolescents to determine optimal priority interventions

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Annex 2.1.3 **Evidence to decision making framework A1.1 When to start in asymptomatic HIV+ individuals, paediatrics**

In children and adolescents younger than 15 years, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?

In children and adolescents living with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?	
Population	Children and adolescents younger than 15 years living with HIV (WHO clinical stage 1 or 2)
Intervention	ART initiated CD4 >500 cells/mm^3
Comparator	ART initiated CD4 ≤500 cells/mm^3
Outcome(s)	Children and adolescents: immune recovery, HIV drug resistance, adherence, retention, TB incidence and neurodevelopment
Subanalyses	Age: Children 5 to <10 years Adolescents 10 to <15 years

Setting

This assessment will focus on settings adopting the public health approach for providing testing and treatment for infants and children. An attempt will be made to reflect the context of different epidemic settings.

Perspective

The scaling up of HIV treatment for children continue to lag significantly behind adults, with only 23% coverage estimated by December 2013. Infants and young children are at an exceptionally high risk of HIV-related disease, but by five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those among young adults.

In 2013, the review of evidence, together with operational considerations and values and preferences expressed by care providers, have led to a revised recommendation on the initiation of ART among children up to five years. This decision was taken to enhance programmatic simplicity and, recognizing that where access to immunological testing is limited, the burden of HIV disease among children is high and ART coverage among children is low, simplifying the eligibility criteria for initiating ART may significantly improve overall health outcomes for children living with HIV. National programmes were therefore advised to consider this recommendation and to adopt it based on their own specific settings, ensuring, however, that priority is given to children younger than two years of age due to their higher risk

Background:

2013 ARV guidelines recommendations

Initiate ART in all children with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age or CD4 count (strong recommendation, moderate-quality evidence).

Initiate ART for all children living with HIV younger than five years of age regardless of CD4 count or WHO clinical stage.

- Infants diagnosed HIV-positive in the first year of life (strong recommendation, moderate-quality evidence).
- Children living with HIV between 12 and 59 months of age (conditional recommendation, very-low-quality evidence)

Special note: Conditions for which this recommendation is applicable include limited access to immunological testing, high burden of HIV disease among children and low ART coverage among children, since simplifying the eligibility criteria for initiation of ART may significantly improve overall health outcomes for children living with HIV. Children younger than two years of age should be given priority due to higher mortality risk. If this recommendation is not adopted: initiate ART with WHO HIV clinical stage 3 and 4 or with CD4 count ≤750 cells/mm^3 or <25%, whichever is lower, regardless of WHO clinical stage (strong recommendation, very-low-quality evidence).

Initiate ART for children five years of age and older with CD4 cell count □ 500 cells/mm^3, regardless of clinical symptoms (or WHO stage).

- CD4 count <350 cells/mm^3 (strong recommendation, high- to moderate-quality evidence).
- CD4 count between 350 and 500 cells/mm^3 (conditional

of death and disease progression. For children 5 years of age and older, the criteria for initiating ART were aligned with the criteria for adults.

Very limited research has been undergoing to directly address this question, and United States and European guidelines have been conservative in moving towards earlier treatment for all children and adolescents. By contrast, there has been a broad uptake of this recommendation in sub-Saharan Africa, and countries such as Ethiopia, Namibia, South Sudan, Uganda and the United Republic of Tanzania have adopted a policy to treat all children and adolescents younger than 15 years irrespective of clinical and immunological conditions. Cameroon and Kenya have officially adopted treating all children younger than 10 years (and not 15 years) due to concerns related to the poor adherence observed in adolescents.

Poor adherence, unreliable supply of drugs for children and challenges in providing care for children by health care workers remain some of the concerns to address as consideration to this change is given.

The Clinical Guideline Development Group is therefore asked to re-examine the available evidence and consider the potential risks and benefits at the individual and programmatic level of treating all children younger than 15 years irrespective of clinical and immunological criteria.

Subgroup considerations

Although HIV has been indicated as the second leading cause of death among adolescents in Africa, highlighting the urgent need to increase access to testing and treatment for adolescents living with HIV, well known challenges with retention in care and adherence put them at high risk for treatment failure.

recommendation, very-low-quality evidence).

	Criteria	Judgements	Research evidence	Additional considerations
PROBLEM	**Is the problem a priority?**	***Yes***	• ART coverage in children and adolescents younger than 15 years lags significantly behind that of adults (23% versus 37% in 2013). • Mortality and disease progression risk child survival curves derived from two historic cohorts – HPPMCS (United States and Europe) and 3Cs4Kids (Africa) demonstrate that, after 5 years of age, the risk of mortality and disease progression is similar to the one estimated for adults (Dunn 2013). • HIV has been reported as the second cause of mortality among adolescents living with HIV	

	Criteria	Judgements	Research evidence	Additional considerations
			globally and the first in sub-Saharan Africa. • Currently, WHO recommends treating everyone <5 years and treating for stage 3 or 4 or CD4 500 cells/mm^3 older than 5 years. In previous years, recommendations on when to start for children younger than 5 years were developed on a programmatic basis. • The treatment initiation criteria recommended by WHO have been widely adopted in sub-Saharan Africa (~70%). • Some countries (such as Ethiopia, Kenya, Uganda and Zambia) are introducing immediate ART for children younger than 10 or 15 years on programmatic grounds. • Limited access to CD4 and poor WHO clinical staging prevent treatment initiation in children and adolescents who are already eligible. • Emerging evidence highlights that factors other than CD4, such as pubertal development, need consideration when making decisions about timing of ART initiation in older children (Szubert et al., AIDS 2015).	
QUALITY OF EVIDENCE	**How substantial are the desirable anticipated effects?** **How substantial are the undesirable anticipated effects?**	***Low quality of evidence***	• A review of existing literature did not add to the findings from a previous systematic review conducted in 2012 (Siegfried et al.) Two randomized controlled trials were identified for the systematic review. The first commenced in December 2001 and was designed as a feasibility study in 43 children before the larger PREDICT trial, which had a sample size of 300. Both studies enrolled children older than 1 year with CD4 above 15% and no clinical stage C disease and randomized them to either immediate treatment or deferred treatment until the CD4 fell below 15%. • Overall very-low-quality evidence supports immediate treatment based on the critical outcomes of morbidity and disease progression. For the growth outcomes of height and weight gain, the quality of evidence was graded (using GRADE) as low quality. (A significant degree of indirectness attached to the definition of "early " and "deferred" initiation, which differ from	

	Criteria	Judgements	Research evidence	Additional considerations
	What is the overall certainty of the evidence of effects?	***Low quality of evidence***	those currently under consideration, should be noted.) • A causal modelling analysis, comparing the effect of different treatment initiation criteria on death and growth response, for children aged 5–16 years (children who present before their 16th birthday). The analysis is based on a total of 8665 children aged 1–5 years, 7358 children aged 5–10 years, and 4553 adolescents aged 10–16 years, from IeDEA Southern Africa (IeDEA-SA), IeDEA West Africa (IeDEA-WA), and the COHERE collaboration. These analyses suggest that earlier treatment initiation yields lower mortality and better growth outcomes. The differences between immediate ART initiation and delaying until CD4 count <500 cells/mm^3 (or weight-for-age *z*-score <–2 for children aged 5–10 years) when evaluating mortality, however, were small and not always present. Nevertheless, if the subgroup of children who present with CD4 count >500 cells/mm^3 is considered, differences with respect to both mortality and growth response are more clearly pronounced – except when evaluating the mortality of adolescents. In general, for children aged 5–10 years, the differences between immediate ART initiation and delayed ART initiation can be more clearly seen than for adolescents. Given these considerations, as well as the limitations of the methods and the mixed pool of patients in the adolescent group, the results for the adolescent group need to be interpreted with caution. • A rapid assessment conducted in May 2015 to assess the implementation of the test-and-treat policy for children younger than 15 years in Uganda has enabled the documentation of key programmatic findings. – Implementing the policy resulted in a 74% increase in the number of children newly initiated on ART: from 11 624 in 2013 to 20 262 in 2014. The increase was greater among the children aged 5–14 years and 2–4 years (134% and 64% respectively), but among children younger than 2 years of age, there was a 3% reduction of the number of children initiated on treatment. There was a steady increase in the number of children initiated on ART from Q1 to Q3 of 2014, however, in Q4, 2014, the numbers of children initiated on ART declined. However, among children younger than 2 years of age, the numbers remained stable for most of the year, ranging between 803 and 1096. – ART coverage among children increased from 22% in 2013 to 32% in December 2014. By September 2014, 54 680 children were receiving ART.	

	Criteria	Judgements	Research evidence	Additional considerations
			– Decentralization: the proportion of children receiving ART in public health facilities (HC2, HC3 and HC4) increased from 42% in December 2013 to 46% in September 2014. And the proportion newly initiated at these facilities increased from 51% to 57%. – The time from eligibility to ART initiation has significantly decreased. – Overall, there was a drop in 6-month retention of children initiated after versus before implementing the test-and-treat guideline, but the difference was not statistically significant (78% before versus 75% after; *P*=0.2). – Overall retention was higher among children (5–14 years) who were initiated when they were "not sick" compared with children initiated when they were "sick", but the difference was not statistically significant (82% "not sick versus 79% "sick"; *P*=0.45). – Overall, the 12-month retention rates were similar for children initiated before versus after implementation of the guidelines (87% before versus 86% after). – Among the 793 who received viral load monitoring, overall 84% of the children were virally suppressed.	

	Criteria	Judgements	Research evidence	Additional considerations
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	***No major variability***	**In children and adolescents with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?** **Population: dults, adolescents and children with HIV infection (WHO clinical stage 1 or 2)** **Intervention: ART initiated CD4 >500 cells/mm^3** **Comparator ART initiated ≤CD4 500 cells/mm^3** **Answer Options** | **Mean** | **Rating**	.

	Criteria	Judgements	Research evidence	Additional considerations

Death	7	Critical
Progression to AIDS	7	Critical
TB and other opportunistic infections	7	Critical
Viral suppression	8	Critical
Severe treatment related adverse events (harm)	7	Critical
HIV transmission	7	Critical
Non-AIDS-related events (bacterial infections, cancer, cardiovascular disease, diabetes, renal disease, nervous system disease and liver disease)	7	Critical
Immune recovery	6	Important
Uptake of treatment	8	Critical
Adherence	8	Critical
Retention	8	Critical
HCV transmission (for people HIV and HCV coinfected)	5	Important
HBV transmission (for people HIV and HCV coinfected)	5	Important
Children: immune recovery	6	Important
Children: HIV drug resistance	7	Critical
Children: Neurodevelopment	7	Critical

BENEFITS & HARMS OF THE OPTIONS

Does the balance between desirable effects and undesirable effects favour the option or the comparison?

Benefits > harm

Benefits:

- Growth: Poor response to growth has been reported in older children living with HIV after ART.[12] Children younger than 3 years are 2–3 times more likely to attain population norms for weight-for-age *z*-score compared with older children.[3] Similar findings are reported in the IeDEA West African cohort, where adjusted catch-up growth was more likely for children <5 years of age at ART initiation compared to children ⩾5 years for weight-for-age *z*-score, height-for-age *z*-score ($P<0.001$), and for weight-for-height/BMI-for-age z-score ($P=0.03$).[4]
- Pubertal development: Delaying ART initiation until older childhood substantially delays pubertal development and menarche, independently of immunosuppression. Similar findings have been reported in the United States with children living with HIV (compared with HIV-exposed but uninfected children) having delayed onset of puberty, which was reduced with earlier initiation on ART.[5]

	Criteria	Judgements	Research evidence	Additional considerations
			• Neurocognitive outcomes: HIV infection appear to be associated with lower cognitive scores, but ART appeared to eliminate most of these deficits.[6] In addition, delays in ART initiation appeared to worsened cognitive impairment. A literature review of neurodevelopment in older children and adolescents found that, if ART was postponed, this was likely to be associated with improvements in neurodevelopmental scores.[7] • Coinfection and complications: ART may reduce the incidence of TB among children. A study in South Africa, where ART coverage of children living with HIV increased from 43% to 84%, found a decrease in incidence (per 100 000) of culture-confirmed TB by 63% (P<0.0001).[8] • Lung disease: As children get older, they are at increased risk of developing HIV-associated chronic lung disease. Lymphocytic interstitial pneumonitis responds well to ART, but delayed initiation of antiretroviral drugs can lead to long-term sequelae in adolescence.[9] Earlier initiation of ART during early childhood might prevent these disorders.[10] Studies have shown that delayed initiation of ART in older children and adolescents will not improve lung functioning.[11] • Immune recovery: Age at initiation is a significant predictor for CD4 recovery,[12] and the current treatment guidelines may not optimize long-term immune health[13] based on the findings of a number of studies described. Based on findings from a model developed from the ARROW trial, younger children younger than 6 years of age are more likely to achieve high CD4 counts later in adulthood. In addition, initiating ART in children >5 years based on current WHO criteria results in lower CD4 counts when they become adults. Children living with HIV who remain ART-naive beyond 10 years are unlikely to normalize CD4 count.[14] Similarly, the IeDEA cohort has shown that immune recovery was significantly lower in children initiated on ART at an age older than 5 years.[15] • Programme simplification: Simplification appears to be favourable to enabling decentralization and task-shifting. • Reduction of HIV-driven chronic immune activation, to prevent from premature ageing of the immune system and cause more adverse outcomes on immune health. Inflammation markers potentially associated with an increased risk of cardiovascular disease have been described to normalize once children are started on ART.[16] • Prevention of secondary transmission from establishing ART by the time of sexual debut. **Risks**	

	Criteria	Judgements	Research evidence	Additional considerations
			• Antiretroviral drug toxicity: The short-term side effects, such as dizziness and gastrointestinal disorders (diarrhoea, nausea and vomiting), can predispose children to suboptimal ART adherence and subsequently ART failure.[17,18] The long-term effects are particularly important as they influence the quality of life in adulthood. Lipodystrophy, insulin resistance, diabetes, lactic acidosis or mixed forms, has been observed to occur in 20–50% of the people receiving ART for prolonged periods.[19,20,21] In advanced HIV disease, the clinical benefits of ART outweigh the toxic effects of antiretroviral drugs, but in children who are asymptomatic and especially with good immunological stages, such as long-term non-progressor,[14,22] early exposure to ART may be harmful. • Antiretroviral drug resistance: triple class failure was observed in 10% of 1007 children in the COHERE cohort, with the risk being higher with time on ART and older age at ART initiation; notably only 24% of the children were triple class exposed.[19] Antiretroviral drug resistance could be exaggerated in situations of universal ART if, as a results of an increasing demand on the health system, stock-outs are more frequent and counselling is not adequately provided.[23] • Programmatic risks: Early treatment would mean more second- and third-line regimens being used, but options are still limited for children. Further, longer ART could result in treatment fatigue and lack of adherence, especially among adolescents with a low risk of disease progression. Finally, this could result in less emphasis on treating the infants who are clearly at risk and for whom there is a strong recommendation and rationale for immediate treatment.	

	Criteria	Judgements	Research evidence	Additional considerations
RESOURCE USE	**How large are the resource requirements (costs)?**	***More resource intensive***	**Zambia:** The total estimated cost of providing universal access to ART among children (age 0–14 years) between 2014 and 2018 (5 years) under the Zambia 2013 HIV consolidated guidelines is US$ 297 million, with an average cost per person per year of US$ 453. A projected 131 908 children would be receiving ART at the end of 2018 under the new guidelines and programmatic scale-up. The total estimated cost of providing universal access to ART among adolescents (age 15–19 years) between 2014 and 2018 under the Zambia 2013 HIV consolidated guidelines is US$ 40 million, with an average cost per person per year of US$ 249. A projected 37 754 adolescents would be receiving ART at the end of 2018 under this scenario. Antiretroviral medicines are the most significant cost driver in this analysis, making up 81% of total costs in the age group 0–14 years and 67% of total costs in the age group 15–19 years. Laboratory commodities were the second largest contributor to total cost, followed by human resources and then co-trimoxazole.	
	What is the certainty of the evidence of resource requirements?		Both evaluations presented above were conducted in one specific country, and it is unclear how generalizable these findings would be to other epidemic contexts and other paediatric programmes that may be in different implementation phases.	
	Does the cost–effectiveness of the option favour the option or the comparison?		Cost–effectiveness was not formally assessed.	

	Criteria	Judgements	Research evidence	Additional considerations
EQUITY	**What would be the impact on health equity?**	***More equitable***	None of note, but as is the case in all recommendations where different groups of people living with HIV have different recommendations for when to start, care must taken to ensure that those in greatest need – children who already have signs of disease progression – are fast-tracked to receive ART.	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	***Acceptable with no major variability***	A **community-led global consultation** of people living with HIV (206) and service providers (74) was undertaken to determine the acceptability, challenges and facilitators of **earlier initiation of ART** and viral load monitoring.[24] • **Twenty-four workshops** engaging groups in focus discussions were carried out in **eight countries**,[24] targeting different populations. Forty-three adolescent and young people and the parents and caregivers of adolescents on ART were involved. • **Eighty percent of the participants were on ART,** with 7% starting ART regardless of CD4 count or at CD4 <500 cells/mm^3. • For key overall findings for all participants, see A1.1. **Key findings specific to adolescents and parents and caregivers** • While motivating people living with HIV to **start treatment may be relatively "easy**" to do, **staying on and adhering to treatment over the long-term is challenging**, particularly for certain groups of **children and adolescents.** • Parents and caregivers felt that facilities had **insufficient numbers of trained staff** members to adequately provide care and support the treatment needs of their children. Services were not perceived as being "child-friendly"; service providers were sometimes unable to deal with side effects; and they did not understand issues of caregiver consent. • **Psychosocial support for parents and caregivers** is required, especially around disclosure to the child. **The emotional stress on parents and caregivers is immense.** Support from pastors, peers, child support groups, immediate family and other relatives were cited as critical enablers for seeking care and supporting treatment for the child or children in their care. • Adolescents and young people voiced **being left out of decisions about treatment altogether**, often without their knowledge of their own status or what the treatment is for. This was highlighted as **a major barrier to adherence**. • **Supportive and sensitive health providers, peer support** and sharing experiences especially during transition to adult services is critical for **adherence for adolescents.** • Service providers noted **particular challenges** when initiating and maintaining treatment among certain populations, including adolescents and children.	

	Criteria	Judgements	Research evidence	Additional considerations
			A review of published and grey qualitative literature was carried out to explore the acceptability of the timing of ART initiation. Twenty-two publications were identified: published studies, grey literature reports and conference abstracts. No publication reported specifically the views of those <19 years old; however, of the 11 publications on service providers, 2 (United States, 2013–2014) included views on starting treatment earlier among adolescents and young people. Key findings identified: • For adolescents, providers were concerned about **adolescents' poor adherence and resistance**. Barriers for ensuring adherence for adolescent included: **lifestyle not conducive to daily medication**, social and environmental factors and lack of adolescent-focused approaches.[25,26] • The acceptability for early initiation was dependent on certain conditions such as **readiness, engagement in care and stable life circumstance**. • However some felt that the **preventive benefits outweighed** the potential harm. **Additional unpublished studies exploring adolescent treatment and care** highlighted key themes for consideration. The studies include a global consultation of 470 young people living with HIV,[27] a situation analysis of more than 200 facilities in sub-Saharan Africa and two unpublished multicountry longitudinal qualitative studies with 147 adolescents living with HIV[28] The key themes identified: • **Adherence is an ongoing challenge for adolescents.** • Forgetting and being busy are key barriers, but many **complicated psychosocial issues** impact their adherence at different intensities at different times. • There are **limited opportunities for adolescents to discuss their concerns**, including those beyond ART. • Poor adherence increases stress: worry, guilt and fear about the impact on their health and also the **reaction of clinicians**. • **Ongoing effective support is critical for adherence** – support and environments that provide opportunities for open discussion – through peers and improved attitudes of service providers. Support that ensures understanding of their status and that is empowering and provides solutions.	
FEASIBILITY	**Is the option feasible to implement?**	***Yes, feasible***	This intervention is expected to be feasible since the number of children and adolescents younger than 15 years that are not already eligible based on existing guidance and current practice is expected to small. In many programme settings, late diagnosis of infection in children means that, in practice, many of those identified are already eligible based on current criteria. However, the increased patient numbers from universal access will likely put increased demands on supply chain systems and increased workload to the human resources. Already stock-outs have been observed in several priority countries, including Malawi, Uganda, United	

	Criteria	Judgements	Research evidence	Additional considerations
			Republic of Tanzania and Zimbabwe. There might be a need to strengthen laboratory monitoring, particularly virological monitoring, given that several children will have initiated ART without baseline CD4 testing and without clinical features of advanced disease. The increased demand for HIV commodities, human resources and infrastructure will require increased funding and identification of sustainable funding systems. The experience of the Ugandan National Programme has highlighted that, despite the efforts made in planning for scale-up, some key challenges were encountered. This included ensuring that commodities were available, conducting wide training and ensuring the sustainability of resources.	

Conclusions

Type of recommendation or decision	We recommend against the intervention or for the comparison ☐	Conditional recommendation not to use the intervention or to use the comparison ☐	We suggest using either the intervention or the comparison ☐	Conditional recommendation to use the intervention ☒	We recommend the intervention ☐
Recommendation or decision	**ART should be initiated among all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count. Children living with HIV one year old to less than 10 years old (conditional recommendation, low-quality evidence).**				

Author(s): Nandi Siegfried, Matthias Egger, Mary-Ann Davies, Martina Penazzato, Lulu Mussa Muhe
Date: 2012-11-07 (revised May 2015 , revision conducted by Martina Penazzato (WHO))
Question: Should immediate initiation of combined ART versus deferred initiation of combined ART be used in HIV-positive, treatment-naive children aged 5–15 years ?
Settings: Thailand and Cambodia
Bibliography: Siegfried N, Davies M, Penazzato M, Muhe LM, Egger M. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2–5 years old. Cochrane Database Syst Rev. 2013;10:CD010309.

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate initiation of combination ART	Deferred initiation of combination ART	Relative risk (95% CI)	Absolute		
Death												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/174 (0.57%)	0/169 (0%)	RR 3 (0.12 to 73.06)	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
CDC category C disease (number of children) (follow-up 144 weeks)												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	very serious[4]	none	3/174 (1.7%)	2/169 (1.2%)	RR 1.5 (0.25 to 8.85)	6 more per 1000 (from 9 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
								0.7%		3 more per 1000 (from 5 fewer to 55 more)		
CDC category B disease (numbers of children) (follow-up 144 weeks)												
2	randomized trials	no serious risk of bias[1]	serious[5]	serious[2]	serious[4]	none	24/174 (13.8%)	32/169 (18.9%)	RR 1.42 (0.14 to 14.28)	80 more per 1000 (from 163 fewer to 1000 more)	⊕OOO VERY LOW	
								10.7%		45 more per 1000 (from 92 fewer to 1000 more)		
CDC category B disease (numbers of children) Peto odds ratio												
2	randomized trials	no serious risk of bias[1]	serious[5]	serious[2]	serious[4]	none	24/174 (13.8%)	32/169 (18.9%)	OR 0.7 (0.39 to 1.24)	49 fewer per 1000 (from 106 fewer to 35 more)	⊕OOO VERY LOW	
								10.7%		30 fewer per 1000 (from 62 fewer to 22 more)		
Pulmonary TB (clinically diagnosed acid-fast bacilli smear-negative)												

2	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	very serious[4]	none	5/174 (2.9%)	1/169 (0.6%)	RR 2.59 (0.36 to 18.91)	9 more per 1000 (from 4 fewer to 106 more)	⊕OOO VERY LOW	CRITICAL
								0.3%		5 more per 1000 (from 2 fewer to 54 more)		
Proportion of children on ART with HIV-RNA <50 copies/ml (copy)												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	serious[4]	none	137/173 (79.2%)	53/65 (81.5%)	RR 0.96 (0.84 to 1.09)	33 fewer per 1000 (from 130 fewer to 73 more)	⊕⊕OO LOW	CRITICAL
								72.7%		29 fewer per 1000 (from 116 fewer to 65 more)		
Mean CD4% at week 144 (better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	serious[6]	none	150	150	-	MD 8.4 higher (6.83 to 9.97 higher)	⊕⊕OO LOW	CRITICAL
Proportion of children with CD4% <15% at study end												
1	randomized trials	no serious risk of bias	no serious inconsistency[7]	serious[2]	serious[3]	none	0/24 (0%)	3/19 (15.8%)	RR 0.11 (0.01 to 2.09)	141 fewer per 1000 (from 156 fewer to 172 more)	⊕⊕OO LOW	IMPORTANT
								15.8%		141 fewer per 1000 (from 156 fewer to 172 more)		
Mean weight gain per year in kg (better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency[7]	serious[2]	serious[6]	none	150	150	-	MD 0.1 higher (0.16 lower to 0.36 higher)	⊕⊕OO LOW	IMPORTANT
Mean height gain per year in cm (better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency[7]	serious[2]	serious[6]	none	150	150	-	MD 0.5 higher (0.2 to 0.8 higher)	⊕⊕OO LOW	IMPORTANT
Mean standardized score on Beery VMI at 144 weeks (better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency[7]	serious[2]	serious[6]	none	132	140	-	MD 1.4 lower (4.7 lower to 1.9 higher)	⊕⊕OO LOW	IMPORTANT
Proportion of children with adverse events												
1	randomized	no serious risk	no serious	serious[2]	serious[4]	none	22/24	19/19	RR 0.92 (0.8 to	80 fewer per 1000 (from 200	⊕⊕OO	IMPORTANT

	trials	of bias[1]	inconsistency[7]				(91.7%)	(100%)	1.07)	fewer to 70 more)	LOW	
								100%		80 fewer per 1000 (from 200 fewer to 70 more)		
Proportion of children with ART-related adverse events												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	serious[2]	serious[4]	none	14/174 (8%)	6/169 (3.6%)	RR 1.87 (0.77 to 4.51)	31 more per 1000 (from 8 fewer to 125 more)	⊕⊕OO LOW	IMPORTANT
								11.2%		97 more per 1000 (from 26 fewer to 393 more)		

[1] Since the trials were open-label, neither participants nor caregivers were blinded. However outcome assessors were blinded in the PREDICT trial. Attrition was low in both trials. Information on the randomization procedure was lacking in Ananworanich 2008. However, since this trial is relatively small, we judged the overall risk of bias to be low for the two trials together.
[2] The age group included in the trials ranged from one year to 12 years old and did not focus on the specific population focus of this review: ages 5 and above.
[3] The confidence interval is very large and the event rate very low. There was only one death.
[4] The event rate was very low and the overall sample size is also small.
[5] The trials reported conflicting results and there was substantial unexplained heterogeneity.
[6] The sample size is less than 400 and, according to the GRADE approach, imprecision is present when continuous outcomes are compared in samples less than 400.
[7] The results are from only one trial so consistency cannot be adequately gauged.

Author(s): Nandi Siegfried, Matthias Egger, Mary-Ann Davies, Martina Penazzato, Lulu Mussa Muhe
Date: 2012-11-19 (revised May 2015 , revision conducted by Martina Penazzato (WHO))
Question: Should combination ART initiated >15 days after the start of TB treatment versus ≤15 days be used for children aged 5 years and older with HIV and TB?
Settings: South Africa
Bibliography: Siegfried N, Davies M, Penazzato M, Muhe LM, Egger M. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2–5 years old. Cochrane Database Syst Rev. 2013;10:CD010309.

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination ART initiated > 15 days after start of TB treatment	≤15 days	Relative (95% CI)	Absolute		
Death												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	dose-response gradient[4]	13/275 (4.7%)	22/226 (9.7%)	HR 0.82 (0.48 to 1.41)	17 fewer per 1000 (from 49 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Viral suppression												
1	observational studies	serious[1]	no serious inconsistency[5]	serious[2]	serious[3]	dose-response gradient[4]	155/172 (90.1%)	136/152 (89.5%)	HR 0.98 (0.76 to 1.26)	5 fewer per 1000 (from 75 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Routine data was collected prospectively in an observational cohort study and the analysis was done retrospectively. There is a high risk of selection bias. The analysis employed weighting to adjust for time-dependent confounding.
[2] The study included children aged one to 15 years and did not provide analysis specifically for the age group five years and older.
[3] The total number of events was less than 300.
[4] The hazard ratio for the crude and adjusted analyses decreased over time periods: 15 days cut-off: HR = 0.98; 30 days cut-off: HR = 0.95; 60 days cut-off: HR = 0.84.
[5] The results are from only one study and as a result consistency cannot be gauged.

Author(s): Nandi Siegfried, Matthias Egger, Mary-Ann Davies, Martina Penazzato, Lulu Mussa Muhe
Date: 2012-11-19 (revised May 2015 , revision conducted by Martina Penazzato (WHO))
Question: Should combination ART initiation >1 month from TB treatment versus ≤1 month be used for children aged 24–59 months with HIV and TB?
Settings: South Africa
Bibliography: Siegfried N, Davies M, Penazzato M, Muhe LM, Egger M. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2–5 years old. Cochrane Database Syst Rev. 2013;10:CD010309.

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined ART initiation >1 month from TB treatment	≤1 month	Relative (95% CI)	Absolute		
Death												
1	observational studies	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	dose-response gradient[5]	9/206 (4.4%)	25/288 (8.7%)	HR 0.86 (0.46 to 1.6)	12 fewer per 1000 (from 46 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Viral suppression												
1	observational studies	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	dose-response gradient[5]	112/127 (88.2%)	179/197 (90.9%)	HR 0.95 (0.73 to 1.23)	12 fewer per 1000 (from 83 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Routine data were collected prospectively in an observational cohort study, and the analysis was done retrospectively. There is a high risk of selection bias. The analysis employed weighting to adjust for time-dependent confounding.
[2] The results are from only one study and consistency cannot therefore be gauged.
[3] The study included children aged one to 15 years and did not provide analysis specifically for the age group five years and older.
[4] The total number of events was less than 300.
[5] The hazard ratio for the crude and adjusted analyses decreased over time periods: 15 days cut-off: HR = 0.98; 30 days cut-off: HR = 0.95; 60 days cut-off: HR = 0.84.

Author(s): Nandi Siegfried, Matthias Egger, Mary-Ann Davies, Martina Penazzato, Lulu Mussa Muhe
Date: 2012-11-19 (revised May 2015 , revision conducted by Martina Penazzato (WHO))
Question: Should combination ART initiation >60 days from TB treatment versus combination ART initiation ≤60 days be used for children aged 24 –59 months with HIV and TB?
Settings: South Africa
Bibliography: Siegfried N, Davies M, Penazzato M, Muhe LM, Egger M. Optimal time for initiating antiretroviral therapy (ART) in HIV-infected, treatment-naive children aged 2–5 years old. Cochrane Database Syst Rev. 2013;10:CD010309.

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination ART initiation > 60 days from TB treatment	Combination ART initiation ≤60 days	Relative (95% CI)	Absolute		
Death												
1	observational studies	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	dose-response gradient[5]	8/111 (7.2%)	26/378 (6.9%)	HR 1.32 (0.55 to 3.16)	21 more per 1000 (from 30 fewer to 133 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Viral suppression												
1	observational studies	serious[1]	no serious inconsistency[2]	serious[3]	serious[4]	dose-response gradient[5]	53/59 (89.8%)	238/265 (89.8%)	HR 0.84 (0.61 to 1.15)	45 fewer per 1000 (from 146 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Routine data was collected prospectively in an observational cohort study and the analysis was done retrospectively. There is a high risk of selection bias. The analysis employed weighting to adjust for time-dependent confounding.
[2] The results are from one study, so inconsistency could not be gauged.
[3] The study included children aged one to 15 years and did not provide analysis specifically for the age group five years and older.
[4] The total event rate was less than 300.
[5] The hazard ratio for the crude and adjusted analyses decreased over time periods: 15 days cut-off: HR = 0.98; 30 days cut-off: HR = 0.95; 60 days cut-off: HR = 0.84.

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Annex 2.1.4 Evidence to decision making framework E1.1 Use of PrEP for preventing HIV infection among people at substantial risk

Should oral pre-exposure prophylaxis (PrEP) (containing tenofovir (TDF)) be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches?

Should oral pre-exposure prophylaxis (PrEP) (containing tenofovir (TDF)) be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches?	
Population	People at substantial risk of HIV infection
Intervention	Oral PrEP (containing tenofovir (TDF))
Comparator	(1) placebo and (2) non-use of PrEP (or no use)
Outcome(s)	(1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) drug resistance and 5) sexual and reproductive health outcomes, including hormonal contraception effectiveness, any adverse pregnancy event, condom use and number of sexual partners
Subgroup analyses	• Primary mode of sexual HIV acquisition (rectal versus vaginal/penile exposure) • Adherence to study drugs (based on overall drug detection levels in blood specimens) • PrEP dosing (daily versus intermittent PrEP) • PrEP regimen (TDF versus FTC + TDF) • Sex (males versus females) • Age (<25 versus ≥25)

Setting: *There continue to be more than 2 million new HIV infections every year despite widespread knowledge of HIV transmission and the protective benefits of HIV treatment, condoms and clean syringes.*
Perspective: *The safety and efficacy of oral pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate (TDF) with and without emtricitabine (FTC) has been evaluated in randomized, blinded and placebo-controlled trials among men and women, including men who have sex with men, transgender women and people who inject drugs.*
Subgroup considerations*: Oral TDF has limited bioavailability, leading to concentrations in the rectum that are 20- to 100-fold higher than in the blood and vaginal tissues. The level of adherence that is required for high-level protection may differ by mode of transmission (rectal versus other). Rectal exposure is the predominate mode of transmission to men who have sex with men and transgender women and contributes*

Background:

2012 guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at substantial risk of HIV: recommendations for use in the context of demonstration projects.

In countries where HIV transmission occurs among serodiscordant couples, where discordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner *(conditional recommendation, high-quality evidence).*

2014 consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations

Men who have sex with men
Among men who have sex with men, PrEP is recommended as an additional HIV prevention choice within a comprehensive HIV prevention package *(strong recommendation, high-quality evidence).*

People who inject drugs
The existing recommendation to offer daily oral PrEP as an additional HIV prevention choice for the negative partner in a serodiscordant relationship remains relevant for people who inject drugs and are in a serodiscordant relationship *(conditional recommendation, high-quality evidence).*

Sex workers

to other male-to-female transmission. Adherence to PrEP may vary by groups according to age, sex, education level and agency (capacity to act one one's own behalf). Stigma associated with HIV exposure, use of antiretroviral drugs for prevention or sexual and drug using practices could affect PrEP uptake and adherence or cause social harm. Women who are sexually exposed to HIV may become pregnant, so pregnancy outcomes and contraceptive efficacy among PrEP users should be considered. Transgender men and women frequently use sex-change hormone therapy, so drug–drug interactions between PrEP agents and sex hormones should be considered. People who inject drugs may have parenteral exposure to HIV, so prophylactic efficacy for parenteral exposure should be considered. Substance use among people who inject drugs and others could affect adherence to PrEP. Sex workers typically have sexual exposure from clients and primary partners, and condom use may differ by type of partnership.

The existing recommendation to offer daily oral PrEP as an additional HIV prevention choice for the HIV-negative partner in a serodiscordant couple remains relevant for sex workers who are in serodiscordant-couple relationships *(conditional recommendation, high-quality evidence)*.

Transgender people

Where HIV transmission occurs among transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (specifically the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention *(conditional recommendation, high-quality evidence)*.

	Criteria	Judgements	Research evidence	Additional considerations

PROBLEM	**Is the problem a priority?**	***Yes***	• An estimated 2.1 million [1.9 million–2.4 million] people were newly infected with HIV in 2013 (about 6000 people infected per day) *(1)*.
			• Of these, 1.9 million [1.7 million–2.1 million] are adults acquiring HIV infection *(1)*.
			• HIV infection requires lifelong combination antiretroviral therapy to prevent HIV-related disability, disease and death.
			• HIV-related disease is the sixth most common cause of death worldwide.
			• Among key populations:
			  ○ The burden of HIV infection is 19-fold higher among men who have sex with men and 49-fold higher among transgender women compared with the general population.
			  ○ Rates of infections among men who have sex with men are increasing.
			  ○ Although condoms used by sex workers will decrease their occupational HIV risk, condoms are less likely to be used in their primary partnerships.
			  ○ Use of clean syringes by people who inject drugs will decrease risk from injections but does not mitigate their sexual risk.
				• Continuing high incidence among key populations demonstrates the need for additional prevention options.
				• A substantial portion of new HIV infections derive from people during acute HIV infection before HIV diagnosis and antiretroviral therapy can occur.

Resource planning

	Criteria	Judgements	Research evidence	Additional considerations

HARMS OF THE	**How substantial are the desirable anticipated effects?**	*High quality evidence*	• Meta-analysis of 10 placebo-controlled PrEP studies estimate that people assigned oral PrEP containing tenofovir had a 51% reduction in the risk of HIV infection (RR = 0.49, 95% CI: 0.33–0.73, *P*=0.001). **When the results are restricted to studies of high adherence** (defined as tenofovir detection in more than 70% of participants randomized to PrEP), **there is a 70% reduction in the risk of HIV infection (RR = 0.30, 95% CI: 0.21–0.45, *P*<0.0001).**
			• Meta-analysis of two studies comparing immediate PrEP to delayed PrEP demonstrates significantly lower HIV infection rates among people during PrEP use (RR=0.15, 95% CI: 0.05–0.46, *P*=0.001).
			• Results from sensivity analysis show that **the effect of PrEP on HIV infection is robust** and is not overly influenced by the inclusion or exclusion of any trial.
			• Results across studies demonstrate that **the relationship between PrEP and HIV infection is moderated by the level of adherence**, with trials demonstrating high adherence showing high effectiveness and trials of low adherence demonstrating no protective benefits. In other words, **PrEP protects against HIV infection if taken as recommended.**
			• Results from meta-regression demonstrate that PrEP effectiveness is not significantly affected by:
			  ○ mode of acquisition (rectal versus penile/vaginal exposure)
			  ○ drug regimen (TDF versus FTC + TDF combination)
			  ○ drug dosing (daily versus intermittent)
			  ○ biological sex (male versus female)
			  ○ age (<25 years to ≥25 years), although younger participants tended to be less adherent in some populations (such as people who inject drugs and men who have sex with men).
			• Results from meta-analysis show **no sigificant effect of PrEP on any adverse event** (RR=1.01, 95% CI: 0.99–1.03, *P*=0.27) **or any grade 3 or 4 adverse event** (RR=1.02, 95% CI: 0.92–1.13, *P*=0.76). Clinical trials evaluated multiple parameters of safety, including haematological blood counts, renal function, liver health, pancreas health, weight, bone mineral density, total fat distribution and clinical symptoms. PrEP was	

	How substantial are the undesirable anticipated effects?			
	What is the overall certainty of the evidence of effects?			

	Criteria	Judgements	Research evidence	Additional considerations
			associated with small subclinical decreases in estimated creatinine clearance and bone mineral density *(2)*. There were no cases of renal failure and no excess in bone fractures. • **The risk of resistance to FTC or TDF occurred primarily among people who were already infected with HIV when they began PrEP**. The proportion of HIV infections that had markers of drug resistance were higher among those who had received FTC + TDF, although the risk of drug-resistant HIV infection was not different because of lower overall infection rates. • **Results from meta-analysis show no sigificant effect of PrEP on behavioural outcomes**, including condom use and number of sexual partners **or reproductive health outcomes**, including adverse pregnancy events and contraception effectiveness.	

	Criteria	Judgements	Research evidence	Additional considerations
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	***No major variability***	• Results from a review of values and preferences show high acceptability for PrEP, although results were unbalanced across populations, geographical regions, and research contexts *(3)*. • For serodiscordant couples, PrEP has the added benefit of **enabling safer conception**. • Among sex workers, there is enthusiasm for offering PrEP but also concerns regarding stigma and discrimination surrounding PrEP use *(4)*. There is also concern that **PrEP could undermine the highly successful and acceptable condom programming that has already helped reduce incidence among sex workers,** especially where PrEP use may be encouraged by clients to lessen the need for condom use, although evidence for such condom migration is lacking. Therefore the judicious consideration of PrEP for sex workers is needed (geographical considerations and groups of sex workers – young, etc.) – a priority where incidence remains high and there are significant barriers to condom use. Many sex workers are primarily exposed to HIV through their primarily sexual partnerships; PrEP should be available to them according to their sexual exposure rather than their occupational status. • Among people who inject drugs, there is wide support for offering PrEP as an additional choice for preventing sexual transmission of HIV. There are concerns about PrEP undermining community-based harm-reduction activities, including provision of clean syringes *(5)*. **HIV prevention among people who inject drugs should occur within a harm-reduction context, which has wider health benefits, including parenteral prevention of HIV and other infections**. • Among transgender people, there is also enthusiasm for **offering PrEP within a culturally competent framework in which current gender is acknowledged.** There	.

	Criteria	Judgements	Research evidence	Additional considerations
			were concerns about rejection and discrimination from health-care providers *(6)*, although these were not specific to PrEP. There were also concerns about drug interactions with sex hormones, although no such interactions are expected based on the different metabolic pathways for sex hormones and PrEP medications. • Adherence and uptake of PrEP were low in two trials that targeted only women, while adherence was substantial among women enrolled in trials that included both men and women. Factors associated with low uptake and adherence among women in women-only trials included lack of support from sexual partners, stigma related to PrEP use and participation in blinded clinical trials, mixed community support for trial participation and uncertainty around product effectiveness *(7)*. PrEP adherence was substantial among women in an open-label trial of PrEP conducted after safety and efficacy was proven *(8)*. **This suggests that PrEP adherence may be higher in real-life implementation in which PrEP is a choice and people are aware they are taking active and effective medication.**	
BENEFITS & HARMS OF THE OPTIONS	**Does the balance between desirable effects and undesirable effects favour the option or the comparison?**	***Benefits > harm***	• The results from the systematic review and meta-analysis show that **PrEP has substantial benefits regarding HIV prevention and few undesirable clinical effects.** Combining randomized and open-label phases of study, PrEP safety has been evaluated over periods as long as 4.2 years. The safety of FTC and TDF for treatment has been evaluated over periods longer than 10 years. • Demonstration projects, including iPrEx OLE, Partners PrEP demonstration project, and PROUD indicate that **HIV infection rates are substantially reduced, or extremely lower than expected, when PrEP is offered within a comprehensive package of prevention services** that includes periodic HIV testing, testing and treatment of sexually transmitted infections, antiretroviral therapy for HIV-positive people, access to condoms and access to clean syringes.	

	Criteria	Judgements	Research evidence	Additional considerations
RCE	**How large are the resource requirements (costs)?**	***Higher costs***	• Drug costs: ○ Generic manufacturers in India market a dual fixed-dose combination of FTC + TDF for **US$ 71 per person per *year*** *(9)*. Truvada®, manufactured by Gilead	Drug costs are an important consideration – if generics are used versus the market costs.

	Criteria	Judgements	Research evidence	Additional considerations

			Pharmaceuticals, costs **US$ 319–548 per person per year** *(9)*.
			• Service delivery costs:
			  ○ In generalized epidemic settings in low- and middle-income settings, service delivery costs estimates range from **US$ 16 to US$ 200** per person-year *(10)*.
			  ○ In high-income settings among concentrated epidemics, service delivery cost estimates range from **US$ 1020 to US$ 10 083** per person-year *(10)*.
			  ○ In concentrated epidemics in low- and middle-income settings, service delivery costs range from **US$ 310 to US$ *830*** *(10)*.
			• The cost–effectiveness of PrEP varies widely depending on epidemic type, location and model parameter estimates, including efficacy, cost of PrEP, HIV incidence and target population. A systematic review of PrEP cost–effectiveness studies found the following *(10)*:
			  ○ **PrEP in generalized epidemics**: Across 4 modelling studies, impact was estimated to be greater if PrEP use had priority for people at substantial risk of HIV infection (groups with higher sexual activity and the HIV-negative members of serodiscordant couples). The results were mixed among studies examining interactions between oral PrEP and expanding ART programmes. Some studies found PrEP to be cost-effective within the context of ART expansion; others found no benefit.
			  ○ **PrEP in concentrated epidemics among men who have sex with men:** The results from modelling studies suggest that PrEP use among men who have sex with men in the United States could significantly affect the domestic HIV epidemic. Some found PrEP to be cost-effective under certain assumptions (priority for high-risk men who have sex with men, high product effectiveness or low drug cost). Drug costs were identified as a barrier to cost–effectiveness. Drug resistance was not found to strongly influence cost–effectiveness estimates. In Peru, PrEP could be a cost-effective addition to current prevention interventions among men who have sex with men (up to US$ 1702 per DALY).
			  ○ **Drug users in mixed epidemic *settings*** *(11)*: At a PrEP cost of US$ 950, methadone maintenance therapy was the most cost-effective strategy, followed by methadone maintenance therapy and ART, and further adding PrEP (25% access) was cost-effective by WHO standards at US$ 1700 per QALY gained. PrEP alone became as cost-effective as methadone maintenance therapy at a cost of US$ 650.
			• PrEP effectiveness is greater than 90% among active PrEP users (as indicated by having any detectable drug in the blood); **people who stop using PrEP will not generate costs to PrEP services unless their retention is incentivized.** Incentives for visits are routinely used in clinical trials but are not used in clinical practice; indeed most clinical practice involves co-payments that would further avoid dispensing PrEP to people who are not using it.	

	Criteria	Judgements	Research evidence	Additional considerations
	What is the certainty of the evidence of resource requirements?		The cost of the resources required would vary by setting. **Generic drug pricing is available in the 105 poorest countries, and tiered pricing is available in middle-income countries**. The price is negotiated by private and public payers with drug manufacturers and varies from US$ 72 per year to US$ 18 000 a year for co-formulated FTC + TDF. Laboratory monitoring includes testing for HIV and creatinine. These costs can be minimized by using point-of-care testing. Effort is required for drug procurement and distribution, laboratory testing, sexual health counselling and clinical monitoring (for users having renal adverse events or significant side effects).	

	Does the cost–effectiveness of the option favour the option or the comparison?		• The cost–effectiveness of PrEP varies according to the HIV incidence that would otherwise occur among PrEP users, the costs of the medications and the costs of laboratory testing. In general, **medication costs and laboratory costs scale with thresholds for cost-effective and cost-saving implementation, such that the underlying HIV incidence becomes the critical factor.** In general, cost-effective implementation is expected if PrEP is used in groups that would otherwise have HIV incidence greater than 3 per 100 person-years, and cost-saving implementation is expected if the HIV incidence would be greater than 6 per 100 person-years. People having such high incidence can be readily identified depending on the epidemiological context.
			• **Critical threshold of HIV incidence above which PrEP is cost-saving**:
			  ○ One modelling study suggests that PrEP would be cost-saving with **an incidence of 5 per 100 person-years and efficacy of 50%**, assuming laboratory tests were required every 3 months *(12)*.
			  ○ Using estimates that providing PrEP costs about 44% of the annual cost of providing treatment *(13)*, the critical HIV incidence threshold for cost-savings would be **5.8 per 100 person-years** if PrEP efficacy is 54% (from intention-to-treat analysis in iPrEx). If PrEP efficacy is 80% among PrEP users incurring PrEP costs, the critical HIV incidence threshold for cost-savings in clinical practice would be **3.6 per 100 person-years**.	

	Criteria	Judgements	Research evidence	Additional considerations

	Criteria	Judgements	Research evidence	Additional considerations
EQUITY	**What would be the impact on health equity?**	***More equitable***	• **Preventing HIV infection among PrEP users would sustain their health and the health of their sexual partners.** • PrEP access provides **opportunities for sexual health services**, including family planning services; evaluation and treatment for sexually transmitted infections such as syphilis, gonorrhoea and chlamydia; vaccination for hepatitis B and human papillomavirus and testing and curative treatment for hepatitis C. • Offering PrEP services in trials and demonstration projects **identified substantial numbers of undiagnosed people with HIV who were then offered treatment services**. • The **capacity to manufacture generic and branded medications is high** and could be expanded further. Increasing the volume of drug manufacturing to supply PrEP is expected to decrease unit costs. • The cost of PrEP and clinic visits associated with PrEP use could prevent some people from gaining access. However, people who are at substantial HIV risk are also medically underserved and often marginalized and have few other effective HIV prevention options. • **Preventing HIV in populations with a high HIV incidence will reduce future treatment cost**. • **Extending PrEP recommendations** from narrowly defined groups (men who have sex with men and serodiscordant couples) **allows for more equitable access** by including individuals who do not have an identified primary partner and people whose sexual orientation is not known or not disclosed. • **A broader recommendation will also decrease PrEP-related stigma**, which may increase engagement in health-care services and self-care behaviour.	• Offering PrEP services is not expected to decrease the utilization of treatment services. • Treatment is underutilized in many settings due to ineffective drug procurement processes, social stigma related to HIV, fear of medication toxicity, lack of HIV testing and lack of skill in using antiretroviral mediations among non-specialty providers. Offering PrEP is expected to be neutral or beneficial with respect to these barriers to HIV treatment. • Use of antiretroviral medications by HIV-uninfected people may decrease the stigma associated with antiretroviral drugs and may decrease fear of people living with HIV.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	***Variable***	• A study conducted among members of the HIV advocacy and research field found that offering PrEP within a package of prevention services is acceptable to key stakeholders. Concerns were raised about the following issues that may arise as PrEP is offered *(14)*: ○ **Community participation in PrEP implementation** and identifying community needs related to all aspects of HIV prevention and care is critical. ○ Concerns about **drug toxicity and drug resistance** exist and should continue to be addressed. ○ **PrEP should be presented as an available choice among all HIV prevention options** and not in place of them. Many men who have sex with men and sex workers rely on condoms as their primary method of HIV risk reduction, and successful reduction in HIV incidence among sex workers empowered to insist on condom use has occurred in some settings. People who inject drugs prefer to use clean syringes, and this practice is successful when available. Nevertheless, stakeholders supported offering PrEP in addition to these preferred protective strategies.	
B	**Is the option**		• **Oral PrEP for men who have sex with men, transgender people, serodiscordant**	

	Criteria	Judgements	Research evidence	Additional considerations
	feasible to implement?	***Variable***	**couples, people who inject drugs and heterosexual men and women has proven feasible in various trial settings and demonstration projects**. Two blinded and placebo-controlled trials found that targeted women alone, significant barriers to uptake and adherence. Real-world programme settings and incentives will differ from those of blinded and placebo-controlled trials, and PrEP adherence among women has been high when open-label PrEP is provided. Targeting PrEP to only one group (such as women or men who have sex with men) may increase stigma and undermine PrEP uptake and use, which contributed to low PrEP use and null effectiveness results in some clinical trials. • The iPrEx OLE project and the Partner's PrEP Demonstration project reflect more real-world implementation of PrEP and show that **PrEP implementation is feasible for men and women.**	

Conclusions

	We recommend against the intervention or for the comparison	Conditional recommendation not to use the intervention or to use the comparison	We suggest using either the intervention or the comparison	Conditional recommendation to use the intervention	We recommend the intervention
Type of recommendation or decision	☐	☐	☐	☐	☒

Recommendation or decision	**Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches** ***(strong recommendation, high-quality evidence)***

Evidence profile for systematic review on pre-exposure prophylaxis effectiveness, safety and sexual and reproductive health outcomes
Author(s): Virginia Fonner and Sarah Dalglish
Date: 2015-05-25
Question: Should oral PrEP (containing tenofovir) be used for preventing HIV infection among people at substantial risk of HIV infection?
Setting: Global
Bibliography: 15 randomized controlled trials and 3 observational studies (full bibliography listed after GRADE tables)

Quality assessment							No of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral PrEP (containing tenofovir)	Control	Relative (95% CI)	Absolute		
HIV infection – PrEP versus placebo – adherence >70%												
3[1]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	39/3866 (1%)	79/2284 (3.5%)	RR 0.30 (0.21 to 0.45)	24 fewer per 1000 (from 19 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus placebo – adherence 40–70%												
2[3]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/2455 (2.2%)	97/2457 (3.9%)	RR 0.55 (0.39 to 0.76)	18 fewer per 1000 (from 9 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus placebo – adherence <40%												
2[4]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/3002 (4.9%)	95/2031 (4.7%)	RR 0.95 (0.74 to 1.23)	2 fewer per 1000 (from 12 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
HIV infection – PrEP versus no PrEP												
2[5]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/367 (0.82%)	22/353 (6.2%)	RR 0.15 (0.05 to 0.46)	53 fewer per 1000 (from 34 fewer to 59 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse event												
10[6]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7670/9922 (77.3%)	5718/7308 (78.2%)	RR 1.01 (0.99 to 1.03)	8 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Any grade 3 or 4 adverse event												

11[7]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1289/9680 (13.3%)	839/7058 (11.9%)	RR 1.02 (0.92 to 1.13)	2 more per 1000 (from 10 fewer to 15 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug resistance (drug-resistant HIV infection among participants with acute infection at enrolment)												
4[8]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	7/25 (28%)	1/17 (5.9%)	RR 3.34 (1.11 to 10.06)	138 more per 1000 (from 6 more to 533 more) Per seroconversion	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance (drug-resistant HIV infection among participants who became infected post-randomization (incident infections))												
3[10]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	5/155 (3.2%)	2/119 (1.7%)	RR 2.27 (0.48 to 10.6)	21 more per 1000 (from 9 fewer to 161 more) Per seroconversion	⊕⊕⊕O MODERATE	CRITICAL
Drug resistance – overall risk (relative risk of acquiring or developing drug-resistant HIV infection among everyone at risk)												
3[10]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	5/3612 (0.14%)	2/2637 (0.08%)	RR 1.74 (0.36 to 8.38)	1 more per 1000 (from 0 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – FEM-PrEP (assessed with: women using contraceptives comparing PrEP to placebo arms)												
1[11]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	69/602 (11.5%)	48/614 (7.8%)	aHR 1.20 (0.9 to 1.8)	15 more per 1000 (from 8 fewer to 58 more)	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – Partners PrEP COCs (assessed with: comparing pregnancy rates among women using oral contraception to women not using contraception in the PrEP arm[13])												
1[14]	randomized trials	no serious risk of bias	no serious inconsistency[15]	no serious indirectness	serious[12]	none	37/209 (17.7%)	11/108 (10.2%)	aHR 0.96 (0.58-1.58)	-- [13]	⊕⊕⊕O MODERATE	CRITICAL
Contraception effectiveness – Partners PrEP Injectables (assessed with: comparing pregnancy rates among women using injectable contraception to women not using contraception in the PrEP arm[13])												
1[14]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	29/564 (5.1%)	17/319 (5.3%)	aHR 0.26 (0.16-0.41)	--[13]	⊕⊕⊕O MODERATE	CRITICAL
Adverse pregnancy event												

2[16]	randomized trials	no serious risk of bias	no serious inconsistency[17]	no serious indirectness	serious[12]	none	99/266 (37.2%)	48/147 (32.7%)	RR 1.25 (0.64 to 2.45)	82 more per 1000 (from 118 fewer to 473 more)	⊕⊕⊕O MODERATE	CRITICAL
Condom use[18]												
9[19]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
Number of sexual partners[18]												
11[20]	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012) and CDC Safety Study (Groshkopf et al., 2013).
[2] Data are only for participants aged 18 years and older. This footnote applies to all outcomes, since trials only included participants aged 18 years and older.
[3] iPrEx (Grant et al., 2010) and Bangkok Tenofovir Study (Choopanya et al., 2013).
[4] FEM-PrEP (Van Damme et al., 2012) and VOICE (Marrazzo et al., 2015).
[5] PROUD (Molina et al., 2015) and CDC Safety Study (Groshkopf et al., 2013).
[6] Bangkok TDF Study (Choopanya et al., 2013), FEM-PrEP (Van Damme et al., 2012), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Ipergay (Molina et al., 2015), iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007) and VOICE (Marrazzo et al., 2015).
[7] Bangkok Tenofovir Study (Choopanya et al., 2013), CDC Safety Study (Groshkopf et al., 2013), FEM-PrEP (Van Damme et al., 2012), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Ipergay (Molina et al., 2015), iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007) and VOICE (Marrazzo et al., 2015),
[8] iPrEx (Grant et al., 2010), Partners PrEP (Baeten et al., 2012), TDF2 (Thigpen et al., 2012) and VOICE (Marrazzo et al., 2015).
[9] The total number of events was less than 50; therefore, evidence was downgraded for serious imprecision. Evidence was not further downgraded for imprecision because the outcome (drug-resistant HIV infection) was an extremely rare event among a relatively large sample size (*n*=6249) involving four methodologically sound randomized controlled trials.
[10] FEM-PrEP (Van Damme et al., 2012), TDF2 (Thigpen et al., 2012) and VOICE (Marrazzo et al., 2015).
[11] FEM-PrEP (Callahan et al., 2015).
[12] Total number of events was less than 300; therefore, evidence was downgraded for imprecision.
[13] Adjusted hazard ratios compare pregnancy events among women using contraception to women not using contraception in the PrEP arm. The results comparing PrEP and placebo arms show no statistical difference for COCs (P=0.26) and Injectables (P=0.19). Adjusted hazard ratios for women in the placebo arm are not shown.
[14] Partners PrEP (Murnane et al., 2014).
[15] Raw data show trends toward higher rates of pregnancy among women using hormonal contraception receiving PrEP. Rates become nonsignificant once controlled for confounders.
[16] FEM-PrEP (Van Damme et al., 2012) and Partners PrEP (Baeten et al., 2012).
[17] For the FEM-PrEP study, authors note the higher pregnancy-related adverse event rate in the FTC + TDF group (P = 0.04) but also note that there were more pregnancies in this group than in the placebo group (IR=11.2 per 100 person-years versus 7.5 per 100 person-years, respectively).
[18] Data could not be pooled due to differences in outcome measurements. The results are presented narratively in report and presentation.
[19] 9 randomized controlled trials: FEM-PrEP (Van Damme et al., 2012), iPrEx (Grant et al., 2010), Partners PrEP randomized controlled trial (Baeten et al., 2012), Partners PrEP OLE (Baeten et al., 2014), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007), CDC Safety Study (Liu et al, 2013), Project PrEPare (Hosek et al., 2013), and PROUD (McCormick et al., 2015). 1 Observational study: iPrEx OLE (Grant et al., 2014)
[20] 11 randomized controlled trials: Bangkok Tenofovir Study (Martin et al., 2014), FEM-PrEP (Van Damme et al., 2012), iPrEx (Grant et al., 2010), IAVI Kenya Study (Mutua et al., 2012), IAVI Uganda Study (Kibengo et al., 2013), Partners PrEP

randomized controlled trial (Baeten et al., 2012), Partners PrEP OLE (Baeten et al., 2014), TDF2 (Thigpen et al., 2012), West Africa Study (Peterson et al., 2007), CDC Safety Study (Liu et al., 2013), and PROUD (McCormick et al., 2015). 2 Observational Study: Bangkok Tenofovir Study OLE (Martin et al., 2015) and iPrEx OLE (Grant et al., 2014).

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WHO/HIV/2015.36

Universal Antiretroviral Therapy for Asymptomatic Adults and Adolescents with HIV-1 Infection and CD4$^+$ T-cell Counts ≥500 cells/µL: a Systematic Review and Meta-Analysis

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Abstract

Objectives: The objective of this review was to inform revision of the 2015 WHO guidelines for antiretroviral therapy (ART) with updated evidence on when to initiate ART.

Design: A systematic review and meta-analysis.

Methods: We searched the published literature and conferences abstracts for randomised controlled trials (RCT) and cohorts. Outcomes were mortality, severe HIV disease or malignancy, clinical progression, AIDS events, non-AIDS events, tuberculosis, severe treatment-related adverse events, and HIV transmission. We also examined combined outcomes, such as mortality and severe HIV disease or malignancy. We pooled data across studies separately for RCTs and cohorts and estimated summary effect sizes. We graded the quality of evidence from the literature for each outcome.

Results: We identified 20 studies; 3 were reports from a single RCT. Studies found statistically significant decreased hazard of HIV disease progression (1 cohort: hazard ratio [HR]=0.20, 95% 0.10-0.42), and the combined outcome of death, severe HIV disease, or malignancy (1 RCT: HR=0.56, 95% CI 0.33-0.94). One RCT found a reduced risk of HIV transmission (relative risk [RR]=0.11, 95% CI 0.06-0.19), although this was not supported in two cohorts (RR=1.17, 95% CI 0.46-2.98). Studies found no significantly reduced risk of mortality [1 RCT: RR=0.91, 95% CI 0.27–3.08; 3 cohorts: RR=0.68, 95% CI 0.39–1.21], severe HIV disease or incident malignancies (1 RCT: RR=0.60, 95% CI 0.30-1.22), non-AIDS events (1 RCT: RR=0.99, 95% CI 0.20-4.89), AIDS events or death (2 cohorts: RR=0.63, 95% CI 0.16-2.49), malignancies (1 RCT: RR=0.91, 95% CI 0.06-14.38) or tuberculosis (1 RCT: RR=0.52, 95% CI 0.22-1.21). There was no increased risk of any Grade 3/4 adverse event from RCT data, but there was evidence of increased risk of any severe laboratory adverse event (RR=1.43; 95% CI 1.13-1.81) and hepatic adverse events (RR=1.45, 95% CI 1.03-2.04) from one cohort study. The quality of evidence was moderate for the combined outcome of death, severe HIV disease or malignancy and for the Grade 3 or 4 laboratory abnormalities, and the quality of evidence was low or very low for clinical and other adverse events outcomes due to indirectness and imprecision.

Conclusions: Our findings suggest that there is moderate quality evidence that the initiation of ART at CD4 cell counts ≥500 cells/μL in the absence of other treatment indications leads to less severe HIV morbidity (i.e. death, severe HIV disease, or malignancy). There is also low or very low quality evidence that earlier ART is associated with lower risk of HIV disease progression and transmitting HIV to uninfected partners. There is moderate quality evidence that earlier therapy is not associated with increased risk of Grade III/IV severe adverse events but very low quality evidence that it may be associated with risk of any severe adverse event or hepatic adverse events.

Introduction

As a result of antiretroviral therapy's (ART) clinical benefit in individuals infected with HIV-1 and its impact on the risk of viral transmission of HIV, several HIV treatment guidelines committees have recommended initiating ART at earlier stages of HIV infection and at higher CD4 cell counts.[1,2] The International Antiviral Society – USA[1] and the United States Department of Health and Human Services[3] recommend starting ART as close to diagnosis as possible without regard to clinical symptoms or degree of immune dysfunction, while the World Health Organization's (WHO) current guidelines recommend starting ART in all patients with fewer than 500 CD4 cells/µL or in all patients, regardless of CD4 count, for those who meet some clinical or programmatic indications (e.g., concurrent tuberculosis).[2] European guidelines are slightly less broad; the 2013 European AIDS Clinical Society guidelines *recommend* starting ART in all patients with fewer than 350 CD4 cells/µL, and *suggest* considering initiation for those with between 350 and 500 CD4 cells/µL unless one of several clinical conditions is present.[4]

A previous systematic review evaluated all available literature evaluating the impact of early versus delayed treatment and found evidence suggesting that early ART initiation (with baseline CD4 count between 350 and 500 cells/µl) may reduce the risk of HIV disease progression or death, reduce the risk of being diagnosed with a non-AIDS defining illness and may increase the likelihood of immunologic recovery.[5] Further, this previous review found grade 3 or 4 laboratory abnormalities are more often found in patients who initiate ART early rather than defer their treatment to CD4 counts below 350 cells/ µl).[5]

As the availability of antiretroviral drugs in many countries is limited, since 2002 WHO has carefully considered the body of evidence in developing ART guidelines. As such, the current threshold for initiating treatment was raised in the 2013 guidelines to 500 cells/µL,[2] while the guidelines, after consideration of available evidence, also recommended starting therapy irrespective of CD4 cell count among pregnant women, children <5 years old, patients with WHO clinical stage 3 or 4 disease and

patients with concurrent hepatitis B virus infection with severe liver disease and for HIV infected persons in a serodiscordant partnership.[6,7]

The current systematic review is an update of a previously published review,[5] though herein we re-evaluate the evidence of the clinical impact of earlier ART in HIV-1 infected patients using a higher threshold for treatment initiation (CD4 ≥ 500 cells/μl). We systematically reviewed the literature to estimate differences in risk of mortality, disease progression, and treatment adverse events between subjects whose baseline CD4 count at ART initiation was ≥500 cells/μL and subjects whose baseline CD4 count was between 200-499 cells/μL. Additionally, we estimated the risk of transmission to an uninfected sexual partner among subjects whose baseline CD4 count at ART initiation was ≥500 cells/μL compared with subjects whose baseline CD4 count was between 200-499 cells/μL. These results will help inform the 2015 WHO guidelines for use of antiretroviral drugs for the treatment and prevention of HIV infection.

Methods

We included both trials and observational studies that compared clinical and laboratory outcomes in HIV-1-infected patients who began antiretroviral therapy at <500 CD4 cells/μL with those who began therapy at ≥500 CD4 cells/μL.

Search methods for identification of studies

Using Cochrane Collaboration methods, we formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies.[8] We searched PubMed, CENTRAL, SCOPUS (including EMBASE 1996-present), Web of Science, and WHO's Global Index Medicus. The search strategy included Medical Subject Heading (MeSH) terms and a range of relevant keywords. The search period ranged from 1 January 1996 to 27 February 2015. The search strategy was iterative, in that references of included studies were searched for additional references. All languages were included. Additionally, we

searched for potentially relevant abstracts presented at key scientific conferences (the Conference on Retroviruses and Opportunistic Infections, the International AIDS Conference, and International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention) held within the search period.

Selection of studies

Inclusion criteria

We included randomised controlled trials (RCT) with randomisation at either the individual or cluster level, non-randomised controlled trials (non-RCT) with allocation at either the individual or cluster level and prospective observational cohort studies with comparators.

Furthermore, studies estimating the impact of timing of ART initiation on clinical outcomes needed to compare patients with HIV-infection and no other clinical indications for early ART plus CD4 counts ≥500 cells/μL at the time of initiation with patients whose CD4 cell counts were <500 cells/μL at the time of initiation. For HIV transmission outcomes, studies needed to compare patients with HIV-infection or serodiscordant couples and CD4 counts ≥500 cells/μL at the time of initiation with patients with HIV-infection or serodiscordant couples whose CD4 counts were <500 cells/μL at the time of initiation.

Exclusion criteria

We excluded single arm pre-post studies without distinct controls, case-control studies and cross-sectional studies.

Data extraction and management

We imported search results into bibliographic citation management software (EndNote X4, Thomson Reuters, New York, New York USA) and excluded duplicate references. Reviewing only article titles, one author (HH) excluded all references that were clearly irrelevant. Two authors (GWR and AA), working independently, then reviewed the titles, abstracts and descriptor terms of the remaining citations to identify potentially eligible reports. We obtained full text articles for all references identified as

potentially meeting inclusion criteria. GWR and AA reviewed these full text articles and applied inclusion criteria to establish each study's eligibility or ineligibility. Our plan was to resolve any differences of opinion through discussion and, if necessary, a neutral third party arbiter.

After identifying trials for inclusion, two authors (GWR and AA) working independently examined and extracted data from each study. GWR and AA separately entered these data into standardized data extraction forms and then compared extracted data. There were no disagreements.

Assessment of methodological quality

We used the Cochrane Collaboration tool for assessing risk of bias in the included RCTs.[8] The Cochrane tool assesses risk of bias in individual studies in six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential biases. We used the Newcastle-Ottawa Scale to assess quality and risk of bias in the non-RCTs and observational studies.[9] This scale judges three general areas: selection of study groups, comparability of groups, and ascertainment of outcomes (in the case of cohort studies).

Statistical analysis and data synthesis

We used published estimated relative risks (RR) if provided in study reports, but, when necessary, we calculated the RR for dichotomous outcomes and the 95% confidence interval (CI). We pooled data across studies and estimated summary effect sizes. We performed all meta-analyses in Review Manager 5.2 (Cochrane Collaboration, London, UK). Due to anticipated heterogeneity between study designs and populations, we modeled meta-analyses using a DerSimonian-Laird random-effects model. We present estimates of heterogeneity, determined by I^2; estimates of I^2 are interpreted as the percentage of variability in effect estimates due to heterogeneity rather than chance.

Sensitivity analysis

The observational literature for two major outcomes, mortality and clinical progression or mortality, included a number of studies that reported data from the same patient cohorts. To minimise the problem of duplication of patients, we conducted a sensitivity analysis of studies with no or minimal overlap.

Assessment of evidence quality (GRADE)

We assessed the quality of evidence from the literature, as opposed to individual studies, for each outcome using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach.[10] GRADE ranks the quality of evidence on four levels: high, moderate, low and very low. Evidence from RCTs starts at high but can be downgraded based on study limitations, inconsistency of results, indirectness of evidence, imprecision (small numbers of events in the intervention and control groups) or reporting bias. For purposes of this review, we consider imprecision to be a serious problem if there were fewer than 200 events in the intervention and control arms combined and very serious if there were fewer than 50 events in the two arms combined. Evidence from observational studies starts at low but can be upgraded to moderate if the magnitude of treatment effect is very large, if there is a significant dose-response relation or if all possible confounders would decrease the magnitude of an apparent treatment effect.[10] Evidence from observational studies can also be downgraded to very low.

Results

The search yielded 5,404 articles and meeting abstracts, of which 2,040 were duplicates; of the remaining 3,364, 3,087 were clearly not relevant. Of the remaining 277 articles and abstracts, we identified 10 new studies that met our inclusion criteria and another 10 studies that we had identified in our previous review (Figure 1). Of these, three were RCTs,[11–13] and 17 were observational studies.[14-30] Studies were conducted in Africa, Asia, Australia, Europe and North America and reported a variety of outcomes including mortality, progression to AIDS, progression to AIDS or death, cancer (AIDS and non-AIDS), tuberculosis

(disseminated and pulmonary), serious non-AIDS events and non-opportunistic diagnoses, severe adverse events, and Grade 3 or 4 laboratory abnormalities (Table 1). All RCT reports were from a single RCT (Bénéfices et risques du traitement ARV précoce et prévention par INH chez des adultes infectés par le HIV ayant entre 250 et 500 CD4/mm^3: à Abidjan, Côte d'Ivoire (TEMPRANO, ANRS 12136)).

Six observational studies reported the results from single cohorts that did not appear in other studies,[14–19] while the remaining 11 observational studies had overlapping study populations. When possible, we synthesized data from the single cohorts and the two large pooled cohorts predominantly from North America (N=22 cohorts)[20] and Europe (N=23 cohorts)[21]; these two large studies had 17,517 and 9,455 participants, respectively. Only 154 (0.6%) patients, all from the Southern Alberta Cohort, appeared in both analyses.

Mortality

One RCT[11] and 6 observational studies[19–24] reported a mortality outcome. Four of the six observational studies found a decreased risk of death in persons who initiated ART at CD4 cell counts ≥500 cells/μL,[20,22–24] although only one found a statistically significant decrease (RR=0.52, 95% CI 0.36-0.74).[20] In the one RCT, Danel and colleagues reported no difference in the hazard of mortality (hazard ratio [HR]=0.91; 95% CI 0.27-3.08) (Figure 2).[11] The six observational studies reported data from 55 cohorts. Of these 55 cohorts, data from 34 were reported in more than one study (Table 3). One observational study reported mortality results from a single cohort not appearing in other studies.[19] We analyzed data from this one cohort that was reported only once plus data from two other large studies that reported large numbers of cohorts predominantly from North America (N=22 cohorts)[20] and Europe (N=23 cohorts)[21] with minimal overlap. The RR of mortality from the cohort that was only reported in one publication was 1.72 (95% CI 0.11-27.19).[19] The pooled RR of mortality from this cohort plus the largest, least overlapping studies was 0.68 (95% CI 0.39-1.21)[19–21] (Figure 2). Although the pooled point

estimate for overall mortality from all six studies is very similar (0.64, 95% CI 0.51-0.81), it becomes significant with all overlapping studies pooled, though this is largely due to the two HIV-CAUSAL Collaboration publications (and they contain a large proportion of data from the CASCADE Collaboration).

The quality of evidence from the RCT literature for mortality was low and downgraded due to very serious imprecision owing to fewer than 50 events. The quality of the observational literature for the entire six studies was very low due to the substantial overlap in patients among the studies and as a result of indirectness owing to dissimilar comparator groups. Further, the quality of the literature for the three mostly non-overlapping studies was very low, as well.[19–21]

Severe HIV disease or malignancy

One RCT, which compared patients initiating ART at ≥500 CD4 cells/μL to those deferring until their CD4 counts were <500 cells/μL, found no difference in the hazard of developing severe HIV disease (defined as development of any AIDS-defining disease or a non-AIDS-defining invasive bacterial infection occurring in a solid organ or normally sterile body cavity) or having a non-AIDS-defining incident malignancy among persons initiating of early compared to deferred treatment (RR=0.60; 95% CI 0.30-1.22).[11*] The quality of the RCT literature was rated as low and was downgraded because having fewer than 50 events reported, which in turn yields unstable estimates.

HIV disease progression

One observational study, which compared patients initiating ART at ≥500 CD4 cells/μL to those deferring until their CD4 counts were <500 cells/μL, found a significantly lower hazard of developing an

[*] The oral presentation of this study at the 2015 Conference on Retroviruses and Opportunistic Infections used the term "severe infection" for this outcome. We have removed "severe infection" as an outcome in favour of this more descriptive category, which was used in the unpublished report we received from TEMPRANO investigators.[11]

AIDS-defining opportunistic infection among persons initiating ART early compared to those deferring treatment (HR=0.20; 95% CI 0.10-0.42) (Figure 3).[16] The quality of the observational literature was very low due to due to lack of adjustment in some of the estimates and indirectness due to a comparison of early versus deferred treatment cohorts (assumed to be ≥500 versus <500 CD4 cells/µL).

Severe HIV disease or malignancy or mortality

One RCT estimated the effect of early (≥500 CD4 cells/µL) compared to deferred ART initiation (<500 cells/µL) on the combined outcome of risk of death or severe HIV disease or incident malignancy.[11] Patients who initiated treatment earlier had a significantly lower hazard of death, severe HIV disease or incident malignancy than patients who deferred treatment (HR=0.56; 95% CI 0.33-0.94) (Figure 4). The quality of the RCT literature for this outcome is moderate and downgraded for imprecision.

Five observational studies estimated the effect of early versus deferred ART initiation on HIV disease progression or mortaltiy,[21,22,24–26] and four found a decreased risk of progression to AIDS or mortality among the early treated cohorts; two studies found a statistically significant reduction.[22,24] Compared to delayed ART initiation, early initiation of ART was not found to be associated with reduced risk of progression to AIDS or death in a pooled analysis of two studies with unique patients (RR=0.63; 95% CI 0.16–2.49) (Figure 5).[21,26] However, data from one observational study (ICONA)[25] were fully contained in CASCADE 2011,[21] and five of the 12 cohorts in a large HIV cohort collaboration (HIV-CAUSAL) were also contained in CASCADE 2011.[21] An additional meta-analysis including the large HIV cohort collaboration in the pooled analysis and ignoring the non-independence of the data did not substantively change the non-significant results (RR=0.77; 95% CI 0.49-1.21). Among the observational studies, two of these five studies reported adjusted estimates.[21,25] Additionally, four of the five studies were consistent in their finding of treatment effect. The quality of the observational literature for this outcome is very low

due to its observational status, inconsistency, and risk of bias resulting from a lack of confounder adjustment.

Malignancies (AIDS-related and non-AIDS related)

One RCT found no difference in risk of incident malignancies (AIDS-related and non-AIDS related) among ART-naïve patients beginning therapy early versus patients who delayed treatment (RR=0.91; 95% CI 0.06-14.38).[11] A single case of cancer was diagnosed in each treatment arm. The quality of the RCT literature was low owing to very serious imprecision because of the very small number of events.

Tuberculosis (pulmonary and disseminated)

One RCT found a no significant decrease in risk of developing tuberculosis in patients treated early versus those who delayed treatment (RR=0.52; 95% CI 0.22-1.21).[11] The quality of the RCT literature was low owing to very serious imprecision because of the very small number of events.

HIV transmission

One RCT found significantly decreased risk of transmission of HIV among patients treated early versus those who delayed treatment (RR=0.11; 95% CI 0.06-0.19) (Figure 6).[12] Two observational studies also evaluated the risk of transmission, though neither found a significant difference between patients treated early and those who received a delayed treatment (pooled RR=1.17; 0.46-2.98).[18,27] The quality of the RCT literature was very low owing to very serious imprecision because of the very small number of events and indirectness (compared patients initiating ART at <350 CD4 cells/µL to those initiating therapy at >500 cells/µL). The quality of the observational literature was also very low largely due to the lack of confounder adjustment in estimates and very small number of events. Of note the HPTN 052 study was excluded because it examined risk of transmission from patients who initiated ART at CD4 counts between 351 and 550 cells/µL and those who initiated ART at ≤350 cells/µL.[31] There was no

subanalysis of patients who initiated ART at <500 CD4 cells/μL (taken from both arms) and those from the intervention arm who initiated ART between 500 and 550 cells/μL.

Severe adverse events and laboratory abnormalities

One RCT reported severe adverse events between early and deferred treatment groups.[11] Investigators found no difference between treatment arms for any of the reported critical outcomes. Specifically, there was no noted increase in grade 3/4 laboratory abnormalities (which did not include neutropoenia) (HR=0.58; 95% 0.30-1.11), hepatic severe adverse events (RR=0.76; 95% CI 0.20-2.85) (Figure 7), renal several adverse events (RR=0.09; 95% CI 0.01-1.54) (Figure 8), neurological severe adverse events (RR=1.42; 95% CI 0.24-8.46), and cardiovascular severe adverse events (RR=0.32; 95% CI 0.01-7.73).[11] One observational study compared reported severe adverse events between early and deferred treatment cohorts.[14] Investigators found a significantly increased risk of any severe laboratory adverse event among those who were treated early when compared to those who initiated treatment with CD4 counts <350 cells/μL (RR=1.43; 95% CI 1.13-1.81). Additionally, they found a significantly increased risk of hepatic severe adverse events in those patients who initiated treatment early when compared to those who delayed treatment (RR=1.45; 95% CI 1.03-2.04) (Figure 7). However, no significant differences were noted between treatment arms for renal (RR=0.90; 95% CI 0.40-2.01) (Figure 8), haematologic (RR=1.40; 95% CI 0.87-2.26) or other severe adverse events (RR=1.40; 95% CI 0.94-2.08). The quality of the RCT literature for all outcomes, except for grade 3/4 laboratory abnormalities, was low due to low numbers of events and, hence, imprecise estimates. On the other hand, the quality of the RCT literature for the grade 3/4 laboratory abnormalities outcome was moderate and downgraded because of the relatively small number of events. The quality of the observational studies literature for these outcomes was low with no observed study limitations aside from the study's observational design (although no other considerations improved the overall quality of the literature).

Findings in key populations

Aside from discordant couples (see the HIV transmission outcome above), there is no particular breakdown of outcomes by age (children, adolescents, older adults), co-infection (hepatitis B, hepatitis C), pregnancy status or membership in key population (e.g., injection drug users, commercial sex workers, transgender individuals, men who have sex with men) in the studies we reviewed.

Methodological quality of included studies

All three RCT reports adequately discussed how the randomisation sequence was generated, and all allocation was adequately concealed prior to assignment. No studies suffered from attrition bias resulting from incomplete outcome data reporting (e.g., follow-up in all studies was adequate), and no studies suffered from reporting bias resulting from selective outcome reporting. However, the three RCT reports may have potentially been biased because of a lack of blinding of assigned treatment (treatment was determined by pre-determined clinical characteristics and was open label) (Figure 9).[11–13]

No observational study suffered from obvious selection bias; all observational studies had study populations that were either truly or somewhat representative of average, HIV-infected persons, and all participants were drawn from the same community. Additionally, all treatment data were ascertained through health care records, and outcomes of interest were not present at the start of the study. The comparability between intervention and control arms was not very strong as several studies did not adjust for confounding factors such as age or sex. Outcomes were adequately assessed in all studies either through independent blind assessment or record linkage. Follow-up was long enough for outcomes to occur in all studies, although six observational studies did not report follow-up rates of participants (Table 2).[14–17,27,28]

Discussion

We found moderate quality evidence that early ART initiation in asymptomatic HIV-infected patients with baseline CD4 counts of ≥500 cells/μL is associated with a lower risk of death, severe HIV infection or malignancy. We also found evidence from an observational study that early ART initiation is associated with reduced risk of HIV disease progression this evidence was, however, of very low quality. Furthermore, we found evidence from an RCT that early initiation of ART reduces the risk of HIV transmission, but this was also of very low quality. Current WHO ART guidelines rate the quality of evidence for this outcome as high; those recommendations were, however, made based on the literature for serodiscordant couples in which the infected partners had ≥350 CD4 cells/μL. The literature is substantially less robust for infected partners with ≥500 CD4 cell/μL, although the estimates of efficacy are quite similar. Finally we found moderate quality evidence from an RCT that early initiation of ART was not associated with an increased risk of a grade 3/4 adverse events. There is, however, low quality evidence from an observational study of an increased risk of liver-related adverse events; the clinical significance of this, especially in light of different findings in an RCT, is unclear.

The present review should be considered with its multiple limitations. As with all systematic reviews, the results are only as good as our identified literature—our ability to identify relevant studies. To reduce the possibility of missing key studies, we searched four targeted scientific databases and reviewed the bibliographies of included studies as well as abstracts from recent conferences. It should be noted, however, that the bulk of our identified literature comes from Europe, North America and Australia with only a few studies contributing data from Africa and Asia. In turn, the generalisability of our results to areas with the greatest need is limited. While publication bias is a reasonable risk in systematic reviews, the present review included large synthesized cohorts, (e.g., NA-ACCORD, EUROSIDA, ICONA,

CASCADE, HIV-CAUSAL), which may have reduced the likelihood of publication bias. Unfortunately, we identified too few studies to objectively test for publication bias.

Additionally, we calculated estimates of efficacy from RCTs and effectiveness from cohort studies. The three identified RCTs[11–13] used data from the same study population (TEMPRANO), and the incidence of some of the major clinical outcomes was particularly low. As a result, the precision of the estimates of mortality from RCTs, for example, was low; using GRADE criteria, the overall quality of the RCT literature for mortality was downgraded because of this. Due to the lack of RCT data, and to be comprehensive in our data collection efforts, we also examined cohort studies. GRADE criteria dictate that cohort studies should provide a lower quality of evidence, and this is usually because of residual confounding.

Additionally, our overall effectiveness estimates were likely biased as a result of a lack of independence between study populations. Namely, all six observational studies reporting mortality outcomes contained data from some of the same cohorts.[19–24] We attempted to minimise the lack of independence between studies by conducting sensitivity analyses, removing studies with the most overlap in populations. For example, for mortality we examined three studies--one from Italy,[19] one large synthesized cohort from North America[20] and one large synthesized cohort mostly from Europe,[21] which had minimal overlap with each other. The point estimate from this synthesis (RR=0.68) was only 6 percent greater than the point estimate from the pooled estimate from the full sample (RR=0.64), suggesting that the lack of independence between study populations did not greatly affect the point estimates. Expectedly, however, the variability decreased considerably with the much larger sample size. A better approach to synthesising these data would be to perform an individual patient database meta-analysis for each outcome variable. Additionally, cohorts can suffer from a number of biases, including confounding and lead-time bias. As a result of evaluating a subgroup of patients whose CD4 at ART initiation was greater than 500 cells/µL, which until recently was not routinely studied, much of our analyses were performed

post-hoc using unadjusted estimates. Lastly, though the GRADE system for rating the quality of the literature has its limitations and some have reservations about its use at WHO for guideline development,[32] it is the current gold standard and has been adopted by WHO for its guideline development process.[33]

In conclusion, depending on the outcome in question, our findings provide evidence of the benefit of initiating ART at CD4 counts of 500 cells/µL and above compared to initiating it later in the course of HIV disease when CD4 counts have fallen below 500 cells/µL. In this systematic review, this effect was demonstrated for the combined risk of death, severe HIV disease or incident malignancy, for the risk of HIV disease progression and for the risk of HIV transmission to an uninfected partner. The literature was more mixed regarding severe adverse events with an RCT finding no differences in grade 3/4 laboratory abnormalities but an observational study finding an increased risk of any severe laboratory adverse event and specifically hepatic adverse events in the early treatment group. The literature for beginning ART at CD4 counts ≥500 CD4 cells/µL is far less robust than the evidence outlined in the previous systematic review (beginning ART at CD4 counts between 350 and 500 cells/µL).[5] We anticipate that four RCTs that are currently in the field, Strategic Timing of AntiRetroviral Treatment (START),[34] ANRS 12249,[35] PopART,[36] SEARCH[37] and its pilot study EARLI,[38] as well as possible additional data analysis from TEMPRANO[12] will add additional evidence to answer the question of when to start ART definitively, both for individuals and at the population level.

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Annex 2.2.1 Universal antiretroviral therapy for asymptomatic adults and adolescents with HIV 1 infection and CD4 T cell counts ≥500 cells/µL: a systematic review and meta- analysis

Figure 1. Articles identified, screened, assessed and included

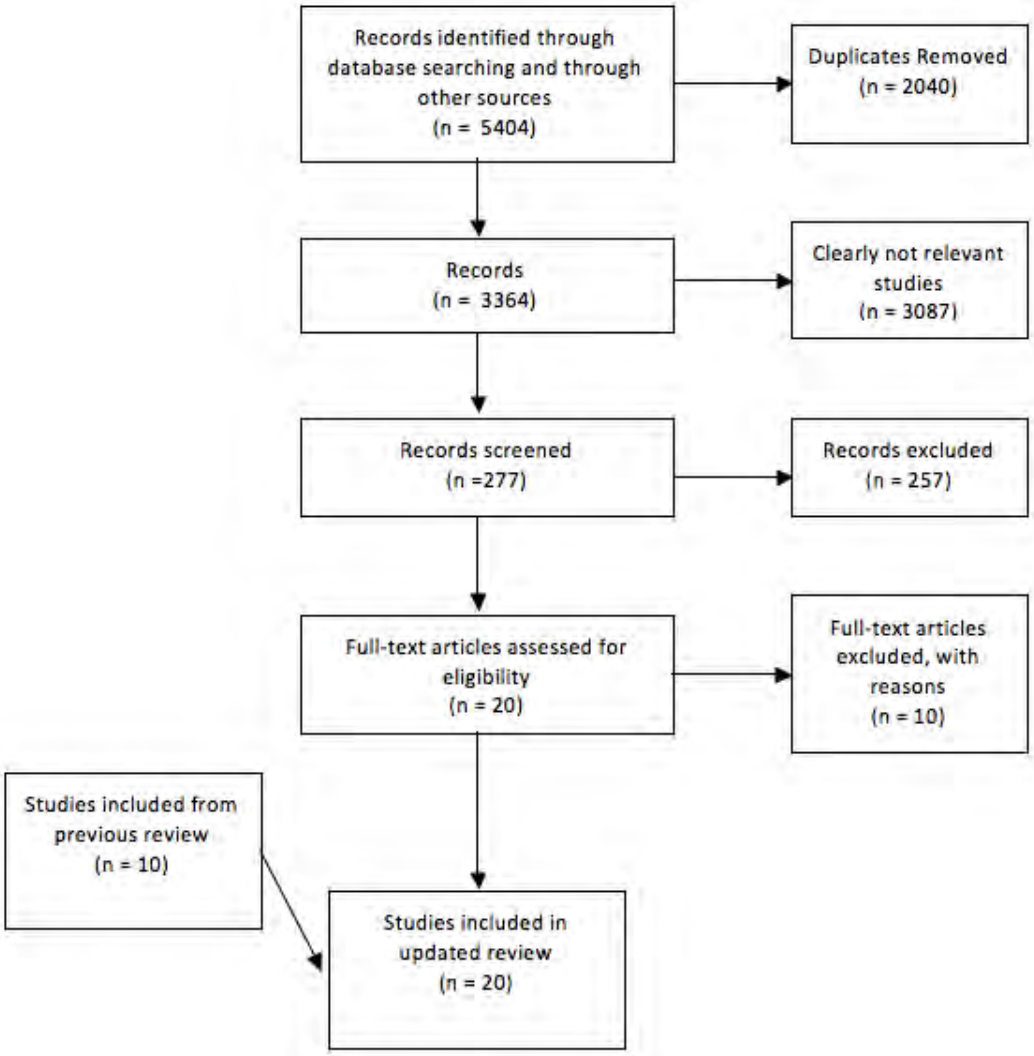
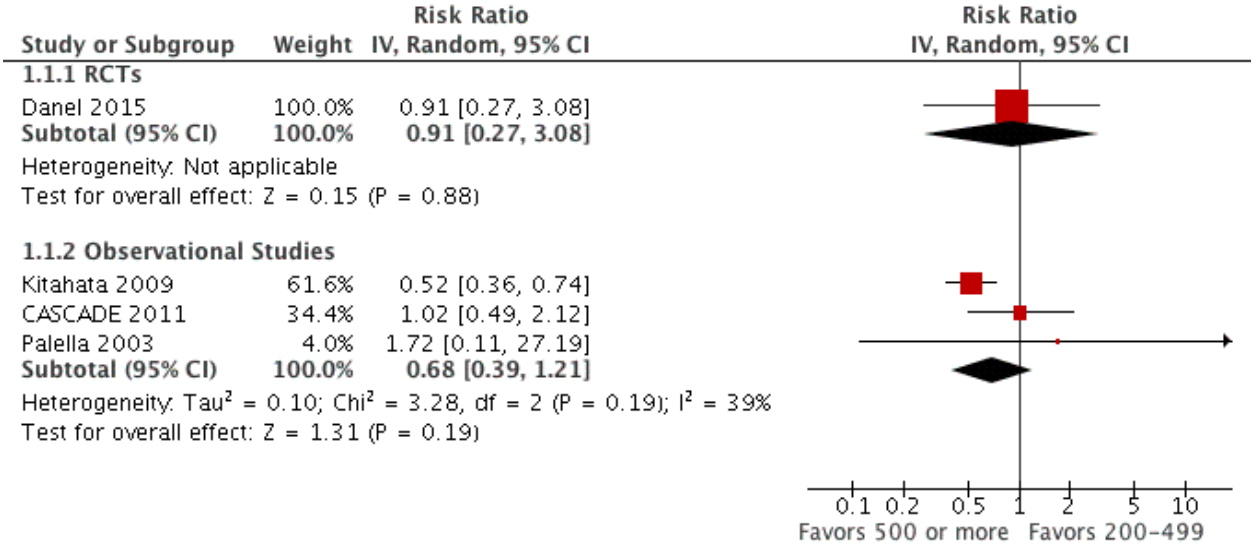
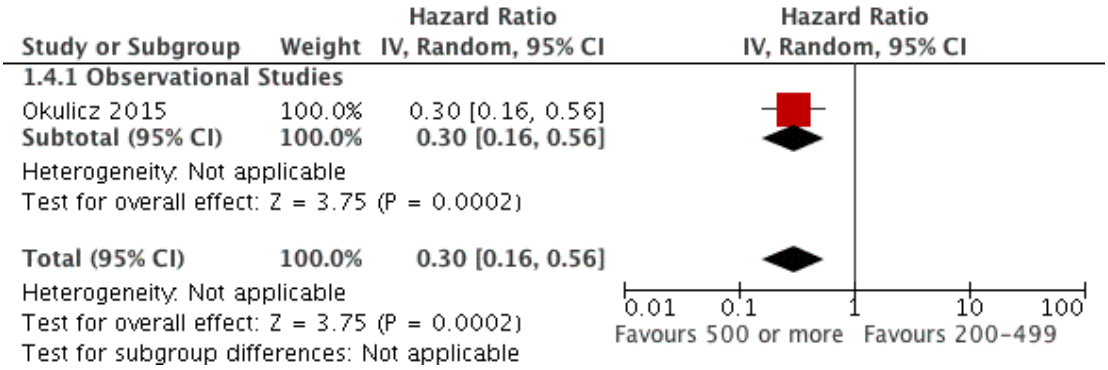


Figure 2: Forest plot of mortality



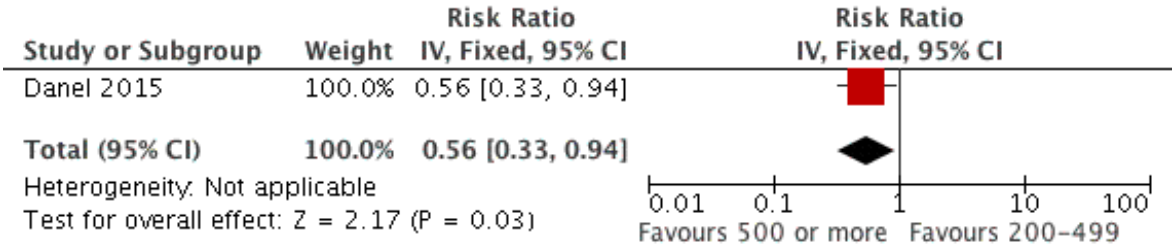
CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial

Figure 3: Forest plot of HIV progression



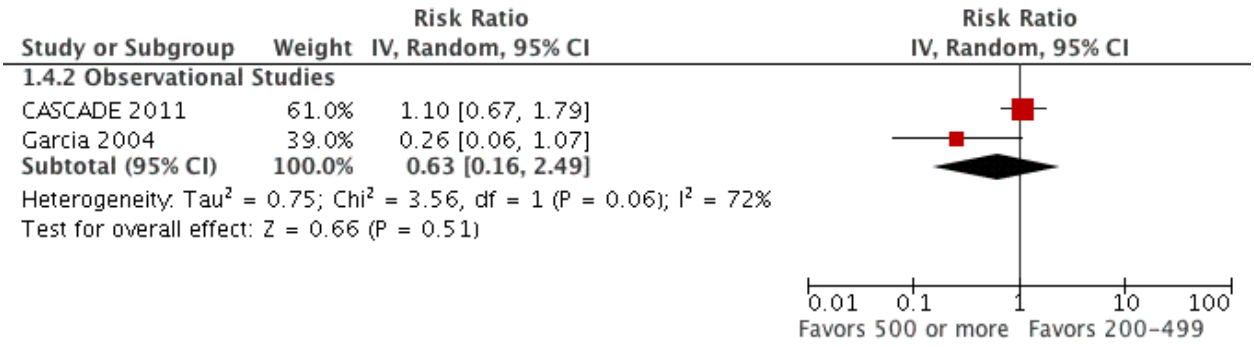
CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial

Figure 4: Forest plot of mortality, severe HIV disease or malignancy



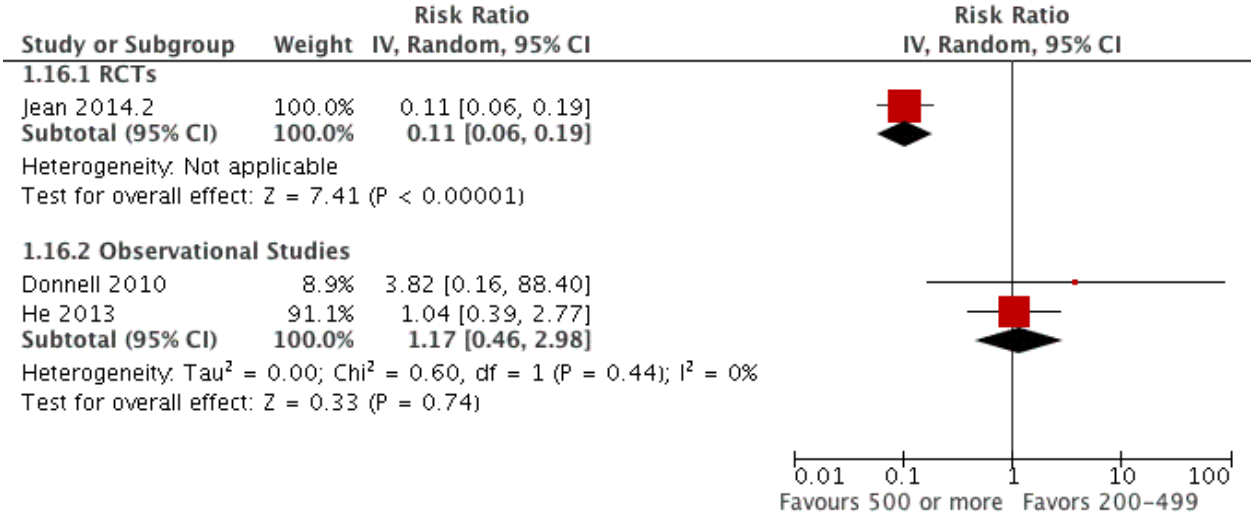
CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial

Figure 5: Forest plot of AIDS progression or death



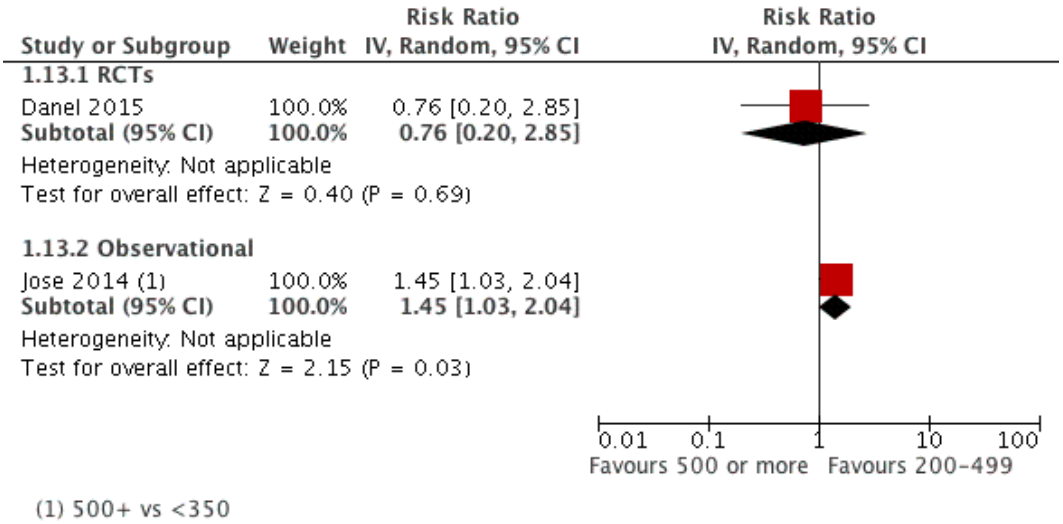
CI confidence interval; df, degrees of freedom; IV, inverse variance; RCT, randomised controlled trial

Figure 6: Forest plot of HIV transmission



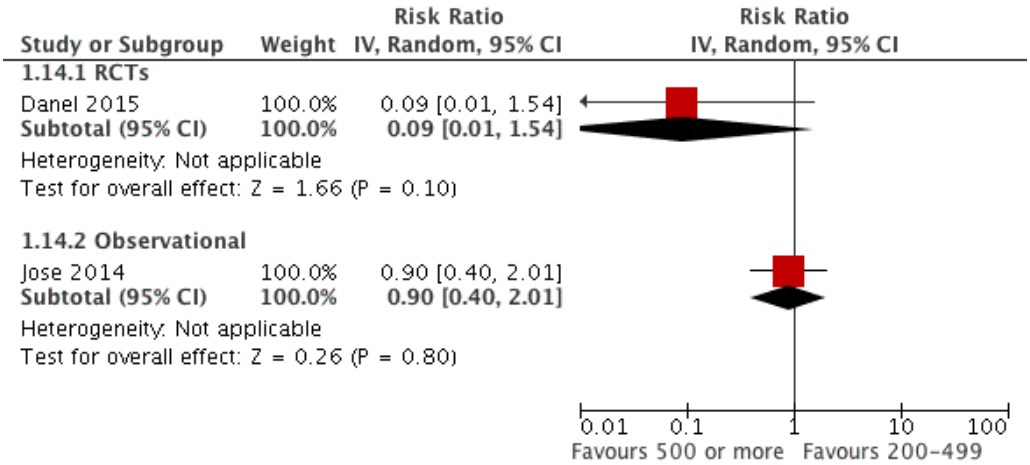
CI confidence interval; IV, inverse variance; RCT, randomised controlled trial

Figure 7: Forest plot of Hepatic SAE



CI confidence interval; IV, inverse variance; RCT, randomised controlled trial

Figure 8: Forest plot of Renal SAE



CI confidence interval; IV, inverse variance; RCT, randomised controlled trial

Figure 9: Risk of bias in randomised controlled trials

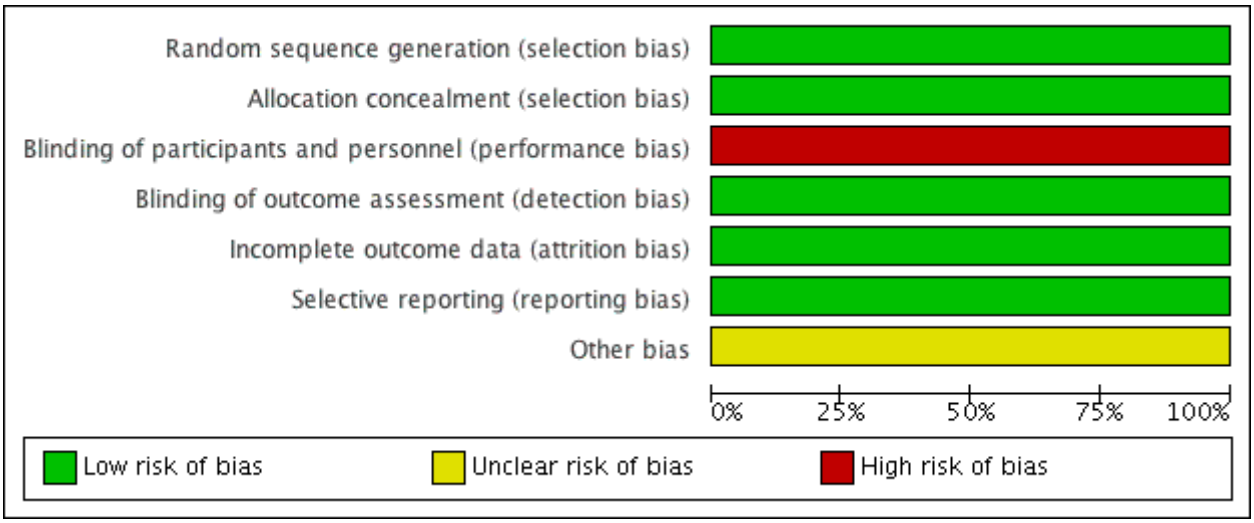


Table 1. Characteristics of included studies.

Study and reference	Methods	Setting	Participants	Intervention	Outcomes Of Interest
CASCADE 2003[33]	Meta-analysis of 20 cohort studies	Australia, Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Switzerland, United Kingdom	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs 0-500 cells/µl)	None
CASCADE 2011[21]	Meta-analysis of 23 cohort studies	Australia, Canada, Denmark, Estonia, France, Germany, Greece, Italy, Kenya, The Netherlands, Norway, Poland, Portugal, Russia, Rwanda, South Africa, Spain, Switzerland, Uganda, Ukraine, United Kingdom, Zambia, Zimbabwe	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 500-799 cells/µl (vs 0-499 cells/µl)	Mortality, disease progression or mortality
Danel 2015[11]	Randomized controlled	Côte d'Ivoire	ART-naïve HIV-	Initiate ART with CD4	Mortality, Severe

	trial		infected patients initiating ART	cell count >500 cells/µl (vs <350 cells/µl)	morbidity, TB (pulmonary and disseminated), AIDS-related cancers, non-AIDS related cancers, other non-AIDS related events
Donnell 2010[18]	Multicenter cohort study	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	HIV transmission
Garcia 2004[26]	Cohort study	Spain	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	Disease progression or mortality
Gras 2007[34]	Multicenter cohort study	The Netherlands	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	None
He 2013[27]	Cohort study	China	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	HIV transmission
HIV-CAUSAL 2010[23]	Meta-analysis of 12 cohort studies	France, The Netherlands, Spain, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	Mortality

HIV-CAUSAL 2011[24]	Meta-analysis of 12 cohort studies	France, The Netherlands, Spain, Switzerland, United Kingdom, United States of America	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	Mortality, disease progression or mortality
Jean 2013[12]	Randomised controlled trial	Côte d'Ivoire	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs <350 cells/µl)	HIV transmission
Jean 2014[13]	Randomised controlled trial	Côte d'Ivoire	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs <350 cells/µl)	None
Jia 2012[28]	Cohort study	China	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >550 cells/µl (vs 0-550 cells/µl)	HIV transmission
Jose 2014[14]	Cohort study	United Kingdom	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs ≤350 cells/µl)	Any AE, liver AE, renal AE, blood AE, other AE
Kitahata 2009[20]	Meta-analysis of 22 cohort studies	Canada, United States	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs 351-500 cells/µl)	Mortality
Le 2013[15]	Cohort study	United States	ART-naïve HIV-infected patients initiating	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499	None

			ART	cells/µl)	
Merito 2006[25]	Multicenter cohort study	Italy	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs 0-500 cells/µl)	Disease progression or mortality
Okulicz 2015[16]	Cohort study	United States	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count ≥500 cells/µl (vs 0-499 cells/µl)	Disease progression
Palella 2003[19]	Cohort study	United States	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count 501-750 cells/µl (vs 351-500 cells/µl)	Mortality
Schneider 2013[17]	Cohort study	United States	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >500 cells/µl (vs 0-500 cells/µl)	None
When to Start Consortium 2009[22]	Meta-analysis of 18 cohort studies	Australia, Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, The	ART-naïve HIV-infected patients initiating ART	Initiate ART with CD4 cell count >450 cells/µl (vs 0-450 cells/µl)	Mortality, disease progression or mortality

		Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, United Kingdom, United States			

Table 2. Summary of critical appraisal of included studies using the Newcastle-Ottawa Quality Assessment Scale for observational studies

Study	Selection				Comparability	Outcome		
	Representativeness	Selection of non-exposed	Ascertainment of exposure	Demonstration outcome not present at start	Comparability of cohorts	Assessment of outcome	Follow up long enough	Adequate follow-up rate (≥80%)
CASCADE 2003	★	★	★	★	★★	★	★	★
CASCADE 2011	★	★	★	★	★★	★	★	–
Donnell 2010	★	★	★	★	★	★	★	★
Garcia 2004	★	★	★	★	★	★	★	★
Gras 2007	★	★	★	★	★	★	★	★
He 2013	★	★	★	★	★	★	★	
HIV-CAUSAL 2010	★	★	★	★	★★	★	★	★
HIV-CAUSAL 2011	★	★	★	★	★★	★	★	★
Jia 2012	★	★	★	★	★	★	★	
Jose 2014	★	★	★	★	★★	★	★	
Kitahata 2009	★	★	★	★	★★	★	★	★
Le 2013	★	★	★	★	★★	★	★	
Merito	★	★	★	★	★★	★	★	★

2006								
Okulicz 2015	★	★	★	★	★★	★	★	
Palella 2003	★	★	★	★	★★	★	★	★
Schneider 2013	★	★	★	★	★	★	★	
When to Start Consortium 2009	★	★	★	★	★★	★	★	★

Table 3. Cohort studies reporting a mortality outcome by study.

Cohort	Country/ Region	Reference					
		When to Start Consortium*	CASCADE 2011*	HIV-CAUSAL 2010*	HIV-CAUSAL 2011*	Kitahata*	Palella
ALIVE	USA					x	
ALLRT	USA					x	
Amsterdam Cohort Study in Homosexual Men and IDUs	Netherlands	x	x				
ANRS CO3 Aquitaine Cohort	France	x	x				
ANRS PRIMO	France		x	x	x		
ANRS SEROCO	France	x	x	x	x		
ATHENA	Netherlands	x		x	x		
Badalona IDU Cohort	Spain	x	x				
Barcelona IDU Cohort	Spain	x	x				
BCCfE-HIV	Canada	x					
CHORUS	USA	x					
Copenhagen HIV Seroconverter Cohort	Denmark	x	x				
CoRIS/CoRIS-MD	Spain			x	x		
Edinburgh	UK	x	x				

Hospital Cohort							
EuroSIDA	Europe, Argentina, Israel	x					
FHCC	Germany	x					
FHDH-ANRS CO4	France	x	x	x	x		
GEMES	Spain			x	x		
German HIV-1 Seroconverter Cohort	Germany	x	x				
Greek Haemophilia Cohort	Greece	x	x				
HIVRN	USA					x	
HOMER	USA					x	
HOPS	USA					x	x
ICONA	Italy	x	x				
Italian Seroconversion Study	Italy	x	x				
JHHCC	USA					x	
Köln/Bonn Cohort	Germany	x					
KPNC	USA					x	
Lyon Primary Infection Cohort	France	x	x				
MACS	USA	x				x	
Madrid Cohort	Spain	x	x				
MONT	Canada					x	

MRC Biostatistics Cohort	UK	x	x				
OHTN	Canada					x	
Oslo and Ulleval Hospital Cohorts	Norway	x	x				
PCRD	USA					x	
PISCIS	Spain	x		x	x		
Polaris	Canada					x	
REACH	USA					x	
Royal Free Haemophilia Cohort	UK	x	x				
Royal Free Hospital Cohort	UK	x					
SAC	Canada	x	x			x	
SCOPE	USA					x	
SHCS	Switzerland	x	x	x	x		
Sydney AIDS Prospective Study	Australia	x	x				
Sydney Primary HIV Infection Cohort	Australia	x	x				
UAB	USA	x				x	
UCHCC	USA					x	
UK CHIC	UK			x	x		
UK Register of HIV Seroconverters	UK	x	x	x	x		
VACS	USA	x		x	x	x	

Valencia IDU Cohort	Spain	x	x				
VAND	USA					x	
WIHS	USA					x	

*Reported using methods to account for lead-time bias

ALIVE, AIDS Link to the Intravenous Experience; ALLRT, AACTG Longitudinal Linked Randomized Trials; APROCO, Antiprotease Cohort; ATHENA, AIDS Therapy Evaluation in the Netherlands; BCCfE-HIV, British Columbia Center for Excellence in HIV/AIDS; CHORUS, Collaborations in HIV Outcomes Research US; CoRIS/CoRIS-MD, Cohorte de la Red de Investigación en SIDA; FHCC, Frankfurt HIV Clinic Cohort; FHDH-ANRS CO4, French Hospital Database on HIV; GEMES, Grupo Español Multicéntrico para el Estudio de Seroconvertores-Haemophilia; HIVRN, HIV Research Network; HOMER, HAART Observational Medical Evaluation and Research; HOPS, HIV Outpatient Study; ICONA, Italian Cohort of Antiretroviral-Naïve Patients; JHHCC, Johns Hopkins HIV Clinical Cohort; KompNet Cohort, German Competence Network for HIV/AIDS; KPNC, Kaiser Permanente Northern California; MACS, US Multicenter AIDS Cohort Study; MONT, Montreal Chest Institute Immunodeficiency Service Cohort; OHTN, Ontario HIV Treatment Network Cohort Study; PCRD, Case Western Reserve University Immunology Unit Patient Care and Research Database; PISCIS, Proyecto para la Informatización del Siguimiento Clinicoepidemiológico de la Infección por HIV y SIDA; REACH, Research in Access to Care in the Homeless; SAC, Southern Alberta Clinic Cohort; SCOPE, Study of the Consequences of the Protease Inhibitor Era; SHCS, Swiss HIV Cohort Study; UAB, University of Alabama at Birmingham 1917 Clinical Cohort; UCHCC, University of North Carolina, Chapel Hill HIV Clinic; UK CHIC, UK Collaborative HIV Cohort; VACS, Veterans Aging Cohort Study and Virtual Cohort; VAND, Vanderbilt-Meharry CFAR Cohort; WIHS, Women's Interagency HIV Study

Table 4. Cohort studies reporting a mortality or progression outcome by study

Cohort	Country/ Region	Reference					
		When to Start Consortium*	CASCADE 2011*	HIV-CAUSAL 2010*	HIV-CAUSAL 2011*	Garcia	Merito*
Amsterdam Cohort Study in Homosexual Men and IDUs	Netherlands	x	x				
ANRS CO3 Aquitaine Cohort	France	x	x				
ANRS PRIMO	France		x	x	x		
ANRS SEROCO	France	x	x	x	x		
ATHENA	Netherlands	x		x	x		
Badalona IDU Cohort	Spain	x	x				
Barcelona Hospital Clinic	Spain					x	
Barcelona IDU Cohort	Spain	x	x				
BCCfE-HIV	Canada	x					
CHORUS	USA	x					
Copenhagen HIV Seroconverter Cohort	Denmark	x	x				
CoRIS/CoRIS-MD	Spain			x	x		
Edinburgh Hospital Cohort	UK	x	x				

EuroSIDA	Europe, Argentina, Israel	x					
FHCC	Germany	x					
FHDH-ANRS CO4	France	x	x	x	x		
GEMES	Spain			x	x		
German HIV-1 Seroconverter Cohort	Germany	x	x				
Greek Haemophilia Cohort	Greece	x	x				
ICONA	Italy	x	x				x
Italian Seroconversion Study	Italy	x	x				
Köln/Bonn Cohort	Germany	x					
Lyon Primary Infection Cohort	France	x	x				
MACS	USA	x					
Madrid Cohort	Spain	x	x				
MRC Biostatistics Cohort	UK	x	x				
Oslo and Ulleval Hospital Cohorts	Norway	x	x				
PISCIS	Spain	x		x	x		
Royal Free Haemophilia	UK	x	x				

Cohort							
Royal Free Hospital Cohort	UK	x					
SAC	Canada	x	x				
SHCS	Switzerland	x	x	x	x		
Sydney AIDS Prospective Study	Australia	x	x				
Sydney Primary HIV Infection Cohort	Australia	x	x				
UAB	USA	x					
UK CHIC	UK			x	x		
UK Register of HIV Seroconverters	UK	x	x	x	x		
VACS	USA	x		x	x		
Valencia IDU Cohort	Spain	x	x				

*Reported using methods to account for lead-time bias

ALIVE, AIDS Link to the Intravenous Experience; ALLRT, AACTG Longitudinal Linked Randomized Trials; APROCO, Antiprotease Cohort; ATHENA, AIDS Therapy Evaluation in the Netherlands; BCCfE-HIV, British Columbia Center for Excellence in HIV/AIDS; CHORUS, Collaborations in HIV Outcomes Research US; CoRIS/CoRIS-MD, Cohorte de la Red de Investigación en SIDA; FHCC, Frankfurt HIV Clinic Cohort; FHDH-ANRS CO4, French Hospital Database on HIV; GEMES, Grupo Español Multicéntrico para el Estudio de Seroconvertores-Haemophilia; HIVRN, HIV Research Network; HOMER, HAART Observational Medical Evaluation and Research; HOPS, HIV Outpatient Study; ICONA, Italian Cohort of Antiretroviral-Naïve Patients; JHHCC, Johns Hopkins HIV Clinical Cohort; KompNet Cohort, German Competence Network for HIV/AIDS; KPNC, Kaiser Permanente Northern California; MACS, US Multicenter AIDS Cohort Study; MONT, Montreal Chest Institute Immunodeficiency Service Cohort; OHTN, Ontario HIV Treatment Network Cohort Study; PCRD, Case Western Reserve University Immunology Unit Patient Care and Research Database; PISCIS, Proyecto para la Informatización del Siguimiento Clinicoepidemiológico de la Infección por HIV y SIDA; REACH, Research in Access to Care in the Homeless; SAC, Southern Alberta Clinic Cohort; SCOPE, Study of the Consequences of the Protease Inhibitor Era; SHCS, Swiss HIV Cohort Study; UAB, University of Alabama at Birmingham 1917 Clinical Cohort; UCHCC, University of North Carolina, Chapel Hill HIV Clinic; UK CHIC, UK Collaborative HIV Cohort; VACS, Veterans Aging Cohort Study and Virtual Cohort; VAND, Vanderbilt-Meharry CFAR Cohort; WIHS, Women's Interagency HIV Study

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Option B+ vs. Option B for improving outcomes for women with HIV infection and their infants: a systematic review

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ABSTRACT

Background: In a 2012 programmatic update to its 2010 antiretroviral guidelines, the World Health Organization (WHO) recommended lifelong antiretroviral therapy (ART) known as Option B+ as one recommended approach to prevent mother-to-child HIV transmission. Depending on the setting, Option B (a short course of ART throughout the antenatal period and the duration of breastfeeding) also was recommended as a viable treatment. However, the rapid adoption of Option B+ raises concerns regarding implementation challenges and lack of clearly validated benefits.

Objectives: To systematically review the scientific literature and assess the effectiveness of lifelong ART versus ART for the duration of pregnancy and breastfeeding in pregnant and breastfeeding women living with HIV.

Methods: We used Cochrane Collaboration methods to search a range of relevant databases and abstracts from major conferences for reports of randomized controlled trials (RCT) and cohort studies comparing Option B+ with Option B. Due to limited data comparing the interventions we could not conduct a comparative review and therefore conducted a non-comparative review of Options B and B+. Primary outcomes of interest included: maternal mortality, maternal morbidity, adverse events, adherence, mother-to-child transmission, HIV transmission to sexual partners, development of antiretroviral resistance retention in treatment, stopping and restarting ART (Option B), tuberculosis (TB) incidence, fertility rate, maternal CD4 or clinical staging (when initiated Option B), and viral load. Secondary outcomes included sustainability of service delivery and acceptability to patients.

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Results: Searches identified 525 studies for screening. We screened 34 full-text articles. We did not identify any RCTs or observational studies that directly compared outcomes of women on Option B+ with those on Option B. Although no studies met inclusion criteria, we provide a narrative synthesis of the evidence resulting from 16 Option B studies and 13 Option B+ studies not meeting inclusion criteria but which were, nevertheless, highly relevant. These studies were single-arm, non-comparative studies conducted in Burkina Faso (n=1), Haiti (n=1), Kenya (n=6), Malawi (n=12), Puerto Rico and the United States (n=1), Uganda (n=2), and multiple countries in sub-Saharan Africa (n=1) and investigated maternal mortality, adherence to ART, mother-to-child transmission, retention in treatment, maternal CD4, viral load, and patient acceptability to Option B+. We also identified key themes on rapid initiation on Option B+ and service delivery modes of Option B+.

Conclusions: Based on our analysis of these 27 studies, sub-optimal retention and poor adherence to treatment suggest that more emphasis is needed on addressing implementation of Option B+. Better patient counseling may help retain more patients over time. In addition, infant follow-up is crucial to ensure the full scope of the PMTCT cascade is addressed.

BACKGROUND

In 2012, the World Health Organization (WHO) updated its 2010 guidelines for HIV-infected pregnant women receiving triple antiretroviral regimens for prevention of mother-to-child HIV transmission (PMTCT) to include the option of combination antiretroviral therapy (ART) for life from the point of diagnosis (WHO 2010, WHO 2012). This recommendation was reiterated in WHO's 2013 Consolidated ART Guidelines (WHO 2013). The 2013 Guidelines recommend a once-daily fixed-dose combination regimen for adults, including pregnant and breastfeeding women, with tenofovir (TDF) as the preferred nucleotide reverse transcriptase inhibitor (NRTI) and efavirenz (EFV) as the preferred non-nucleotide reverse transcriptase inhibitor (NNRTI), taken in combination with either lamivudine (3TC) or emtricitabine (FTC) (WHO 2013). WHO recommended two options for duration of ART for women who were not otherwise eligible for ART (e.g., asymptomatic and CD4 count <500 cells/μL): from diagnosis until cessation of breastfeeding (Option B) and lifelong therapy from diagnosis (Option B+).

Option B+ has promising benefits: available as a fixed-dose combination, safe for both pregnant and breastfeeding women and their fetuses and infants, reduced risk of developing TB, lower monitoring requirements, a low drug resistance profile, increased ART coverage, prevention of sexual transmission, compatibility with other drugs used in clinical care and harmonisation with recommendations for non-pregnant adults (Kieffer 2014, UNAIDS 2012, UNICEF 2012, WHO 2013). Notably WHO estimates that 60% of pregnant HIV-infected women will meet the 2013 treatment guidelines thresholds for initiating ART. Option B, on the other hand, recommends that all pregnant and breastfeeding women with HIV otherwise ineligible for ART be offered three-drug ART beginning in the antenatal period and continuing throughout the duration of breastfeeding or, for women electing not to breastfeed, stopping after delivery (WHO 2013). At the end of breastfeeding those women who do not yet require ART for their own health discontinue prophylaxis and continue to monitor their CD4 count and clinical status, eventually re-starting ART when the CD4 falls <500 cells/μL, other indications for ART are diagnosed or they become pregnant again (WHO 2013)..

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In 2013, a number of the Global Plan priority countries continued their important strides in expanding and improving access to HIV services for women and children. For the first time, all these countries have guidelines officially endorsing the more efficacious antiretroviral medicines (whether on Option B or Option B+) and the phasing out of Option A[1], which is no longer recommended by WHO (WHO 2013, UNAIDS 2014). However, the rapid adoption raises concerns regarding implementation challenges and lack of validated benefits of Option B+.

OBJECTIVE

To systematically review the scientific literature and assess the effectiveness of lifelong ART (Option B+) versus ART for the duration of pregnancy and breastfeeding (Option B) in pregnant and breastfeeding women living with HIV who are not otherwise clinically eligible for ART.

METHODS

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Search strategy

Electronic searches

Journal and trial databases:

We searched the following electronic databases, in the period from 1 January 2009 to 31 March 2015:

- CENTRAL (Cochrane Central Register of Controlled Trials)

[1] Option A: Zidovudine (AZT) for the mother during pregnancy, single-dose nevirapine (sd-NVP) plus AZT and 3TC for the mother at delivery and continued for a week postpartum.

- Excerpta Medica Database (EMBASE)
- PubMed
- Web of Science
- World Health Organization (WHO) Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO).

Along with appropriate Medical Subject Heading (MeSH) terms and relevant keywords, we used the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE (Higgins 2008), and the Cochrane HIV/AIDS Group's validated strategies for identifying references relevant to HIV infection and AIDS. The search strategy was iterative, in that references of included studies were searched for additional references. All languages were included. See Annex 1 for our PubMed search strategy, which was modified and adapted as needed for use in the other databases.

Conference databases:

We searched conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), for all available abstracts presented at these conferences from 1 January 2009 through 31 March 2015.

Searching other resources

In addition to searching electronic databases we examined the bibliographies of relevant articles in an effort to identify additional pertinent materials. We searched WHO's International Clinical Trials Registry Platform (ICTRP) to identify ongoing trials.

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Types of interventions

Intervention:

Any intervention for pregnant and/or breastfeeding women with HIV infection who do not qualify for ART on immunologic or clinical grounds who start ART and continue for life (Option B+)

Comparator:

Any intervention for pregnant and/or breastfeeding women with HIV infection who do not otherwise qualify for ART and who begin combination ART and discontinue after cessation of breastfeeding (or after delivery if no breastfeeding) (Option B)

Outcomes of interest

Primary:

- Maternal mortality*
- Maternal morbidity† (operationalized as clinical, immunological or virological failure)
- Adverse events† (Grade 3/4 serious adverse events)
- Adherence to ART (as measured by investigators)†
- Mother-to-child transmission / Infant HIV infection*
- HIV transmission to sexual partners*
- Development of antiretroviral resistance†
- Retention in treatment

* Outcomes deemed Critical by the WHO Guidelines Development Committee
† Outcomes deemed Important by the WHO Guidelines Development Committee

- TB incidence
- Fertility rate
- Maternal CD4 or clinical staging (when initiated Option B)
- Maternal viral load

Secondary:

- Sustainability of service delivery
- Acceptability to women

Types of studies

We searched for randomised controlled trials (RCT) and cohort studies that described results from one of the two types of interventions (Option B and Option B+) and contained one or more of our outcomes.

Data extraction and management

We imported search results into bibliographic citation management software (EndNote X4, Thomson Reuters, New York, New York USA) and excluded duplicate references. Reviewing only article titles, one author (HH) excluded all references that were clearly irrelevant. Two authors (HA and AL or HA and RK), each working independently, then reviewed the titles, abstracts and descriptor terms of the remaining citations to identify potentially eligible reports. We obtained full text articles for all references identified as potentially meeting inclusion criteria. HA, AL and RK reviewed these full text articles and applied inclusion criteria to establish each study's eligibility or ineligibility. Our plan was to resolve any differences of opinion through discussion and, if necessary, a neutral third party arbiter.

Three authors (HA, GR, KT) working independently examined and extracted data from each study included in this review. The authors used a consensus approach to determine whether the articles met inclusion criteria.

Where more than one article described an outcome, we combined them using a weighted average.

Assessment of evidence quality

We recognize that the quality of evidence from observational studies is generally graded as low, however given that Option B+ is a relatively new treatment recommendation we wanted to be inclusive of studies that focused on B+. Additionally, because the goal was to also assess Option B we included information from studies that used other comparators to Option B (e.g. Option A) but only used data from the Option B arm of these studies.

RESULTS

We conducted electronic database searches on 31 March 2015. The searches yielded 525 citations. One author removed 74 duplicate records and 43 clearly irrelevant records. Two author teams (HA and AL or HA and RK), each working independently, screened 408 records and identified 47 full-text articles for review. On 21 May 2015 we conducted electronic database searches to identify additional Option B studies. The searches yielded 29 citations. Three authors working independently screened 22 full-text articles for this review. See Annex 2 for a flow chart depicting our screening process.

We did not identify any RCTs or observational studies that met our inclusion criteria, that is, that compared Option B to Option B+ directly. However, we did identify 18 studies that reported on Option B outcomes. These included two RCTs, one single-arm trial and 12 cohort studies, all conducted in sub-Saharan Africa. We also identified 9 studies, including one RCT and 8 cohorts that reported on outcomes associated with Option B+. Annexes 3 and 4 provide a summary of key characteristics of each of the 27 studies.

Excluded studies

See Annex 5 for a bibliography of studies excluded after full-text review, with reasons for exclusion.

Outcomes

Option B. The 18 Option B studies we reviewed contained 18 outcomes. Fifteen of these were maternal outcomes and 3 pediatric (Tables 1-2)

Maternal mortality was reported in 8 studies and ranged from 0% to 1.6% (Ayou 2013, Gartland 2013, Giuliano 2013, Kesho Bora 2012, Liotta 2013, Minniear 2014, Shapiro 2010, Shapiro 2013). The average maternal mortality was 0.9% (0.85-095%). Two studies reported *progression to WHO stage 4 disease* and found that 1.5% (0.47-2.53%) of mothers progressed (Kesho Bora 2012, Minniear 2014). Four studies reported risk of *immunological failure* once ART stopped (Ekouevi 2012, Giuliano 2013, Kesho Bora 2012, Minniear 2014). The risk of falling below 350 CD4 cells/µL among women with CD4 counts above the threshold for starting ART increased with time and eventually was 36.3% in one study at 24 months (Ekouevi 2012). *Viral suppression* was reported in three studies and was an average of 89.2% after 6 months in three studies (Okonji 2012, Palombi 2014, Shapiro 2010). Women were largely *adherent*. In two studies 88.8% of women were ≥95% adherent through pregnancy and 84.3% by 6 months postpartum (Ayou 2013, Okonji 2012). Only one study reported *drug resistance* among women who were viraemic at 6 months postpartum. It found 12 (63.2%) of women who had not suppressed viral replication to have resistance markers (Palombi). Lost to follow up varied widely (Ayou 2013, Liotta 2013, Phillips 2014, Gartland 2013, Giuliano 2013, Minniear 2014). In one study of pregnant Kenyan women initiating Option B, 31.9% were lost to follow up before delivery (Ayou 2013). Other studies found average lost-to-follow up rates of 8.8% at 6 months, 19.4% at 12 months but only 8.8% at 24 months.

Infant and child mortality ranged between 5.2% and 7.2% in three studies (Thistle 2013, Minniear 2014, Shapiro 2013). Mother-to-child transmission ranged from 4.7% at 6 weeks (Kesho Bora 2011, Ngemu 2014, Thistle 2013) to 3.3% at 12 months (Gartland 2013, Kesho Bora 2011, Linguissi 2012,

Thistle 2013) to 3.4% at 24 months (Giuliano 2013, Thomas 2011) across different study sites. Four studies reported HIV-free survival, which varied from 93.2% at 3 months to 85.8% at 24 months (Nyandiko 2010, Minniear 2014, Giuliano 2013).

Option B+. The 9 Option B+ studies reported 9 outcomes. Four of these were listed as critical or important outcomes by WHO (Tables 3-4).

Maternal mortality was reported by 4 studies (Kamuyango 2014, Kim 2015, Tenthani 2015, Tweya 2014). Overall it averaged 0.7% at 6-12 months post enrolment. One study reported *virological suppression* at found that 96.0% of women were suppressed at 6 months (Speight 2013). Two studies reported adherence and found that 94.3% of women were adherent to Option B+ regimens at 6-12 months post enrolment (Kamuyango 2014, Speight 2013). Seven studies reported on *retention* between 3 and 6 months post enrolment (Coulborn 2013, Kim 2015, Lu 2015, Namukwaya 2013, Price 2013, Speight 2013, Tenthani 2013). Retention ranged from 70.0% at 6 months (Speight 2013) to 90.5% at 3 months (Coulborn 2013). Overall adherence averaged 75.7% between 4 and 6 months.

A comparison between Option B and Option B+ outcomes is shown in Table 5. While these results are not directly comparable, studies of Option B+ in general have found lower maternal mortality, higher virological suppression and better adherence. Studies of Option B have sound better retention at 4-6 months.

DISCUSSION

The information from this review contributes to the conversation on PMTCT using Option B and the benefits and challenges of implementation of Option B+. In order to make meaningful treatment recommendations we must have data that allow us to compare, on key indicators, the most current information about mother and child outcomes for Options B and B+. To date sufficient data do not exist to answer the question of whether Option B+ is the optimal prevention and treatment regimen for reducing new HIV infections in children, improving the health of mothers and decreasing sexual risk of transmission. The WHO Guidelines Development Committee defined certain primary and secondary

outcomes of interest as critical or important. Critical categories include maternal mortality, mother to child transmission/infant infection and HIV transmission to sexual partners. Important outcomes include maternal morbidity, adverse events, adherence to ART, resistance and retention (Annexe 6). Unfortunately no study that we identified addressed HIV transmission to sexual partners. We were able to identify data from a variety of studies that addressed the other outcomes both when Option B was used and when Option B+ was used. For four outcomes, data exist for both Option B and Option B+ -- maternal mortality, virological suppression, adherence and retention. These should not be directly compared but give a general idea of the outcomes associated with each intervention..

Since the recommendation to utilize Option B+, there has been a substantial increase in the number of pregnant women initiating ART (Coulborn 2013; Herce 2015; Kieffer 2014; Lu 2015; Mushabe 2014; Namukwaya 2013; Price 2014; Tenthani 2014). Kieffer and colleagues noted that during the period 2012–2013, Lesotho, Uganda, Mozambique, and Tanzania began implementation of Option B+, and large increases were immediately seen in the percentage of pregnant women accessing ART in ANC. This was particularly striking because the first programs to begin Option B+ were generally the ones with the lowest proportion of HIV-infected pregnant women receiving ART. For instance, in the southwestern region of Uganda, the percent of HIV-infected pregnant and breastfeeding women initiating ART rose from 20.5% at the end of 2012 to 89.6% by March 2014. During the same period in Gaza province, Mozambique, HIV-infected pregnant women in ANC accessing ART increased from 15.2% to 84.7%. This steep rise in ART initiation across countries suggest that implementation of Option B+ is off to a promising start. While encouraging, it has been found that upon follow-up, a number of these women are lost to follow up, where in some cases women do not return for ANC even for their first follow-up visit. Other themes that emerged that were not outcomes we initially identified but that may contribute to the ultimate success or failure of Option B+ included location and setting of services, human resources and improved data collection and monitoring systems.

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This review has limitations. The ideal review would systematically review the scientific literature and assess the effectiveness of lifelong ART versus short course ART for pregnant and breastfeeding women living with HIV as examined in well conducted RCTs. A comprehensive search was done of the literature, and three independent reviewers extracted data. We did not find any relevant RCTs or cohorts that directly compared Options B and B+ and therefore had to conduct a non-comparative review on similar outcomes. As a result, our comparison of Option B and Option B+ needs to be viewed with caution. A conservative interpretation of these data is that the two options are roughly equivalent, that is, there is no compelling evidence that one is better than the other. There are concerns around starting and stopping ART in Option B. Strategic treatment interruptions, which were examined in depth primary among people with more advanced HIV disease, were found not to be beneficial (Pai 2006). However, as pointed out by di Vincenzi and colleagues, the women who initiative Option B are for the most part healthier than participants in the structured treatment interruption trials (Kesho Bora 2012). On the other hand, there are data PACTG P1025 that inflammatory markers may decrease more rapidly in women continuing ART after delivery than women discontinuing ART (Hoffman, 2013).

We conclude that at present there is no definitive evidence that Option B+ is superior to Option B or that Option B is superior to Option B+. Additional studies are needed to understand fully the differences between the two approaches and how best to implement them. However, if universal ART for anyone with infection, regardless of clinical symptoms, degree of immunological suppression or other indications, is recommended, the focus will then need to turn to how best to implement Option B+.

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Table 1. Option B studies and results.

Author and year	Location	Outcome	n	N	Proportion	Notes
Ayou 2013	Kenya	Disengagement from antenatal care	1367	4284	31.9%	Discontinued follow up at birth
		Maternal mortality	18	4284	0.4%	
		Discontinued ART during pregnancy	10	4284	0.2%	
		Adherence during pregnancy	3030	3412	88.8%	
Ekouevi 2012	Cameroon, Côte d'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Uganda, Zambia	By 24-month decline in CD4 to <350 among women with ≥400 CD4 cells/µL at baseline	309	112	36.3%	No infant outcomes
Gartland 2013	Zambia	MTCT at 12 months	1	104	1.0%	
		Maternal death	0	104	0%	
		LTFU @ 12 mo	25	129	19.4%	
Giuliano 2013	Malawi	MTCT at 24 months	9	278	3.2%	
		By 18-month decline in CD4 to <350 among women with ≥350 cells/µL at baseline	26	126	20.6%	
		HIV free survival at 24 months	247	288	85.8%	
		Maternal mortality	1	147	0.7%	
		LTFU @24 months	47	292	16.1%	

Kesho Bora 2011	Burkina Faso, Kenya, South Africa *Women with ≥350 CD4 cells/µL at enrolment*	MTCT @ 6 weeks	5	166	3.0%	
		MTCT @ 12 months	8	144	5.4%	
Kesho Bora 2012	Burkina Faso, Kenya, South Africa *Women with ≥350 CD4 cells/µL at enrolment*	Maternal death	1	169	0.6%	
		Progression to WHO stage 4 disease	0	169	0%	
		≥1 CD4 count <350 cells/µL	43	169	25.4%	
Linguissi 2012	Côte d'Ivoire	MTCT at 12 months (?)	0	114	0%	Timing of MTCT not stated
Liotta 2013	Malawi, Mozambique *Median CD4 431 cells/µL*	Maternal death	87	8172	1.1%	
		LTFU (abandonment of care post delivery)	636	8172	7.8%	
Minniear 2014	Kenya	Maternal death	6	366	1.6%	Kisumu Breastfeeding Study
		Maternal diagnosis of tuberculosis	8	366	2.2%	
		LTFU at 24 months	8	366	2.2%	
		By 6-month decline in CD4 to <350 *among women with >500 CD4 cells/µL at enrolment*	2	131	1.5%	
		HIV free survival at 6 months	329	366	89.9%	
		Infant death	29	366	7.9%	
		MTCT at 6 months	9	366	2.5%	

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Ngemu 2014	Kenya	MTCT at 6 weeks	5	45	11.1%	Increase in mean CD4 count from 436 at baseline to 496 cells/µL at 6 months post discontinuation Decrease in VL from 17 555 to 11 324 copies/mL over same period
Nyandiko 2010	Kenya	HIV free survival at 3 months	701	752	93.2%	
		HIV free survival at 18 months	389	441	88.2%	
		MTCT at 3 months	26	733	3.6%	
		MTCT at 18 months	27	416	6.5%	
Okonji 2012	Kenya	Adherence >95% through 24 weeks postpartum	366	434	84%	Kisumu Breastfeeding Study; *Used data from Minnear 2014 for MTCT rate (among those discontinuing ART only)
		CD4 count <250 cells at 24 weeks	22	440	5.0%	
		CD4 count >500 cells from at 24 weeks	295	428	69.0%	
		Undetectable VL at 24 weeks	344	435	79.1%	
		MTCT by 24 weeks*	24	487	8.4%	
Palombi 2014	Malawi	VL >50 copies/mL at 6 months	25	260	9.6%	Analysis of all women initiating ART regardless of CD4, 23.1% had ≥500. *"Women with mutations had a lower, although not significant, baseline CD4+ count compared with those without mutations (a mean of 297 versus 474 cells/mm^3, P=0.054)."*
		HIV drug resistance	12	19	63.2%	

Phillips 2014	South Africa *Median CD4 count 233 cells/µL*	Disengagement from care by 6 months postpartum	115	358	32.1%	No differentiation by CD4 strata
Shapiro 2010	Botswana *Baseline CD4 count ≥200 cells/µL*	Maternal VL ≤400 copies/mL at delivery	530	560	94.6%	RCT comparing ZDV/3TC/ABC and ZDV/3TC/LPV/r. Results in this table do not include observational (therapeutic ART) group *Used data from Shapiro 2013
		Maternal VL <400 copies/mL at end of breastfeeding	518	560	92.5%	
		MTCT at 6 months *(also reported in Shapiro 2013)**	7	553	1.3%	
		≥1 maternal SAE	34	560	6.1%	
		Maternal death to 6 months postpartum *(also reported in Shapiro 2013)*	1	560	0.2%	
Shapiro 2013	Botswana	Maternal mortality antenatal	0	560	0%	
		Maternal mortality delivery to 6 months postpartum	1	560	0.2%	
		Maternal mortality 6-24 months postpartum	8	559	1.4%	
		Child mortality by 24 months	28	553	5.2%	
		MTCT at 6 months *(also reported in Shapiro 2010)*	7	553	1.3%	
Thistle 2013	Zimbabwe	MTCT at 6 weeks	3	67	4.4%	
		MTCT at 1 year	5	67	7.0%	

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		Neonatal mortality	5	67	7.5%	
Thomas 2011	Kenya *Women with ≥500 CD4 cells/µL at baseline*	MTCT by 24 months	6	157	4.1%	Kisumu Breastfeeding Study

Table 2. Option B outcomes by study

Outcome: Maternal mortality

Author and year	Location	Study type	n	N	%
Ayou 2013	Kenya	Retrospective cohort	18	4284	0.4%
Gartland 2013	Zambia	Prospective cohort	0	104	0%
Giuliano 2013	Malawi	Prospective cohort	1	147	0.7%
Kesho Bora 2012	Burkina Faso, Kenya, South Africa	RCT	1	169	0.6%
Liotta 2013	Malawi, Mozambique	Retrospective cohort	87	8172	1.1%
Minniear 2014	Kenya	Single arm trial	6	366	1.6%
Shapiro 2010 (antenatal)	Botswana	RCT	0	560	0%
Shapiro 2010 (at 6 months)	Botswana	RCT	1	560	0.2%
Shapiro 2013 (at 6-24 months)	Botswana	RCT	8	559	1.4%
Maternal mortality			*122*	*13802*	*0.9%*

Note: Used 9/560 for maternal deaths from Shapiro 2010 and Shapiro 2013.

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Outcome: Progression to WHO Stage 4 disease

Author and year	Location	Study type	n	N	%
Kesho Bora 2012	Burkina Faso, Kenya, South Africa	RCT	0	169	0%
Minniear 2014 (maternal diagnosis of tuberculosis)	Kenya	Single arm trial	8	366	2.2%
Progression to WHO stage 4 disease			*8*	*535*	*1.5%*

Outcome: Decline in CD4 count after discontinuing ART

Author and year	Location	Study type	n	N	%
Ekouevi 2012 (by 24-month decline in CD4 to <350 among women with ≥400 CD4 cells/µL at baseline	Cameroon, Côte d'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Uganda, Zambia	Prospective cohort	309	112	36.3%
Giuliano 2013 (by 18-month decline in CD4 to <350 among women with ≥350 cells/µL at baseline)	Malawi	Prospective cohort	26	126	20.6%
Kesho Bora 2012 (1 CD4 count <350 cells/µL)	Burkina Faso, Kenya, South Africa	RCT	43	169	25.4%
Minniear 2014 (by 6-month decline in CD4 to <350 *among women with >500 CD4 cells/µL at enrolment*	Kenya	Single arm trial	2	131	1.5%

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Outcome: Undetectable viral load

Author and year	Location	Study type	n	N	%
Okonji 2012 (at 24 weeks)	Kenya	Single arm trial	366	434	84.3%
Palombi 2014 (at 6 months)	Malawi	Prospective cohort	235	260	90.4%
Shapiro 2010 (at end of breastfeeding)	Botswana	RCT	518	560	92.5%
6-month undetectable viral load			*1119*	*1254*	*89.2%*

Outcome: Adherence

Author and year	Location	Study type	n	N	%
Ayou 2013 (pregnancy only)	Kenya	Retrospective cohort	3030	3412	88.8%
Okonji 2012 (>95% through 24 weeks postpartum)	Kenya	Single arm trial	366	434	84.3%
Adherence			*3396*	*3486*	*88.3%*

Outcome: HIV drug resistance

Author and year	Location	Study type	n	N	%
Palombi 2014 (6 months)	Kenya	Prospective cohort	12	19	63.2%
HIV drug resistance at 6 months			*12*	*19*	*63.2%*

Outcome: ≥1 maternal SAE

Author and year	Location	Study type	n	N	%
Shapiro 2010	Botswana	RCT	34	560	6.1%
≥1 maternal SAE			*34*	*560*	*6.1%*

Outcome: Lost to follow up

Author and year	Location	Study type	n	N	%
Ayou 2013	Kenya	Retrospective cohort	1367	4284	31.9%
Lost to follow up before delivery			*1367*	*4284*	*31.9%*
Liotta 2013	Mozambique	Observational	636	8172	7.8%

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Phillips 2014	South Africa	Observational	115	358	32.1%
Lost to follow up at 6 months			*751*	*8530*	*8.8%*
Gartland 2013	Zamiba	Prospective cohort	25	129	19.4%
Lost to follow up at 12 months			25	129	19.4%
Giuliano 2013	Malawi	Prospective cohort	47	292	16.1%
Minniear 2014	Kenya	Single arm trial	8	366	2.2%
Lost to follow up at 24 months			*55*	*658*	*8.4%*

Outcome: Child mortality

Author and year	Location	Study type	Timing	n	N	%
Thistle 2013	Zimbabwe	Retrospective cohort	28 days (neonatal mortality)	5	67	7.5%
Minniear 2014	Kenya	Single arm trial	12 months (infant mortality)	29	366	7.9%
Shapiro 2013	Botswana	RCT	24 months	28	553	5.2%

Outcome: HIV-free survival

Author and year	Location	Study type	Timing	n	N	%
Nyandiko 2010	Kenya	Retrospective cohort	3 months	701	752	93.2%
Minniear 2014	Kenya	Single arm trial	6 months	329	366	89.9%
Nyandiko 2010	Kenya	Retrospective cohort	18 months	389	441	88.2%
Giuliano 2013	Malawi	Prospective cohort	24 months	247	288	85.8%

Outcome: Mother-to-child HIV transmission

Author and year	Location	Study type	Timing	n	N	%
Kesho Bora 2011	Burkina Faso, Kenya, South Africa	RCT	6 weeks	5	166	3.0%
Ngemu 2014	Kenya	Retrospective cohort	6 weeks	5	45	11.1%
Thistle 2013	Zimbabwe	Retrospective cohort	6 weeks	3	67	4.4%
MTCT at 6 weeks				*13*	*278*	*4.7%*
Nyandiko 2010	Kenya	Retrospective cohort	3 months	26	733	3.6%

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MTCT at 3 months				*26*	*733*	*3.6%*
Minniear 2014	Kenya	Single arm trial	6 months	9	366	2.5%
Shapiro 2013	Botswana	RCT	6 months	7	533	1.3%
MTCT at 6 months				*16*	*899*	*1.8%*
Gartland 2013	Zambia	Prospective cohort	12 months	1	104	1.0%
Kesho Bora 2011	Burkina Faso, Kenya, South Africa	RCT	12 months	8	144	5.6%
Linguissi 2012	Côte d'Ivoire	Prospective cohort	12 months	0	114	0%
Thistle 2013	Zimbabwe	Retrospective cohort	12 months	5	67	7.5%
MTCT at 12 months				*14*	*429*	*3.3%*
Nyandiko 2010	Kenya	Retrospective cohort	18 months	27	416	6.5%
MTCT at 18 months				*27*	*416*	*6.5%*
Giuliano 2013	Malawi	Prospective cohort	24 months	9	278	3.2%
Thomas 2011	Kenya	Single arm trial	24 months	6	157	4.1%
MTCT at 24 months				*14*	*435*	*3.4%*

Table 3. Option B+ studies and results.

Author and year	Location	Outcome	n	N	Proportion	Notes
Coulborn 2013	Malawi	3-month retention	524	579	90.5%	
		5-month retention	313	393	79.6%	
Herce 2015	Malawi	Facility-level uptake of ART	2046	2121	96%	Baselines 442/1981 (42%), 32,422/48,804 (66%), 16/1157 (1%)
		Uptake of HTC	39,458	45,324	87%	
		Infant NVP prophylaxis	2121	2121	100%	
Kamuyango 2014	Malawi	12-month retention	184	190	96.8%	
		Maternal mortality	1	190	0.5%	
		Defaulted	5	190	(2.6%)	
		≥95% adherence	182	190	95.8%	
		ART regimen switched	0	190	0%	
Kim 2015	Malawi	Maternal mortality at 6 months	3	759	0.4%	
		6-month retention	598	759	78.8%	
Lu 2015	Malawi	6-month retention	1016	1365	74.4%	
Namukwaya 2013	Uganda	Accepted initiation	663	688	96%	
		Failed first appointment	129	500	20.1%	
Price 2014	Malawi	6-month retention	21	26	77.8%	1 additional patient started ART after delivery
Speight 2013	Malawi	6-month retention	1189	1698	70%	
		≥95% adherence	1118	1189	94%	
		Virological suppression at 6 months	1141	1189	96%	
		Infants PCR tested	1034	1698	60.9%	
		MTCT at 6 weeks	22	1698	1.3%	
Tethani 2014	Malawi	6-month retention	17,984	21,939	82%	*Facility-level data*
		Maternal mortality at 6 months	151	21939	0.7%	

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		6-month retention	8777	11534	76.1%	*Individual-level data, women initiating ART during pregnancy and during breastfeeding combined*
		Maternal mortality at 6 months	10	229	4.4%	*3320 pregnant women + 2037 breastfeeding women*
Tweya 2014	Malawi	Missed appointments by ≥3 weeks	2353	2930	78.3%	Of 577, 228 successfully traced. 9 died, 118 stopped ART, 67 transferred to another clinic, 13 got ARV elsewhere, 9 had ART interruptions, 7 had not started

Table 4. Option B+ outcomes by study.

Outcome: retention

Author & Year	Location	Timing	n	N	%
Coulborn 2013	Malawi	3 months	524	579	90.5%
		5 months	313	393	79.6%
Kim 2015	Malawi	6 months	598	759	78.8%
Lu 2015	Haiti	6 months	1,016	1,365	74.4%
Namukwaya 2013	Uganda	4 months	500	629	79.5%
Price 2013	Malawi	6 months	21	27	77.8%
Speight 2013	Malawi	6 months	1,189	1,698	70.0%
Tenthani 2013	Malawi	6 months	8,777	11,534	76.1%
Retention at 3-6 months			*12,414*	*16,405*	*75.7%*

Note: only the 5-month adherence datum from Coulborn 2013 was used to calculate the average.

Outcome: adherence

Author & Year	Location	Timing	n	N	%
Kamuyango 2014	Malawi	12 months	182	190	95.8%
Speight 2013	Malawi	6 months	1,118	1,189	94.0%
Adherence 6-12 months			*1,300*	*1,379*	*94.3%*

Outcome: virological suppression

Author & Year	Location	Timing	n	N	%
Speight 2013	Malawi	6 months	1,141	1,189	96.0%
6-month virological suppression			*1,141*	*1,189*	*96.0%*

Outcome: maternal mortality

Author & Year	Location	Timing	n	N	%
Kamuyango 2014	Malawi	12 months	1	190	0.5%
Kim 2015	Malawi	6 months	3	759	0.4%
Tenthani 2015	Malawi	6 months	151	21,939	0.7%
Tweya 2014	Malawi	NR	10	229	4.4%
Maternal mortality 6-12 months			*165*	*23,117*	*0.7%*

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Table 5. Option B and Option B+ outcomes.

Outcome	Option B		Option B+	
	n/N	% (95% CI)	n/N	% (95% CI)
Maternal mortality	122/13802	0.9% (0.85-0.95%)	165/23117	0.7% (0.59-0.81%)
Virological suppression at 6 months	1119/1254	89.2% (87.5-90.9%)	1141/1189	96.0% (94.9-97.1%)
Adherence at 6-12 months	366/434	84.3% (80.9-87.7%)	1300/1379	94.3% (93.0-95.4%)
Retention at 4-6 months	7779/8530	91.2% (90.6-91.8%)	12414/16405	75.7% (75.0-76.4%)

Annex 1: Core PubMed search strategy (modified and adapted as needed for use in the other databases).

#5	**Search #1 AND #2 AND #3 AND #4, Publication date from 2009/01/01 to 2015/12/31**
#4	Search (“Vertical Transmission”[MeSH] OR pmtct[tiab] OR mtct[tiab] OR "mother-to-child”[tiab] OR "mother to child"[tiab]) AND ("Option B"[tiab] OR “Option B+”[tiab] OR Option B-plus[tiab] OR lifelong[tiab] OR life-long[tiab] OR pregnan*[tiab] OR breastfeeding[tiab] OR lactating[tiab]) AND (woman[tiab] OR women[tiab])
#3	Search (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp]) OR (prospective studies[MeSH] OR control*[tw] OR volunteer*[tw] OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH]))
#2	Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or “sexually transmitted diseases, viral”[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]
#1	Search (HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])

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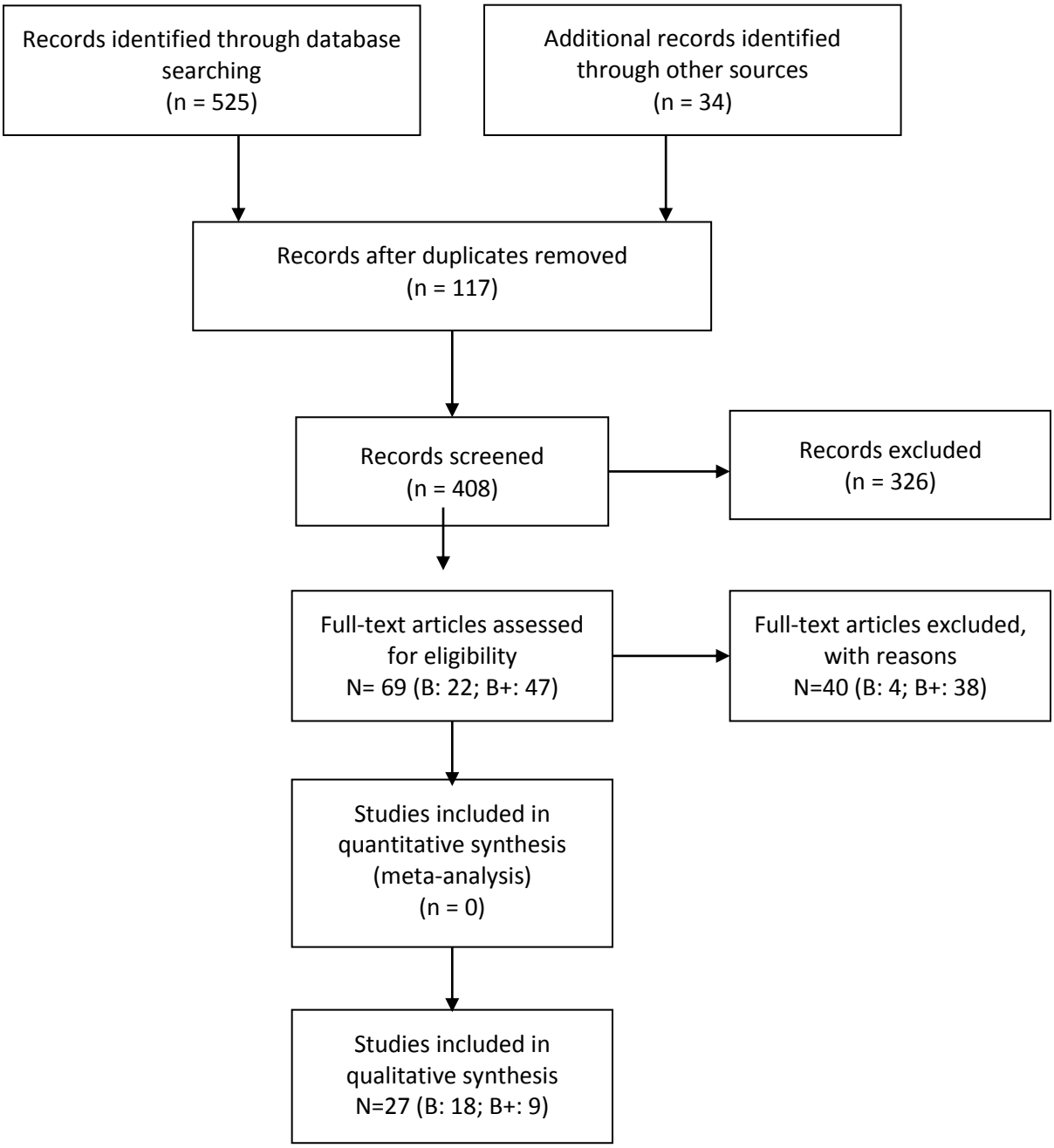
Annex 2: Flow-chart depicting screening process



Annex 3. Summary table, Option B studies

Study	Population and setting	Outcomes	Main messages / key themes
Ayuo 2013 (Retrospective cohort study)	Antiretroviral- naïve adult (≥18 years) pregnant women initiating ART from January 2006 to February 2009 within the AMPATH partnership Western Kenya	Disengagement from the programme, clinician-initiated regimen change/ stop and self-reported medication adherence	Increased age, greater gestational age at ART-initiation, receiving TB medications and care at a district hospital were associated with decreased odds of disengagement. Drugs were discontinued 1-2 weeks post partum. There is no discussion of breastfeeding and no data on post-natal transmission.
Ekouevi 2012 (Observational Study)	ART naïve, HIV positive pregnant women with enrolment CD4+ ≥250 cells/mm Cameroon, Côte d'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Thailand, Uganda, and Zambia	CD4+ decline, was defined as: 1) the 12 and 24 month cumulative probability from delivery (time when ARV prophylaxis was discontinued) to decline in CD4+ to <200 cells/mm^3 (2006 WHO recommended eligibility criteria for ART initiation) among women with enrollment CD4+ ≥250 cells/mm^3; and 2) the 12 and 24 month cumulative probability from delivery to decline in CD4+ to ,350 cells/ mm^3 (current WHO recommended eligibility criteria for ART initiation) among women with enrollment CD4+ ≥40 cells/mm^3	Decline in CD4+ cell count to ART eligibility thresholds by 24 months postpartum was common among women receiving PMTCT prophylaxis during pregnancy and/or delivery. Women with ≥350 cells/µL at baseline who received triple ARV prophylaxis were more likely to decline to <350 cells/µL by 24 months than women who received ZDV+3TC (36.3% v 21.5%)
Gartland 2013 (Prospective Cohort Study)	• HIV-infected pregnant women at ≥28 weeks gestation	(1) Infant HIV infection and (2) infant HIV infection or death, measured at 6 weeks, 6 months, and 12	Compared to combination ART prophylaxis during pregnancy and breastfeeding, Option A (short-course antenatal ZDV and

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	initiating PMTCT services between April 2009 and January 2011 and their newborn infants • Nine primary care clinics in rural Zambia	months postpartum	peripartum NVP) was associated with a higher rate of infant HIV infection (RR=12.6, 95% CI 2.2-73.1) and with infant HIV infection or death (RR=3.4, 95% CI 1.6-7.6). Similar RR were observed among infants whose mothers had CD4 cell counts >350 cells/µL. These measureable improvements in infant outcomes support the expansion of ART prophylaxis to all women irrespective of CD4 count, as is recommended in the WHO's Option B PMTCT policy.
Giuliano 2013 (Observational Study)	• HIV positive pregnant women older than 16, naïve to antiretrovirals (with the exception of single-dose nevirapine), willing to breastfeed up to 6 months with no grade 3 or 4 laboratory toxicity and no active tuberculosis • Malawi	Determinants of residual HIV transmission to HIV-positive pregnant women on ART Infant safety Impact on maternal disease	HIV transmission to infants occurred in a high proportion among women with high CD4+ counts. Strategies to improve adherence are needed to reduce transmission. Mortality in uninfected exposed children was the major determinant of HIV-free survival and was associated to maternal disease stage. Among women who had stopped treatment the risk of progression to CD4+ count < 350/mm3 was 20.6% (95% CI 9.2-31.9) by 18 months of drug discontinuation. Lifelong ART for HIV infected pregnant women should be considered as a high proportion if progression is this rapid.
Kesho Bora	• HIV-infected	Cumulative rate of HIV	Maternal triple ARV prophylaxis

Study Group / Vincenze 2011 (RCT)	pregnant women with clinical stages 1, 2 or 3 and 200-500 CD4 cells/µL • Burkina Faso, Kenya and South Africa	transmission	reduced the risk of MTCT of HIV by 43% at 12 months compared with a standard ZDV/sdNVP regimen. Triple ARV prophylaxis was not associated with significant increases in ARV-related SAEs in mothers or babies compared with ZDV/sdNVP prophylaxis.
Kesho Bora Study Group / Vincenze 2012 (RCT)	• HIV-infected pregnant women with clinical stages 1, 2 or 3 and 200-500 CD4 cells/µL • Burkina Faso, Kenya and South Africa	Maternal mortality, CD4, viral load	No difference in risk of progression among women who received and stopped triple ARV (Option B) and those who received ZDV/sdNVP at 24 months postpartum.
Linguissi 2012 (Observational Study)	• Women attending antenatal service • Burkina Faso	Efficacy of HAART in PMTCT Diagnosis of HIV-1 infection in infants born to seropositive mothers and pregnant women with undetermined serology	The prevalence of HIV-1 by PCR was 0.00% (0/114) and 6.82% (18/264) in children born from mothers under HAART and those under prophylaxis, respectively ($P<0.01$). HIV-1 transmission was significantly reduced in children born from HIV-positive mothers under HAART compared with those whose mothers were under prophylaxis.
Liotta 2013 (Retrospective observational cohort)	• HIV-infected pregnant women initiating HAART during pregnancy • DREAM centers for prenatal care in Malawi and Mozambique	Maternal mortality, CD4	Higher mortality in mothers with shorter antenatal HAART: 2.2% if <30 days; 0.9% if ≥31 days. Higher survival rate when treatment initiated earlier in pregnancy (as compared across women who received HAART less than a month prior to delivery, 1-3 months prior to delivery, and more than 3

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			months prior to delivery).
Minnear 2014 (Kisumu Breastfeeding Study)	• ARV-naïve women at PMTCT clinics in New Nyanza Provincial General Hospital and the Kisumu District Hospital received tARV-PMTCT from 34 weeks' gestation until 6-months PP • Kisumu, Kenya	Maternal tuberculosis, maternal mortality, infant HIV infection, infant death, LTFU from 6mos to 24 mos postpartum.	Similar to Kesho Bora study, women who discontinued tARV had a rapid decline in CD4. <u>During the first 3 months after discontinuation:</u> Group A: (<500/≥500) recorded -61 cells/mm^3/month; Group B: (≥500/≥500) -32 cells/mm^3/month, and Group C: (<500/350-500) -5 cells/mm^3/month. <u>Between 3-18 months after discontinuation:</u> CD4 decline for all three groups plateaued (Group A & B: -4 cells/mm^3/ month; Group C: -3 cells/mm^3/month). Note that women who initiated tARV with CD4<500 cells/µL and discontinued with CD4≥500 cells/µL were still at significant risk of being eligible for treatment within 6 months of stopping treatment, compared to women who initiated tARV with CD4≥500 cells/µL. Infants of mothers who discontinued treatment were more likely to become HIV-infected or die. Early initiation of cART benefits both mothers and infants. Discontinuing treatment was significantly associated with risk of HIV infection and death within the first 6 months of after

			the mother stopped antiretrovirals.
Ngemu 2014	• 50 HIV-infected women accessing prenatal and postnatal services at DREAM centre which provides comprehensive and holistic care • Nairobi, Kenya	Maternal CD4, viral load, infant HIV transmission	Higher mean absolute CD4 count (Z = 15.664, p < 0.001) and lower viral load in mothers (Z = 11.324, p < 0.001) 6 months post-HAART, with 90% of children confirmed to be HIV-uninfected 6 weeks post-delivery.
Nyandiko 2010	• HIV-infected women across 18 HIV clinics • Western Kenya	Infant HIV status and mortality at 3 and 18 months	Significant reduction in infant HIV infection and death was documented at both the 3-month (MTCT = 3.2%) and 18-month (MTCT = 6.5%) time points for infants whose mothers received antiretroviral prophylaxis, with prenatal cART conferring a greater benefit than sdNVP.
Okonji 2012 (Kisumu Breastfeeding Study)	• ARV-naïve women at PMTCT clinics in New Nyanza Provincial General Hospital and the Kisumu District Hospital received tARV-PMTCT from 34 weeks' gestation until 6-months postpartum • Kisumu, Kenya	Adherence, viral load, CD4 count	Cumulative adherence was 84% (n=336), with small variations during specific times: 78% (n = 339) between initiation - delivery, 83% (n = 360) between the delivery -14 weeks postpartum, and 84% (n = 366) between 14 -24 weeks postpartum. Median CD4 count: 394 cells/µL (baseline), 463 cells/µL (delivery), 646 cells/µL (14 weeks PP), and 654 cells/µL (24 weeks PP). Good virologic suppression with most (82%) women who were adherent to treatment achieving

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			an undetectable viral load by 24 weeks postpartum, which may have contributed to low postnatal–associated HIV-1 transmission during breast-feeding in this study (see below). 24 HIV-infected infants by end of 24 weeks (12/24 at 1 week; 8/24 at 1-14 weeks; 4/24 at 14-24 weeks PP). (Mothers who initiated maternal NFV-based triple ARV prophylaxis were more likely to achieve viral suppression at delivery and at 24 weeks postpartum than participants initiated on NVP-based ARV.)
Palombi 2014	• Treatment-naïve pregnant women receiving three-drug nevirapine-based regimen from 25 weeks gestation up to 6 months after delivery • Malawi	Viral load, adherence	<u>At 6 months:</u> 211/260 (81.2%) women did not miss any visits; 49/260 (18.8%) missed ≥1 visit. 235/260 (90.4%) of women had undetectable viral load. Detectable HIV RNA 6 months post-partum was associated with low adherence to the treatment program.
Philips 2014 (Retrospective cohort study)	• Pregnant women initiating ART • Cape Town, South Africa	Disengagement at 6 months follow-up	Missed visits (returning to care 14-56 days late for a scheduled visit) and disengagement (no attendance within 56 days of a scheduled visit) occur frequently, particularly postpartum. 115/358 (32.21%) had

			disengaged from care; 243/358 (67.9%) still in care or transferred out. Being newly diagnosed is a significant predictor for disengagement from care.
Shapiro 2010	• HIV-infected women (CD4≥200 cells/µL and CD4<200 cells/µL) on treatment from week 26 to 34 gestation up to 6 months postpartum • Botswana	Virologic suppression, MTCT	All three regimens of HAART from pregnancy up to 6 months postpartum resulted in high rates of virologic suppression, with overall rate of MTCT of 1.1%. Maternal VL ≤400 copies/mL at delivery (94.6%); maternal VL ≤400 copies/mL at end of breastfeeding (92.5%)
Shapiro 2013	• HIV-infected women (CD4≥200 cells/µL and CD4<200 cells/µL) on treatment from week 26 to 34 gestation up to 6 months postpartum • Botswana	Maternal mortality, CD4 count, infant HIV transmission	Time to maternal death for women CD4 <200 cells/µL was shorter in the triple nucleoside reverse transcriptase inhibitor (NRTI) arm than the protease inhibitor arm, and a concerning number of maternal deaths occurred after stopping HAART used for PMTCT. Maternal mortality antenatal (0%), delivery-6mos postpartum (0.2%), 6-24mos (1.4%). Child mortality at 24 months was reported as 28/553 (5.2%).
Thistle 2011	• HIV-infected pregnant women initiated on HAART up to 6 months PP • Salvation Army	Infant HIV transmission	Significant reduction of HIV vertical transmission at 6 weeks postpartum: MTCT at 6 weeks (4.4%); 12 mos (7.0%). Neonatal mortality was reported at 7.5%

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	Howard Hospital, 85 km north of Harare, Zimbabwe		Feasible approach to PMTCT even during a socio-economic crisis.
Thomas 2011 (Kisumu Breastfeeding Study)	• ARV-naïve women at PMTCT clinics in New Nyanza Provincial General Hospital and the Kisumu District Hospital received tARV-PMTCT from 34 weeks' gestation until 6-months PP • Kisumu, Kenya	Infant HIV transmission, maternal CD4, viral load, adherence	MTCT by 24 months reported at 4.1%. Suggests that maternal triple-ARV regimen from late pregnancy through 6 months of breastfeeding postpartum is safe and feasible.

Annex 4. Summary Table for Option B+ studies

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Study	Population and setting	Outcomes	Main messages / key themes
Coulborn 2013	• Government health facilities • Thyolo district, Malawi	3-mos and 5-mos follow-up after ART initiation	AT 3-month follow-up, 9.5% did not return after ART initiation; at 5-month follow-up, 20.4% did not return after ART initiation.
Herce 2015	• Safeguard the Family (STF): facility-level quality improvement interventions • Central Malawi	Uptake of infant prophylaxis	Increase of 1% to 100% of infant NVP prophylaxis.
Hoffman 2013	• HIV-infected women enrolled in P1025 during pregnancy who initiated ART during pregnancy. 128 women studied, 65 were continuers and 63 were discontinuers. • United States and Puerto Rico	Biomarkers of inflammation and coagulation: highly sensitive C-reactive protein (hsCRP), IL-6, and D-dimer	In this cohort of HIV-infected women with high CD4 counts, postpartum biomarkers markedly declined among all women, regardless of ART status.
Kamuyango 2014	• HIV+ pregnant women at three health facilities • Central and Southern Malawi	Maternal mortality, adherence, default, ART switch	Higher proportion of women documented as defaulting on treatment (2.6%) and having incomplete adherence outcomes (4.2%) in the Option B+ cohort compared to the pre-Option B+ cohort; however these differences were not significant. Women initiating Option B+

Study	Population and setting	Outcomes	Main messages / key themes
			have less advanced HIV infection, improved medication tolerability, and lower mortality.
Kim 2015	• HIV+ pregnant women enrolled in Tingathe PMTCT program at ANC MOH clinics • Urban health centers in Lilongwe, Malawi	Maternal mortality, 6-month retention	At 6 months after initiation, 89.3% pre B+ vs. 78.8% Option B+ were reported as alive an on ART (p<0.0004); 5.8% vs. 11.2% were lost-to-follow-up (p=0.02); 2.2% vs. 8.2% (p=0.002) had stopped ART.
Lu 2015	• Health facilities using iSanté • Haiti	6-month retention	Lower retention rates among women initiating ART during pregnancy (74.4%) compared to non-pregnant adults (81.5%).
Namukwaya 2013	• HIV-infected pregnant women at Mulago Referral Hospital • Kampala, Uganda	ART initiation, follow-up (retention)	79.5% of women who initiated Option B+ at ANC visited clinic at least once prior to delivery; however, the remaining (20.5%) is seen as high, particularly since they did not return after their initial visit to ANC.
Price 2014	• Demographic Surveillance Site (DSS) • Karonga, Malawi	ART initiation, 6-month retention, stopping treatment.	Retention at 6 months reported at 77.8%; 18.5% stopped ART. Nearly half were initiated on-site at ANC clinic.
Speight 2013	• HIV-infected pregnant mothers at ANC, with ongoing	ART initiation, 6-month retention, adherence, viral load	Retention rate at 6 months was reported at 70%. Of those in care, 94% had >95% adherence, and 96% had

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Study	Population and setting	Outcomes	Main messages / key themes
	support by Mothers-2Mothers • Bwaila Maternity Unit • Lilongwe, Malawi		virally suppressed at 6 months and beyond. Of known defaulters, half (255/509) did not return after initial visit.
Tenthani 2014	• Facility-level data across Malawi • Individual patient level data Central and Southern Malawi	Facility level: 6-month retention, LTFU, maternal mortality, stopped ART Patient-level: Maternal mortality, LTFU	High rates of early LTFU for both pregnant (29.4%) and breastfeeding (16.1%) HIV-infected women after 6 month ART initiation. Aggregated national data reported retention at 82%. Maternal mortality was reported at 0.4% among pregnant women, and 0.7% among breastfeeding women. Aggregated national data reported mortality among HIV-infected women at 0.7%.
Tweya 2014	• HIV-infected pregnant and breastfeeding women who missed their appointment traced to ascertain true outcome • ANC clinic, Bwaila Hospital • Lilongwe, Malawi	Maternal mortality, stopped treatment, self-transferred out, on treatment, interrupted treatment, not started	20% (577/2930) of women were LTFU. Having successfully traced 229/577, it was reported that 4.3% died. Of those alive, 53.9% self-transferred, 30.6% received drugs from other sources. Both outcomes highlight that “lost” patients are indeed alive and on treatment.

Annex 2.2.2 Option B+ vs Option B for improving outcomes for women with HIV infection and their infants: a systematic review

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Annex 5: Studies excluded after full-text review, with reasons for exclusion.

Study	Reason for exclusion
Besada 2012	Review; no intervention
CDC 2013	Review; no intervention
Chi 2014	Intervention was not Option B+ (it was a modified Option B approach)
Claessens 2014	Study protocol
Cohan 2013	Study looks at cART switch from LPV/r or EFV to NVP on dermatologic toxicity
Fasawe 2013	Cost-effectiveness modeling study
Gopalappa 2014	Cost-modeling study
Ishikawa 2014	Cost impact study
Kieffer 2014	Review; no intervention.
CDC 2013	Review; no intervention.
Kim 2013	Intervention was Option A
Liu 2013	Review; no intervention
Mahy 2010	No intervention
Mangwiro 2014	Assessment of point-of-care tool
Moodley 2013	Intervention was not Option B.
Mushambe 2014	Insufficient detail provided to calculate patient-level outcomes (B+)
Mwapasa 2014	Study assessed SMS messaging as a tool in Option B+
Ngarina 2014	Qualitative study
Ngarina 2015	Intervention was not Option B
O' Brien 2014	Cost-modeling study
Paredes 2013	Review; no intervention
Parker 2015	Study did not report on primary or secondary outcomes we listed
Schwartz 2015	Study assessed tool in Option B+
Stevens 2014	Review; no intervention
Stover 2014	Review; no intervention
Taha 2011	Review; no intervention
van Lettow 2011	Intervention was not Option B
van Lettow 2014	Insufficient detail provided to calculate patient-level outcomes (B+)
van Schalkwyk 2013	Review; no intervention

Annex 6: Table of outcomes addressed by studies.

	Coulborn 2013*	Dryden-Peterson 2015	Gartland 2013	Giuliano 2013	Herce 2015[i]*	Hoffman 2013[ii]	Kamuvango 2014	Kesho Bora SG / Vincenze 2011	Kesho Bora SG / Vincenze 2012	Kim 2015*	Liotta 2013	Lu 2015*	Minnear 2014	Mushabe 2014*	Namukwaya 2013*	Ngemu 2014	Nyandiko 2010[iii]	Okonji 2012	Palombi 2014	Philips 2014	Price 2014*	Shapiro 2010	Shapiro 2013	Speight 2013	Tenthani 2014*	Thistle 2011	Thomas 2011	Tweya 2014	van Lettow 2014
Primary Outcomes																													
Maternal mortality							x			x	x		x										x		x			x	
Maternal morbidity																													
Adverse events							x	x	x																				
Adherence to ART (as measured by investigators)							x											x	x					x			x		
Mother-to-child transmission / Infant HIV infection	x	x	x	x				x					x			x	x					x	x	x		x	x		
HIV transmission to sexual partners																													
Development of antiretroviral resistance																													
Retention in treatment	x						x			x		x	x	x	x					x	x			x	x			x	x
TB incidence													x																
Fertility rate																													
Maternal CD4 or clinical staging	x			x							x					x		x					x				x		

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	Coulborn 2013*	Dryden-Peterson 2015	Gartland 2013	Giuliano 2013	Herce 2015[i]*	Hoffman 2013[ii]	Kamuvango 2014	Kesho Bora SG / Vincenze 2011	Kesho Bora SG / Vincenze 2012	Kim 2015*	Liotta 2013	Lu 2015*	Minnear 2014	Mushabe 2014*	Namukwaya 2013*	Ngemu 2014	Nyandiko 2010[iii]	Okonji 2012	Palombi 2014	Philips 2014	Price 2014*	Shapiro 2010	Shapiro 2013	Speight 2013	Tenthani 2014*	Thistle 2011	Thomas 2011	Tweya 2014	van Lettow 2014
(when initiated Option B)																													
Maternal viral load																x		x	x			x		x			x		
Secondary Outcomes																													
Sustainability of service delivery																													
Acceptability to women															x														

[i] Reported on HTC among pregnant women, Option B+ treatment uptake, NVP prophylaxis uptake among HIV-exposed infants

[ii] Reported on biochemical outcomes, i.e., biomarkers of inflammation and coagulation.

[iii] Also reported on infant mortality at 3 and 18 months

* Coulborn 2013, Herce 2015, Kim 2015, Lu 2015, Mushabe 2014, Namukwaya 2013, Price 2014, Tenthani 2014 also reported on Option B+ initiation.

Note: **Bolded outcomes** have been voted as "critical" outcomes of interest by the WHO GDG.

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Oral pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis of effectiveness, safety, and sexual and reproductive health outcomes

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Abstract

Background: Over the past 5 years, results from several randomized trials have demonstrated varying levels of effectiveness of oral PrEP in reducing risk of HIV infection. Recent WHO guidelines have recommended the use of oral PrEP for certain populations, but not all, despite an expanding evidence for efficacy among diverse populations. This systematic review and meta-analysis sought to evaluate the evidence for use of oral PrEP as an additional prevention choice for HIV prevention across populations regarding the following outcomes: HIV infection, any adverse event, any grade 3 or 4 adverse event, antiretroviral drug resistance, and sexual and reproductive health outcomes, including contraception effectiveness, adverse pregnancy-related events, condom use, and number of sexual partners.

Methods: A comprehensive search strategy reviewed three electronic databases and multiple HIV-related conferences from January 1990 through April 2015. Pooled effect estimates from eligible studies were calculated through conducting meta-analysis. Results were analysed using GRADE.

Results: Of 3,068 citations screened, 17 studies were included in the review, comprising data from 39 peer-reviewed articles and 6 conference abstracts. Across various populations and PrEP regimens, PrEP significantly reduced the risk of HIV infection as compared to placebo (RR=0.49, 95% CI: 0.33 to 0.73, p=0.001) and to no-PrEP (RR=0.15, 95% CI: 0.05-0.46, p=0.001). Trials with adherence levels of ≥80% demonstrated higher PrEP effectiveness (RR=0.30, 95% CI: 0.21-0.45, p<0.0001) as compared with trials with moderate or low adherence. Rates of adverse events and grade 3 or 4 adverse events did not differ between PrEP and placebo groups. More cases of drug resistant HIV infection were seen among PrEP users who initiated PrEP while acutely infected with HIV, but the overall incidence of acquiring drug resistant HIV was not significantly higher for PrEP users compared to placebo groups. Studies consistently found no association between PrEP use and changes in sexual risk behaviour. PrEP was not associated with increased adverse events related to pregnancy and hormonal contraceptive efficacy was not significantly different after adjusting for confounding factors.

Conclusions: PrEP is protective against HIV infection across populations, presents few significant safety risks, and no evidence of behavioural risk compensation. The effective and cost effective use of PrEP will require the development of best practices for fostering uptake and adherence among diverse people at substantial risk of acquiring HIV infection.

Introduction

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medications by HIV-uninfected individuals to block the acquisition of HIV infection. Over the past 5 years, several randomized trials have demonstrated varying levels of effectiveness of oral PrEP in a variety of populations worldwide. In 2012, WHO developed guidance which recommended PrEP for use among serodiscordant couples, men who have sex with men, and transgender people with the conditionality that demonstration projects were needed to ascertain optimal delivery approaches and target groups[1]. In 2014, WHO developed consolidated HIV guidelines for key populations, including men who have sex with men, people who inject drugs, sex workers, and prisoners[2]. However, no recommendation on the use of PrEP was made for female sex workers and people who inject drugs. Additionally, no recommendations have been made for other populations who could benefit from oral PrEP, including women and heterosexual men at elevated risk of HIV acquisition who do not identify a HIV-infected partner. As experience with PrEP in diverse populations has become available from clinical trials, demonstration projects, and clinical practice, WHO is ready to consider the evidence and develop recommendations and guidance for PrEP among all populations at substantial risk of HIV infection.

The goal of this work is to conduct a systematic review and meta-analysis of the effectiveness of PrEP for people at substantial risk of HIV infection, and to conduct a systematic literature review of community values and preferences for PrEP to answer the following the PICO question:

Should oral PrEP (containing tenofovir (TDF)) be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches?

P: People at substantial risk of HIV infection,
I: Oral PrEP (containing tenofovir (TDF)),
C: 1) placebo and 2) non-use of PrEP (or no use),
O: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) drug resistance (among those initiating PrEP while acutely infected and among those who seroconvert after PrEP initiation), and 5) sexual and reproductive health outcomes, including 5a) hormonal contraception effectiveness, 5b) any adverse pregnancy event, 5c) condom use, and 5d) number of sexual partners.

Methods

Inclusion criteria

To be included in the review, an article or conference abstract had to meet the following criteria:

1) Randomized controlled trial or open-label extension/PrEP demonstration project evaluating the use of oral PrEP (containing tenofovir (TDF)) to prevent HIV infection among people at substantial risk of HIV infection.
2) Measured one or more of the key outcomes outlined in the PICO questions as listed above, comparing those randomized to oral PrEP versus placebo or comparing those receiving oral PrEP versus none use of PrEP (e.g., delayed use of PrEP).
3) Published in a peer-reviewed journal or presented as an abstract at a scientific conference between January 1, 1990 and January April 15, 2015.

No restrictions were placed based on location of the intervention, and no language restrictions were used in the search. No eligible articles in languages other than English were identified. Authors of studies were contacted for clarification on study outcomes when needed.

Following the GRADE approach, randomized controlled trials and high-quality observational studies that presented evidence for similar outcomes were stratified by quality of evidence (e.g., randomized trials vs. observational studies) and presented in two separate rows of the GRADE table. Similarly,

studies with different comparators (placebo or non-PrEP use) were stratified in GRADE and included in separate rows of the final GRADE tables.

Search strategy including search terms and information sources

The following electronic databases were searched using the date ranges January 1, 1990 to April 15, 2015: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EMBASE. Iterative secondary reference searching was also conducted on all studies included in the review until no new studies were identified. Further, selected experts in the field were contacted to identify additional articles not identified through other search methods.

Abstracts from the following conferences were searched: International AIDS Conference (IAC), Conference on HIV Pathogenesis, Treatment, and Prevention (IAS), and Conference on Retroviruses and Opportunistic Infections (CROI). Only abstracts from CROI 2014 and 2015 were available, thus the search was restricted to these two conferences. For IAS/IAC, conferences from 2006- 2014 were searched.

Search terms

The following terms were entered into all computer databases:

("pre-exposure prophylaxis" or "preexposure prophylaxis" or "antiretroviral prophylaxis" or "preexposure chemoprophylaxis" or chemoprevention or PrEP) AND (HIV OR AIDS)

These search terms were used both for the main systematic review (PICO question) and for the values and preferences review.

Screening abstracts

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by a member of the senior study staff. Full text articles were obtained of all selected abstracts and two independent reviewers assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus and through contacting study authors for clarification when necessary.

Citations identified through computer database searching were initially screened into the following categories:

- **Yes** – Used when the article appears to meet the inclusion criteria for the review.
- **Pull to check** – Used when the article may or may not meet the inclusion criteria, and the full text of the article must be reviewed before a final decision about inclusion can be made.
- **No** – Used when the article clearly does not meet the inclusion criteria for the review and no further consideration is necessary.
- **Values and Preferences** – Used when the article does not meet the inclusion criteria for the main review (PICO question), but does meet criteria for the values and preferences review (described below). Values and Preferences will be further categorized by the sub-population involved, including: 1) men who have sex with men; 2) transgender people; 3) women; 4) heterosexual men; 5) sex workers; 6) people who use drugs; 7) serodiscordant couples, 8) young people, etc.
- **Background** – Used when the article clearly does not meet the inclusion criteria for the review, but presents potentially relevant information. Background studies will be further subdivided into categories based on the type of information they provide, including: 1) review articles; 2) qualitative studies; 3) cost or cost-effectiveness analyses; 4) intervention descriptions without an evaluation component; and 5) drug/pharmacokinetic studies. An annotated bibliography of background articles will be created with citation information and abstracts.

Data extraction and management

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior study team member from WHO when necessary.

The following information was gathered from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; description of the intervention; study design; sample size; follow-up periods and loss to follow-up
- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

For randomized controlled trials, risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook, chapter 8.5 – Higgins & Green, 2011). This tool assessed random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) blinding of outcome assessment (detection bias), incomplete outcome data addressed (attrition bias), incomplete outcome data, and selective reporting (reporting bias). Methodological components of studies were assessed and classified as high, low, or uncertain risk of bias.

Data Analysis

Data were analyzed according to coding categories and outcomes. Where there were multiple studies reporting the same outcome, meta-analysis was conducted using random-effects models to combine odds ratios or risk ratios with the program Comprehensive Meta-Analysis v3.0 (CMA). When meta-analysis was warranted, sensitivity analyses were conducted in CMA to assess the robustness of findings by running the primary analysis with and without certain studies based on various characteristics, including overall adherence levels. Data were summarized in GRADE tables, summary of finding tables, and risk/benefit tables.

Because this review covers multiple populations, drug regimens, drug dosing, and comparators, we developed a list of *a priori* sub-group analyses to conduct. Prior to conducting these analyses, we evaluated the credibility of each sub-group analysis based on the following characteristics as recommended by the GRADE process[3]:

- Is the subgroup variable a characteristic specified at baseline (in contrast with after randomization)?
- Is the subgroup difference suggested by comparisons within rather than between studies?
- Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?
- Did the hypothesis precede rather than follow the analysis, and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a small number tested?
- Is the subgroup difference consistent across studies and across important outcomes?
- Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?

The sub-group analyses evaluated include:

1. Sex of study participants (males vs. females)
2. Age of study participants (<25 vs. ≥25)
3. Primary mode of sexual HIV acquisition (rectal vs. vaginal/penile exposure)

4. Adherence to study drugs (based on overall drug detection levels in blood specimens)
5. PrEP dosing (daily vs. intermittent PrEP)
6. PrEP regimen (TDF vs. FTC/TDF)

Results

Description of included studies

The search identified 3,900 citations from the database search, 296 conference abstracts, and 2 citations identified through contacting experts and secondary searching. After duplicates were removed, a total of 3,068 citations were screened. Of these, full texts were obtained for 434 articles and the rest were excluded. Of retained sources, 26 were excluded due to not meeting the inclusion criteria, 175 were categorized as background articles/abstracts, and 188 were categorized as pertaining to the values and preferences review. The remaining 39 articles and 6 conference abstracts covering 17 PrEP-related studies were included in the review. Figure 1 in the Appendices details the disposition of citations during the search and screening process.

Table 1 includes the characteristics of the 17 included studies. Of these 14 were randomized controlled trials (RCTs) and 3 were from observational open-label extension projects (OLE) that began following RCTs with demonstrated PrEP effectiveness[3-5]. Of the 14 included RCTs, seven were double-blind placebo-controlled trials testing the efficacy and safety of daily PrEP, either in the form of tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC)[6-12]. Populations for these trials included people who inject drugs, serodiscordant couples, women, men who have sex with men (MSM) and transgender women, women, and heterosexual men. The trials mostly took place in low- and middle-income (LMIC) settings, with the exception of iPrEx, which took place in both high-income and LMIC sites.

One trial among MSM in England randomized participants to receive immediate or delayed FTC/TDF as PrEP (PROUD)[13], and an additional US-based trial randomized participants to receive TDF or matching placebo, immediately or after 9-month delay (CDC Safety Study)[14]. Another trial among young MSM in the US compared daily PrEP to both placebo and “no-pill” arms[15]. Several trials examined alternative dosing strategies for PrEP. A trial among 400 participants in France and Canada randomized participants to receive “on-demand” FTC/TDF (taken before and after each sexual intercourse) or placebo[16]. Two small studies (n=72 in each) examined the safety and adherence of both daily and intermittent PrEP or placebo among MSM and female sex workers in Kenya and among HIV-negative partners involved in HIV serodiscordant relationships in Uganda[17, 18]. An open-label randomized controlled trial in South Africa is currently examining different PrEP dosing strategies among women randomized to daily, time-driven, and event-driven PrEP[19].

In total, the included studies have involved over 15,000 participants across different settings and populations, with follow-up times ranging from 4-months to 4.2 years. This systematic review includes studies with data available on at least one of the eight outcomes presented in the PICO question; however, it is important to note that there are currently many additional PrEP demonstration projects underway[20].

Quality assessment for included studies (Risk of Bias)

A summary of the risk of bias across the included RCTs is presented in Table 2. Using the Cochrane Risk of Bias tool, the studies were mostly judged to have low risk of bias across the following categories: random sequence generation (selection bias), allocation concealment (selection bias),

blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) (patient-reported outcomes), blinding of outcome assessment (detection bias) (non-patient reported outcomes), incomplete outcome data addressed (attrition bias), and selective reporting (reporting bias). Several studies (Bangkok Tenofovir, CDC Safety Study, Ipergay, Project PrEPare, and VOICE) had unclear risk for reporting bias, either because the study protocol were not publically available or only preliminary results (in the form of conference abstracts) were available to date, so not all primary and secondary endpoints have been reported in full. Two studies (Project PrEPare and PROUD) had unclear risk of bias for performance and detection bias, because in one study this information was not reported (Project PrEPare) and in the other (PROUD), it was deemed that knowledge of randomization to immediate versus delayed PrEP arm by participants may have affected performance and reported behaviours. In addition, it was noted that overall adherence levels to study drug were very low in two studies (FEM-PrEP and VOICE). While no study achieved perfect adherence, the exceptionally low adherence rates seen in these two studies may have impacted their ability to answer the primary research question relating to PrEP effectiveness.

HIV infection

HIV infection was measured in 11 RCTs comparing PrEP to placebo, three RCTs comparing PrEP to no PrEP (e.g., delayed PrEP or "no pill"), and three observational studies. Two of these studies were not included in meta-analysis because no HIV infections occurred (IAVI Uganda and Project PrEPare), thus these studies did not contribute any data to the effectiveness analysis. Across data from 10 trials comparing PrEP to placebo, results from meta-analysis demonstrated a 51% reduction in risk of HIV infection comparing PrEP to placebo (RR=0.49, 95% CI: 0.33 to 0.73, p=0.001). Results for the overall analysis and all sub-group analyses are presented in Table 3 and Figure 2.

When all studies were analysed together, results produced significant heterogeneity (I^2= 70.9). Results from meta-regression, which was conducted to evaluate whether certain variables moderated the effect of PrEP on reducing risk of HIV infection, demonstrate that adherence is a significant moderator (regression coefficient= -0.02, p<0.0001). This relationship holds whether adherence is measured continuously or categorically (results presented in Figures 3 and 4, respectively). When studies were stratified according to adherence levels (high, medium, and low), heterogeneity was greatly reduced (I^2=0) within adherence sub-groups, thus demonstrating that most heterogeneity between studies can be explained by adherence. Within adherence sub-groups, PrEP is most efficacious among the high adherence group (defined as ≥70% drug detection but all studies in this group had adherence ≥80%) and reduces risk of HIV infection by 70% (RR=0.30, 95% CI: 0.21-0.45, p<0.0001). PrEP also significantly reduces risk of HIV infection among studies with moderate levels of adherence (40 to 70% drug detection). Among studies with low adherence (<40% drug detection), PrEP shows no effect in reducing HIV infection (RR=0.95, 95% CI: 0.34-1.23, p=0.70).

When studies were stratified by mode of acquisition (e.g., primarily rectal or vaginal/penile exposure), PrEP showed similar effectiveness across groups (regression coefficient= 0.47, p=0.36). Results demonstrating risk of HIV infection across modes of acquisition are presented in Figure 5. The relative risk for HIV infection comparing PrEP to placebo for rectal exposure is 0.34 (95% CI: 0.15-.80), p=0.01. For penile/vaginal exposure, the relative risk of HIV infection comparing PrEP to placebo is 0.54 (95% CI: 0.32-0.90), p=0.02.

Across other sub-group analyses, PrEP remained significantly protective against HIV infection. There was no significant difference in reduction in risk of HIV infection due to PrEP between gender, PrEP regimens, and PrEP dosing, although data for intermittent PrEP and HIV infection is limited to two

studies. For age, only three studies provided data based on the age comparison established *a priori* of <25 years and ≥25 years (FEM-PrEP, Partners PrEP, and iPrEx). In meta-regression, results demonstrate that age was an insignificant moderator of the relationship between PrEP and HIV infection (regression coefficient= 0.45, p=0.29, results presented in Figure 6); however, in stratified analysis PrEP was not statistically efficacious for younger participants (RR=0.71, 95% CI: 0.47-1.06, p=0.07) across the three trials reporting data for participants <25 years of age. Several trials noted that younger participants had poorer adherence to PrEP as compared to older participants. In summary, results demonstrate that age does not moderate the relationship between PrEP and HIV infection but that less adherence to PrEP among younger participants could explain the diminished effectiveness among this population.

Among studies that compared PrEP to no PrEP, two contributed data on HIV infection (PROUD and CDC Safety Study). When meta-analysed, results show PrEP was significantly protective against HIV infection comparing those who received PrEP to those who received delayed PrEP (RR=0.15, 95% CI: 0.05-0.46, p=0.001). One study comparing daily PrEP to time-driven PrEP to event-driven PrEP found no difference in HIV incidence across study arms (ADAPT)[19].

Among observational studies, results from three open-label extension cohorts show that PrEP use is associated with reductions in HIV incidence when comparing results from the open-label extension period to either HIV incidence rates seen in the RCT-portion of the trial among the placebo group (Bangkok Tenofovir OLE) or HIV incidence comparing PrEP recipients to PrEP non-recipients (iPrEx/US-based studies OLE). In the Partners PrEP Demonstration Project, the HIV incidence rate seen in OLE participants was 0.2 infections per 100 person-years (95% CI 0.0-1.3 per 100 person-years), showing near elimination of HIV incidence when compared to a simulated counterfactual[3]. Results from these three observational studies are presented in Table 4.

Any adverse event

Ten RCTs comparing PrEP to placebo presented data on any adverse event. Risk of experiencing at least one adverse event during follow-up was common in participants in all trials. Across studies, there was no difference in rates of any adverse event comparing PrEP to placebo (RR=1.01, 95% CI: 0.99-1.03, p=0.27). Similarly, there were no differences across sub-groups, including mode of acquisition, adherence, gender, drug regimen, drug dosing, or age. Results are presented in Table 6 and Figure 7. RCTs comparing PrEP to no-PrEP and observational studies did not present data on any adverse event, so synthesis was not possible.

Any grade 3 or 4 adverse event

Eleven RCTs comparing PrEP to placebo presented results on any grade 3 or 4 adverse event. Across studies, there was no difference in rates of any adverse event comparing PrEP to placebo (RR=1.02, 95% CI: 0.92-1.13, p=0.76). There were no differences across sub-group analyses, including mode of acquisition, adherence, gender, drug regimen, or drug dosing, or age. Results are presented in Table 7 and Figure 8.

Several studies have reported small but significant decreases in renal function while taking PrEP[21, 22], although renal function has mostly returned to normal following PrEP discontinuation. Additionally, studies have reported small decreases in liver functioning while taking PrEP[7, 12] and small decreases in bone mineral density related to PrEP[23, 24], although these changes have not led to an increase in

fractures. Effects of PrEP on these specific adverse events are continuing to be monitored in ongoing demonstration projects.

Drug resistance

Six trials (Bangkok Tenovofir Study, FEM-PrEP, iPrEx, Partners PrEP, TDF2, and VOICE) reported on cases of drug resistance to either TDF or FTC, identified using standard phenotypic and genotypic laboratory assays. Results from ultrasensitive analyses were excluded in this analysis because these methods have yet to be validated for clinical use. Within the 6 trials, there were 8 infections having mutations conferring drug resistance to TDF or FTC identified among the 42 individuals who were confirmed to have had acute HIV infection at enrolment. Among individuals who seroconverted post-randomization, 7 infections having mutations conferring drug resistance to TDF or FTC were identified out of 274 cases of incident HIV infection post-randomization. Additional infections occurred having drug resistance to drugs not used in the PrEP regimen, likely due to transmitted or primary drug resistance. Definitely distinguishing between primary (transmitted) and secondary (PrEP selected) drug resistance was not possible for most infections.

Drug resistant mutations identified per trial are presented in Table 8. When comparing PrEP (any regimen) to placebo, the risk of developing/acquiring any mutation to FTC or TDF was significantly higher in the PrEP group (RR= 3.34, 95% CI: 1.11-10.06, p=0.03) among participants with acute HIV infection at enrolment. When stratified by type of mutation, the risk of developing/acquiring an FTC-related mutation for those with acute HIV infection at enrolment was significantly higher among participants who were randomized to receive FTC/TDF as compared to participants randomized to receive placebo (3.72, 95% CI: 1.23-11.23, p=0.02). Risk of developing/acquiring a TDF-related mutation was not statistically different between PrEP and placebo participants, regardless of PrEP regimen, among those who had acute HIV infection at enrolment. Results are presented in Table 9 and Figure 9.

Among participants who seroconverted post-randomization, there was a statistically insignificant increase in the proportion of new infections having any FTC- or TDF-related mutation comparing PrEP to placebo (RR= 2.27, 95% CI: 0.48-10.60, p=0.30). Results remained insignificant when stratified by type of mutation and PrEP regimen.

When comparing the proportion of infections having resistance mutations to FTC or TDF among all participants at risk of HIV infection post-randomization, meta-analysis results (Figure 10) demonstrate that there is no significant difference in risk of acquiring/developing a drug resistant HIV infection comparing PrEP to placebo arms (RR=1.74, 95% CI: 0.68-8.38, p=0.49). In other words, while the proportion of HIV infections that had markers of drug resistance were higher among those who had received FTC/TDF, the risk of drug resistant HIV infection was not different due to lower overall infection rates among those receiving PrEP. Due to the small numbers of drug resistance seen across trials, evidence in GRADE was downgraded due to imprecision.

Hormonal contraception effectiveness

Two studies reported on the effectiveness of hormonal contraception comparing participants randomized to receive active PrEP and those randomized to receive placebo (FEM-PrEP and Partners PrEP). In FEM-PrEP, use of hormonal contraception was required for trial participation. In Partners

PrEP, use of hormonal contraception was not required, but monthly study visits include contraceptive counselling and free on-site access to contraception.

When comparing risk of pregnancy among contraceptive users receiving PrEP and users receiving placebo, results from the raw data demonstrate higher rates of pregnancy for those receiving PrEP as compared to placebo (Table 11). However, because results were significantly influenced by confounders across study arms, pooled effect estimates were not generated. Instead, adjusted risk of pregnancy comparing women in PrEP and placebo groups are presented separately for the two studies (Table 10).

For the FEM-PrEP study, in a multivariate analysis, treatment assignment became an insignificant predictor of pregnancy when adjusted for age, contraception method and site [aHR (95% CI): 1.2 (0.9 to 1.8), P = 0.2][25]. In Partners PrEP, investigators found no difference in risk of pregnancy when comparing PrEP to placebo arms in multivariate analysis (p=0.24 for COCs and p=0.47 for injectables comparing hazard ratios between study arms)[26]. Due to differing comparisons in the multivariate analyses across studies, synthesis of the adjusted data was not possible. Both studies noted a higher pregnancy incidence among women taking COCs as compared to injectable or implant methods of contraception.

Pregnancy adverse events

The same two studies that examined the effects of PrEP on hormonal contraception also evaluated the effect of PREP on adverse pregnancy events (FEM-PrEP and VOICE) comparing PrEP to placebo groups. Across these two studies, the risk of experiencing an adverse pregnancy-related event did not significantly differ between PrEP and placebo arms (RR= 1.25, 95% CI: 0.64-2.45, p=0.52). Results remained insignificant when stratified by adherence level and PrEP regimen. It is important to note that both trials screened women for pregnancy regularly and withheld study drug once pregnancy was confirmed; therefore, this analysis does not reflect women who were taking PrEP throughout the duration of their pregnancy. In addition, due to the relatively small number of pregnancies and pregnancy-related events, evidence in GRADE was downgraded due to imprecision. Results from meta-analysis are presented in Table 12 and Figure 11.

In the Partners PrEP Demonstration Project, the frequency in loss of pregnancy was similar between PrEP regimens (37.5% for FTC/TDF and 36.7% for TDF-only, p-value for difference=0.92)[27]. Similarly, occurrence of other pregnancy-related adverse events, including preterm birth, congenital abnormalities, and growth during the first year of life did not differ between PrEP and placebo groups.

Condom use

Condom use was reported in five RCTs comparing PrEP to placebo (Fem-PrEP, iPrEx, Partners PrEP, TDF2, and the West Africa PrEP Study), three RCTs comparing PrEP to no-PrEP (CDC Safety Study, PROUD, and Project PrEPare), and two observational studies (iPrEx/US-based studies OLE and Partners PrEP Demonstration Project). Due to differences in measurement of condom use across, studies, meta-analysis was infeasible. However, despite this limitation results across studies demonstrated remarkably similar results regarding condom use. Studies overwhelmingly showed no difference in condom across groups. Some studies showed slight increases in condom use across study arms throughout the duration of the trials.

Among studies comparing PrEP to no-PrEP, which is a more similar comparison to real-life scenarios than placebo-controlled RCTs, the CDC Safety Study found a decrease in unprotected anal sex from

baseline, months 3-9, and months 12-24, with a similar change found between immediate and delayed-PrEP study arms (p=0.15)[28]. In Project PrEPare, investigators found no significant difference across all study visits in rates of unprotected anal sex acts in the three study arms—PrEP, placebo, and no-pill[15]. In PROUD, incident STI infections, which was used as a proxy for unprotected sex, were similar across the immediate and delayed PrEP arms[13].

Among observational studies, results from iPrEx OLE found a decrease in non-condom receptive anal intercourse among PrEP users (34% at baseline to 25% during follow-up, p=0.006) and non-PrEP users (27% to 20%, p=0.03)[29]. In the Partners PrEP Demonstration Project, there was a trend toward decreasing frequency of unprotected sex with study partners both before and after unmasking, with no significant changes in unprotected sex with study partner seen after unmasking (p=0.25 for trend)[30]. There was, however, a significant increase in the frequency of unprotected sex over time with outside partners (p=0.04), but study investigators note the consequence of this change in trend was minimal in the estimated versus counterfactual total annual frequency of unprotected sex acts[30].

Results from placebo-controlled RCTS report similar trends in condom use comparing PrEP to placebo arms over time, with some trials reporting a significant increase in condom use from baseline to follow-up (e.g., FEM-PrEP). Overall, results across trial and observational data show no reduction in condom use among PrEP users. Condom use data across studies is presented in Table 13.

Number of sexual partners

Eight placebo-controlled trials examined the number of sexual partners across study arms (Bangkok Tenofovir Study, FEM-PrEP, iPrEx, IAVI Kenya Study, IAVI Uganda Study, Partners PrEP, TDF2, and the West Africa PrEP Study). Two RCTs comparing PrEP to no-PrEP and three observational studies also examined number of sexual partners among participants. Like condom use, differing measurements of number of sexual partners precluded meta-analysis; however, results across studies present a similar picture.

Among RCTs comparing PrEP to placebo, many studies found small reductions in the numbers of sexual partners reported from baseline to follow-up in both PrEP and placebo arms (Bangkok Tenofovir, FEM-PrEP, TDF2) or no change (iPrEx, IAVI Uganda Study, Partners PrEP). The IAVI Kenya study was the only trial to find an increase from 3 to 4 median sex partners from baseline to month 4 of follow-up, but investigators note that was possibly due to an underreporting of partners at baseline[18].

Among studies comparing PrEP to no-PrEP, the CDC Safety Study found a significant decrease in number of sexual partners from baseline (mean=7.25) to 6.02 at months 3-9 and 5.71 at months 12-24 (p<0.001), with declines similar between immediate and delayed PrEP arms[28]. The study also found a significant decline in the mean number of HIV-positive or unknown HIV-status partners throughout the study. PROUD found that the mean number of anal sex partners reported in the last 90 days was similar in the immediate and delayed PrEP study arms[13] during follow-up.

In observational studies, the Bangkok Tenofovir OLE found declines in the number of participants reporting more than one sexual partner in the past 3 months comparing trial to demonstration project data[5]. iPrEx OLE found no significant differences in the number of sexual partners reported by PrEP users and non-PrEP users[4]. The Partners PrEP Demonstration Project found that in 12.4% of study visits participants reporting having sex outside their primary partnership before unmasking compared with 15.2% after unmasking[30].

Like condom use, evidence across trials and cohort studies found no evidence that using PrEP significantly changed the number of sexual partners reported by participants. Data regarding the number of sexual partners reported across studies is presented in Table 14.

Discussion

Summary of the evidence

This review evaluated the effect of oral PrEP in 14 randomized controlled trials and 3 observational studies. Across multiple types of studies, comparisons, and sub-groups, PrEP significantly reduces the risk of HIV infection as compared to placebo or no-PrEP groups. Adherence moderates the impact of PrEP on HIV infection, as PrEP was more effective in reducing risk of HIV infection among studies with higher levels of adherence as compared with studies with low levels of adherence, which found a null effect.

PrEP was effective in reducing risk of HIV across genders, age groups, PrEP regimens, and PrEP dosing schemes. PrEP showed no evidence of increasing rates of adverse events, including grade 3 or 4 events. Regarding drug resistance, PrEP was significantly associated with increasing the proportion infections having an FTC-related mutation among seroconverters who were acutely infected with HIV when initiating PrEP. However, incidence of acquiring drug-resistant HIV infection was not significantly higher for PrEP users as compared to placebo groups due to the lower rates of HIV infection among PrEP users overall. Regarding sexual and reproductive health outcomes, there was no evidence that PrEP led to risk compensation in sexual practices, either in the form of decreased condom use or increased number of sexual partners. PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends toward higher rates of pregnancy among oral contraceptive users who also took PrEP. Once confounders were accounted for in multivariate analysis, this relationship became insignificant. Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy.

It is important to note that across all trials, PrEP was provided in the context of a package of standard HIV prevention interventions, including regular HIV testing and counselling, provision of condoms, STI screening and treatment, adherence counselling, and other options relevant to the study population (e.g., contraception for women, methadone maintenance for people who inject drugs). This review sought to evaluate the effectiveness of PrEP in preventing HIV in the context of access to a combination of standard approaches to HIV prevention.

Limitations of the data at the study and outcome level

This analysis should be seen in light of several limitations. Despite comprehensive search methods, it is possible that eligible studies were not identified in our search strategy and where not included in this review. Within included studies, while attempts were made to contact study authors regarding clarifications on data presented in published articles and conference abstracts when necessary, not all investigators could be reached. Behavioural outcomes, including number of sexual partners and condom use, were mostly based on self-reported data and could therefore be influenced by social desirability bias, although 2 studies (Partners PrEP and iPrEx) also reported decreasing rates of sexually transmitted infections commensurate with reported safer behaviour. In studies where PrEP assignment was known, such as in studies involving immediate and delayed PrEP study arms, it is

possible that knowledge of study assignment influenced participants' reported behaviours. Additionally, several analyses involved outcomes that had few numbers of absolute events, thus leading to imprecision and uncertainty regarding synthesized effect sizes. Finally, PrEP trials varied in participants' adherence to study medication, thereby making it difficult to ascertain the true effect of PrEP in regards to certain outcomes where results were synthesized across trials.

Conclusions

Results of the systematic review and meta-analysis demonstrate oral PrEP (containing Tenofovir) is effective in reducing risk of HIV infection among various populations. There is little evidence of risk compensation and adverse safety events, although some studies have identified subclinical reductions in renal function and bone mineral density. For outcomes with few events, such as drug resistance and reproductive health outcomes, active surveillance during PrEP scale-up is warranted. PrEP uptake and adherence among people at substantial risk for HIV are key determinants of impact. Best practices for optimizing PrEP delivery based on clinical practice and research evidence are being developed separately.

Appendices

Figure 1. Disposition of citations during the search and screening process

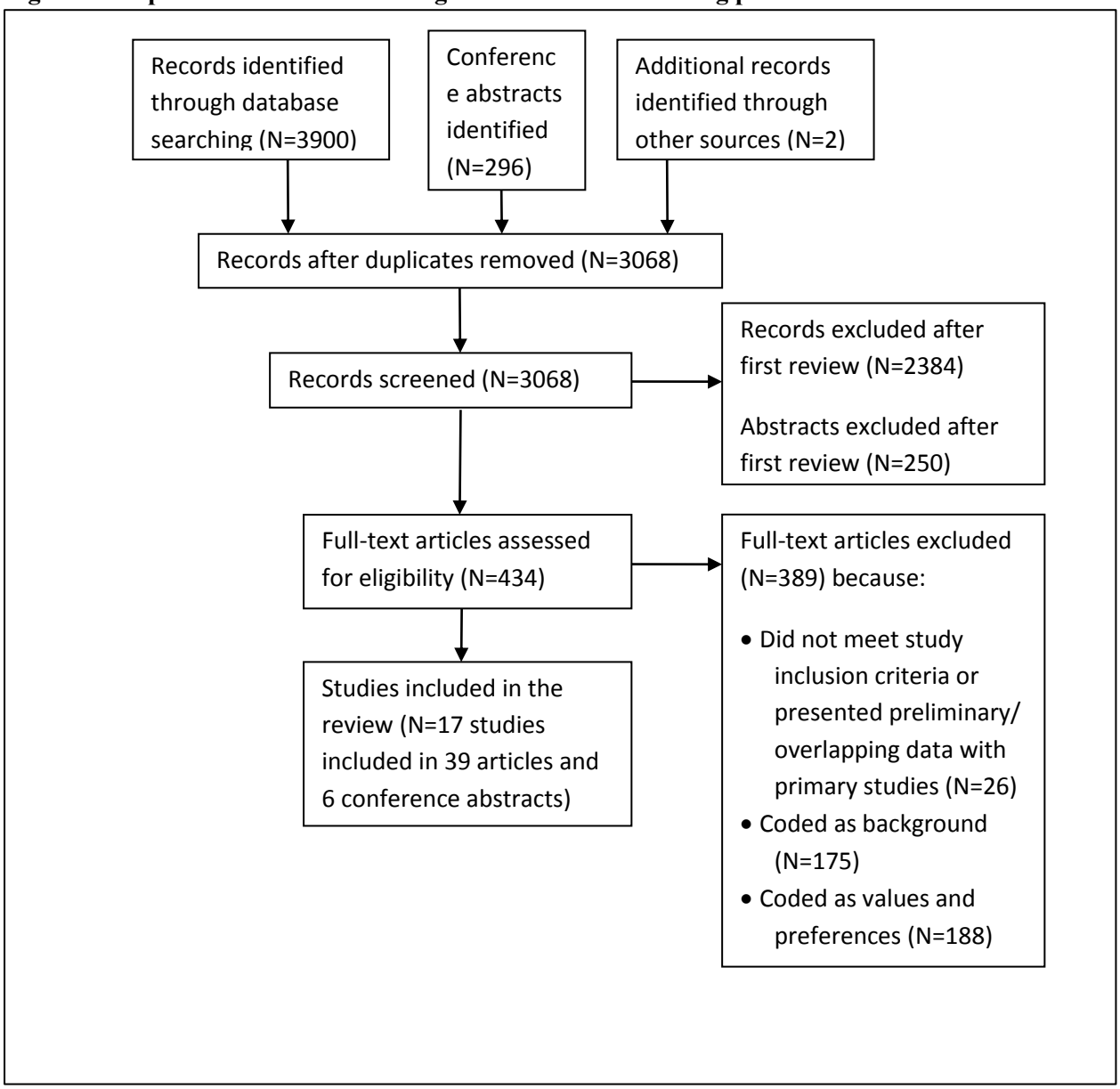


Table 1. List of Included Studies

Study	Design and PrEP Comparison	Location	Study Population
ADAPT	RCT Daily and non-daily FTC/TDF	Cape Town, South Africa	Women
Bangkok Tenofovir Study	RCT Daily TDF to placebo	Bangkok, Thailand	People who inject drugs
Bangkok Tenofovir Open-Label Extension	Cohort Study Daily TDF	Bangkok, Thailand	People who inject drugs
CDC Safety Study	RCT Immediate/delayed TDF to immediate/delayed placebo	San Francisco, CA; Atlanta, GA; Boston, MA (USA)	MSM
FEM-PrEP	RCT Daily FTC/TDF to placebo	Tanzania, South Africa, Kenya, and South Africa	Women
Ipergay	RCT Immediate to delayed FTC/TDF	France and Canada	MSM
iPrEx	RCT Daily FTC/TDF to placebo	Peru, Ecuador, South Africa, Brazil, Thailand, and United States	MSM and transgender women
iPrEx/US-based studies Open-Label Extension	Cohort Daily FTC/TFC to no PrEP	Peru, Ecuador, South Africa, Brazil, Thailand, and United States	MSM and transgender women
IAVI Kenya Study	RCT Daily/intermittent FTC/TDF to daily/intermittent placebo	Nairobi and Kilifi, Kenya	MSM and FSW
IAVI Uganda Study	RCT Daily/intermittent FTC/TDF to daily/intermittent placebo	Uganda	Serodiscordant couples
Partners PrEP	RCT Daily TDF or FTC/TDF to placebo	Kenya and Uganda	Serodiscordant couples
Partners PrEP Open-Label Extension	Cohort Daily TDF or FTC/TDF	Kenya and Uganda	Serodiscordant couples
Project PrEPare	RCT Daily FTC/TDF to placebo to no pill	Chicago, IL (USA)	Young MSM
PROUD	RCT Immediate TDF/FTC to delayed TDF/FTC	England	MSM
TDF2	RCT Daily FTC/TDF to placebo	Francistown and Gaborone, Botswana	Heterosexual men and women
VOICE	RCT Daily TDF or FTC/TDF to placebo	South Africa, Uganda, and Zimbabwe	Women
West African Safety Study	RCT Daily TDF to placebo	Nigeria, Cameroon, and Ghana	Women

Table 2. Quality Assessment (Risk of Bias)

	Risk of Bias Categories					
Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
ADAPT	Low	Low	Low	Low	Low	Low
Bangkok Tenofovir Study	Low	Low	Low	Low	Low	Uncertain
CDC Safety Study	Low	Low	Low	Low	Low	Uncertain
FEM-PrEP[1]	Low	Low	Low	Low	Low	Low
Ipergay	Low	Low	Low	Low	Low	Uncertain
iPrEx	Low	Low	Low	Low	Low	Low
IAVI Kenya Study	Low	Low	Low	Low	Low	Low
IAVI Uganda Study	Low	Low	Low	Low	Low	Low
Partners PrEP	Low	Low	Low	Low	Low	Low
Project PrEPare	Low	Low	Uncertain	Uncertain	Low	Uncertain
PROUD	Low	Low	Uncertain	Uncertain	Low	Low
TDF2	Low	Low	Low	Low	Low	Low
VOICE[2]	Low	Low	Low	Low	Low	Uncertain
West Africa Study	Low	Low	Low	Low	Low	Low

[1]Studies reported less than 40% adherence to the study drug; therefore, there is risk that these studies are not able to fully answer the research questions the studies were designed to answer, including their ability to assess the efficacy of PrEP. However, because no trial demonstrated perfect adherence, this risk is implicit in all trials, but heightened in the trials with lowest adherence.

HIV Infection: Meta-Analysis and Meta-Regression Results

Table 3: Meta-analysis results for HIV Infection across all sub-groups

Analysis	Number of studies	Risk Ratio (95% CI)	p-value	I^2
RCTs comparing PrEP to placebo				
Overall[1]	10	0.49 (0.33-0.73)	0.001	70.9
Mode of Acquisition				
Rectal	4	0.34 (0.15-0.80)	0.01	29.1
Vaginal/penile	6	0.54 (0.32-0.90)	0.02	80.1
Adherence				
High (>70%)	3	0.30 (0.21-0.45)	<0.0001	0.0
Medium (41-70%)	2	0.55 (0.39-0.76)	<0.0001	0.0
Low (≤40%)	2	0.95 (0.74-1.23)	0.70	0.0
Biological sex[2]				
Male	7	0.38 (0.25-0.60)	<0.0001	34.5
Female	6	0.57 (0.34-0.94)	0.03	68.3
Age				
<25 years	3	0.71 (0.47-1.06)	0.09	20.5
≥25 years	3	0.45 (0.22-0.91)	0.03	72.4
Drug Regimen				
TDF	5	0.49 (0.28-0.86)	0.001	63.9
FTC/TDF	7	0.51 (0.31-0.83)	0.007	77.2
Drug Dosing				
Daily	8	0.54 (0.36-0.81)	0.003	73.6
Intermittent	1	0.14 (0.03-0.63)	0.01	0.0
RCTs comparing PrEP to no PrEP				
Overall	2	0.15 (0.05-0.46)	0.001	0.0

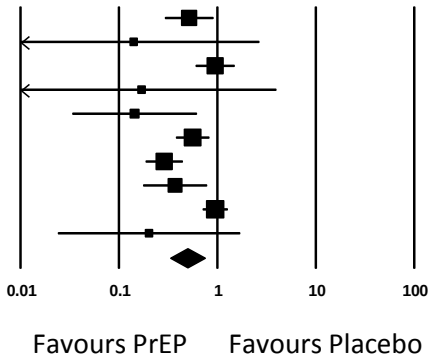
[1] Modified intent-to-treat (MITT) analyses are presented. For the West Africa Safety Study, two HIV infections were removed from the analysis because these infections were detected within 4 weeks of starting study medication and were presumed to be HV-RNA positive at baseline (based on correspondence with study investigators).
[2]For the TDF2 study, the gender of the three study participants excluded from the MITT analysis due to acute HIV infection at enrollment is not provided. Therefore, numbers of total male and female participants were included in this analysis.

Table 4: Summary of changes in rates of HIV incidence from observational studies

Observational Studies-Comparing PrEP to no PrEP			
Study	HIV Incidence rate- no PrEP	HIV Incidence rate- OLE PrEP users	Comparison
Bangkok Tenofovir OLE	0.7 infections per 100 PY (95% CI: 0.07-1)	0.5 infections per 100 PY (95% CI: 0.02-0.23)	Placebo arm of trial to OLE
iPrEx OLE	2.6 infections per 100 PY (95% CI 1.3-2.6)	1.8 infections per 100 PY (95% CI 1.5-4.5)	Non-PrEP users in OLE to PrEP users in OLE
Partners PrEP OLE	5.3 infections per 100 PY (95% CI 3.2-7.6)	0.2 infections per 100 PY (95% CI 0.0-1.3)	Simulated counterfactual to OLE

Figure 2: Forest plot for overall analysis of PrEP and HIV Infection

Study name	Subgroup within study	Comparison	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
BKK TDF Study	Men and Women	daily PrEP vs. placebo	0.517	0.290	0.924	-2.229	0.026
CDC Safety Study	MSM	daily PrEP vs. placebo	0.141	0.007	2.704	-1.299	0.194
FEM-PrEP	Women	daily PrEP vs. placebo	0.950	0.595	1.517	-0.214	0.831
IAVI Kenya Study	MSM and FSW	multiple PrEP dosing	0.170	0.007	4.025	-1.097	0.272
Ipergay	MSM	intermittent PrEP	0.144	0.033	0.627	-2.584	0.010
iPrEx	MSM and TG	daily PrEP vs. placebo	0.561	0.376	0.838	-2.826	0.005
Partners PrEP	Men and Women	daily PrEP vs. placebo	0.289	0.185	0.450	-5.471	0.000
TDF2	Men and Women	daily PrEP vs. placebo	0.373	0.175	0.795	-2.554	0.011
VOICE	Women- All PrEP	daily PrEP vs. placebo	0.951	0.702	1.289	-0.323	0.747
West Africa Study	Women	daily PrEP vs. placebo	0.202	0.024	1.725	-1.461	0.144
			0.490	0.328	0.734	-3.469	0.001



Meta Analysis

Table 5: Results from meta-regression of sub-group variables for HIV infection

Variable	Regression coefficient	p-value
Adherence (as continuous variable)	-0.02	<0.0001
Mode of acquisition (comparing vaginal/penile to rectal)	0.47	0.36
Biological sex (comparing women to men)	0.46	0.19
Age (comparing <25 years to ≥25 years)	0.45	0.29
PrEP regimen (comparing FTC/TDF to TDF)	0.06	0.88
PrEP dose (comparing intermittent to daily)	-1.32	0.14

Figure 3. Meta-regression results –Adherence as moderator (continuous variable)

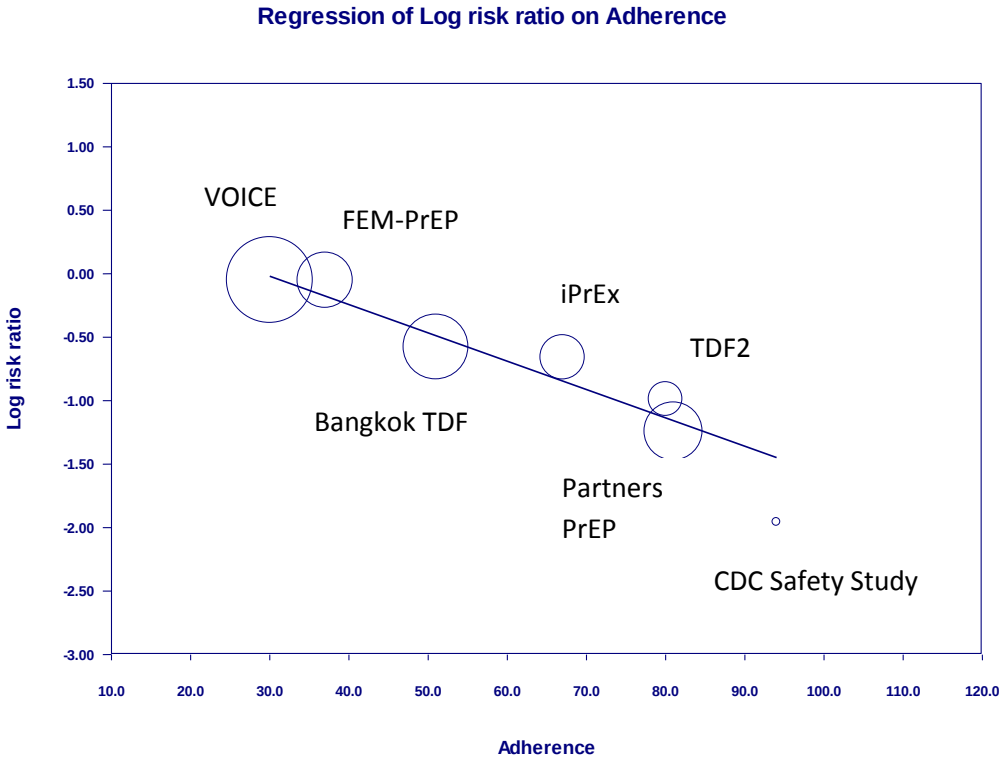


Figure 4. Meta-regression results –Adherence as moderator (categorical variable)

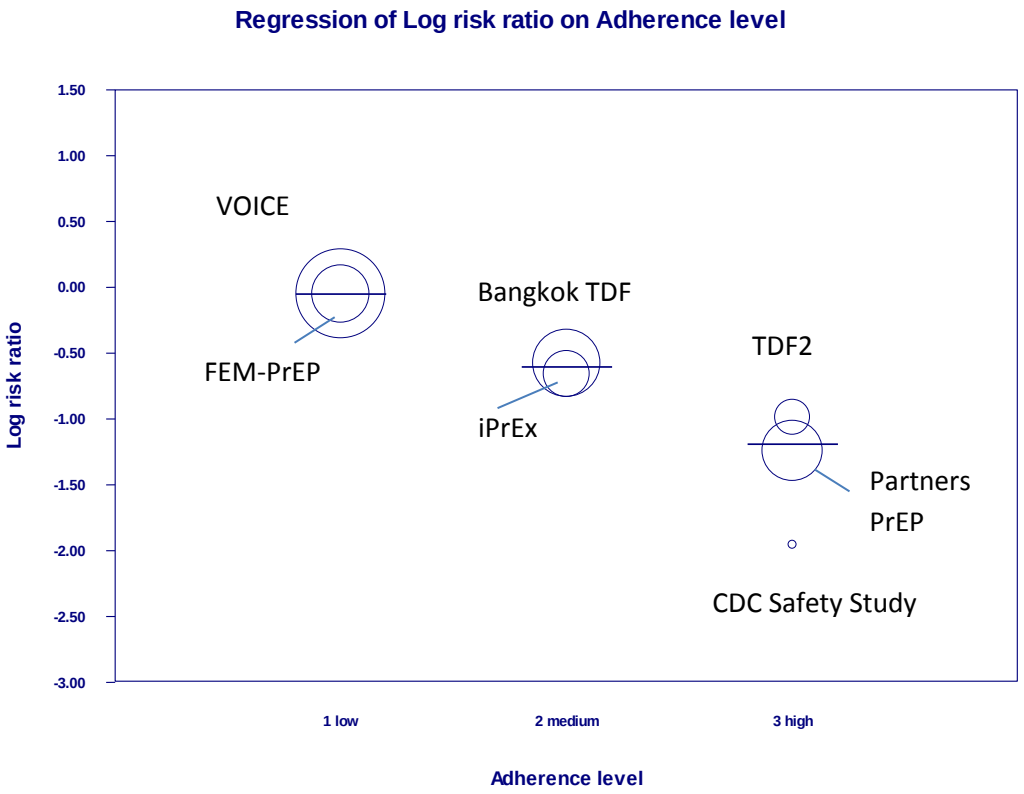


Figure 5. Meta-regression results –Mode of acquisition as moderator

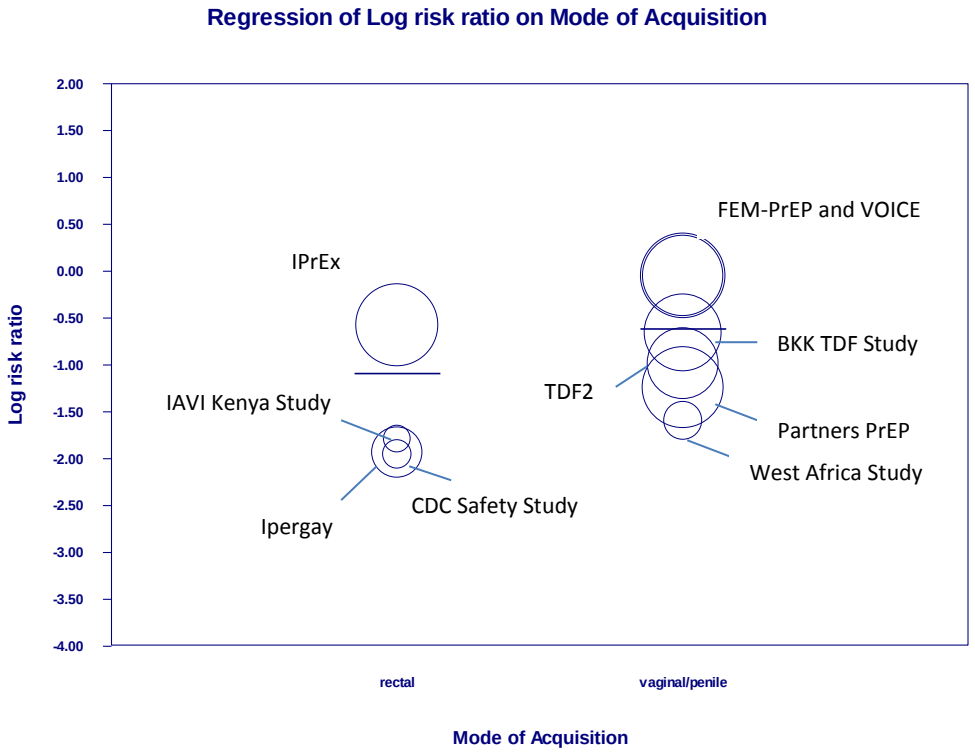
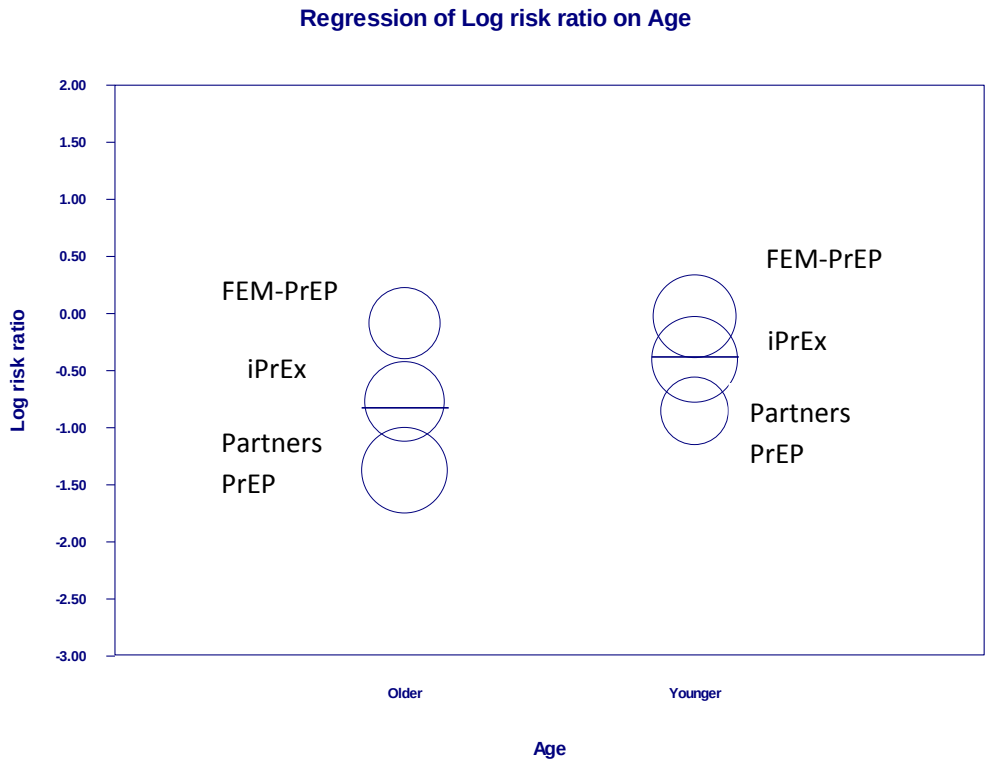


Figure 6. Meta-regression results –Age as moderator

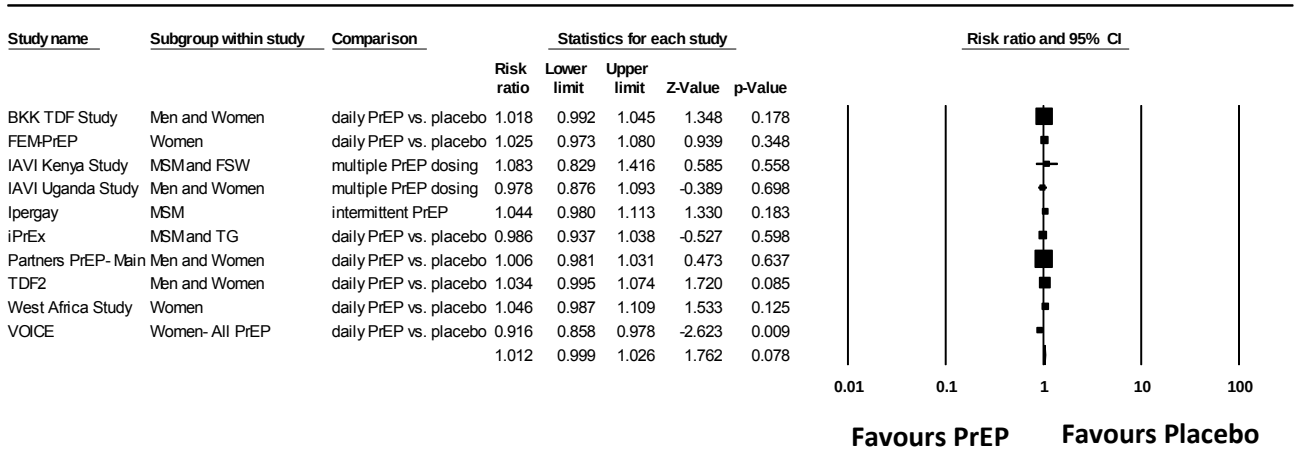


Any Adverse Event: Meta-Analysis Results

Table 6: Meta-analysis results for effects of PrEP on any adverse event

Analysis	Number of studies	Risk Ratio (95% CI)	p-value	I^2
RCTs comparing PrEP to placebo				
Overall	10`	1.01 (0.99-1.03)	0.27	38.1
Mode of Acquisition				
Rectal	3	1.01 (0.97-1.06)	0.60	6.0
Vaginal/penile	7	1.01 (0.99-1.04)	0.39	51.6
Adherence				
Low	2	0.97 (0.87-1.08)	0.60	85.6
Medium	2	1.01 (0.98-1.04)	0.46	13.9
High	2	1.02 (0.99-1.04)	0.23	28.4
Biological sex				
Male	2	1.00 (0.98-1.03)	0.85	0.0
Female	3	1.00 (0.92-1.07)	0.92	80.2
Drug Regimen				
TDF	4	0.98 (0.92-1.04)	0.47	88.5
FTC/TDF	8	1.02 (1.00-1.04)	0.06	0.0
Drug Dosing				
Daily	9	1.00 (0.97-1.03)	0.78	65.6
Intermittent	3	1.05 (0.99-1.11)	0.14	0.0
Age	No safety data stratified by age			
RCTs comparing PrEP to no PrEP				
Data on any adverse event not reported for PROUD and CDC Safety Study				

Figure 7. Forest plot for overall analysis of PrEP and any adverse event:



Any Grade 3 or 4 Adverse Event: Meta-Analysis Results

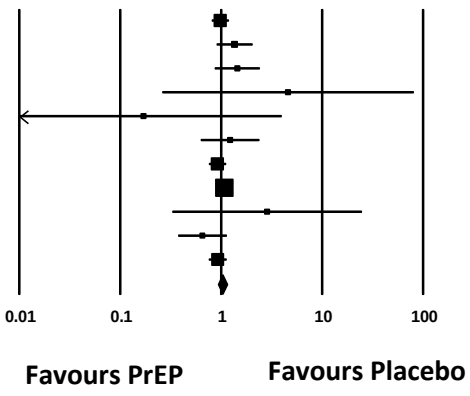
Table 7. Meta-analysis results for effects of PrEP on any grade 3 or 4 adverse event

Analysis	Number of studies	Risk Ratio (95% CI)	p-value	I^2
RCTs comparing PrEP to placebo				
Overall[1]	11	1.02 (0.92-1.13)	0.76	16.5
Mode of Acquisition				
Rectal	5	1.09 (0.84-1.41)	0.52	19.0
Vaginal/penile	6	1.00 (0.88-1.15)	0.96	28.9
Adherence				
Low	2	1.08 (0.71-1.64)	0.71	58.0
Medium	2	0.95 (0.82-1.10)	0.48	0.0
High	3	1.05 (0.78-1.39)	0.76	51.9
Biological sex				
Male	4	1.07 (0.83-1.39)	0.59	22.8
Female	2	1.08 (0.71-1.64)	0.71	58.0
Drug Regimen				
TDF	3	0.95 (0.80-1.13)	0.56	54.1
FTC/TDF	10	1.07 (0.94-1.21)	0.32	17.4
Drug Dosing				
Daily	9	1.01 (0.91-1.13)	0.81	21.2
Intermittent	3	1.14 (0.60-2.18)	0.70	0.0
Age	No safety data stratified by age			
RCTs comparing PrEP to no PrEP				
Data not reported for PROUD; data from CDC Safety Study included in PrEP vs. placebo analysis				

[1]The FEM-PrEP study did not present results for the outcome "any grade 3 or 4 event." For this analysis, results from the outcome "any serious adverse event" were used.

Figure 8. Forest plot for overall analysis of PrEP and any grade 3 or 4adverse event:

Study name	Subgroup within study	Comparison	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
BKK TDF Study	Men and Women	daily PrEP vs. placebo	0.979	0.797	1.203	-0.202	0.840
CDC Safety Study	MSM	daily PrEP vs. placebo	1.357	0.890	2.069	1.420	0.155
FEM-PrEP	Women	daily PrEP vs. placebo	1.446	0.855	2.445	1.376	0.169
IAVI Kenya Study	MSM and FSW	multiple PrEP dosing	4.592	0.257	81.944	1.037	0.300
IAVI Uganda Study	Men and Women	multiple PrEP	0.170	0.007	4.025	-1.097	0.272
Ipergay	MSM	intermittent PrEP	1.226	0.622	2.420	0.589	0.556
iPrEx	MSM and TG	daily PrEP vs. placebo	0.919	0.747	1.129	-0.806	0.420
Partners PrEP- Main	Men and Women	daily PrEP vs. placebo	1.077	0.954	1.215	1.194	0.233
Project PrEPare	MSM	daily PrEP vs. placebo	2.850	0.324	25.069	0.944	0.345
TDF2	Men and Women	daily PrEP vs. placebo	0.652	0.370	1.150	-1.477	0.140
VOICE	Women- All PrEP	daily PrEP vs. placebo	0.925	0.746	1.147	-0.713	0.476
			1.016	0.916	1.127	0.305	0.760



Meta Analysis

Drug Resistance: Meta-Analysis Results

Table 8. Drug resistant mutations identified in each study among seroconverters

Study		Acute HIV Infections at Enrollment			Post-Randomization HIV Infections		
	Study Arm	No. of sero-converters	TDF Mutations	FTC Mutations	No. of sero-converters	TDF Mutations	FTC Mutations
Bangkok Tenofovir Study [1]	PrEP: TDF	0	0	NR	17	0	NR
	Placebo	2	0	NR	33	0	NR
FEM-PrEP	PrEP: TDF-FTC	0	N/A	N/A	33[2]	0	**4**[3]
	Placebo	0	N/A	N/A	35	0	1
iPrEx	PrEP: TDF-FTC	2	0	2	48	0	0
	Placebo	8	0	**1**	83	0	0
Partners PrEP	PrEP: TDF	5	1	0	15	0	0
	PrEP: TDF-FTC	3	0	1	12	0	0
	Placebo	6	0	0	51	0	0
TDF2	PrEP: TDF-FTC	1	**1**[4]	**1**[4]	9	0	0
	Placebo	2	0	0	24	**1**	0
VOICE	PrEP: TDF	5	0	0	58	0	0
	PrEP: TDF-FTC	9	0	2	55	0	1
	Placebo	1	0	0	60	0	0

[1] RNA was amplified in specimens from 49 of 52 HIV-positive participants for molecular genotyping
[2] Three HIV infections identified in the TDF-FTC group occurred within 12 weeks of enrollment. Investigators note the possibility that these individuals could have been acutely infected during enrollment.
[3] One participant with FTC-mutation had not accessed FTC/TDF for 48-weeks prior to seroconversion due to early toxicity.
4 Participant assigned to TDF-FTC arm was falsely screened negative for HIV infection at enrollment and was diagnosed with HIV infection at the month 7 study visit. Mutations for both TDF and FTC were detected.

Table 9 Meta-analysis results for PrEP and drug resistance among seroconverters

Type of Mutation	Timing of HIV Infection	PrEP regimens	No. of studies	RR	95% CI	p-value
Any mutation (TDF or FTC)	Acute HIV infection at enrollment	TDF and FTC/TDF	4[a]	3.34	1.11-10.06	0.03
Any mutation (TDF or FTC)	Post-randomization	TDF and FTC/TDF	3[b]	2.27	0.48-10.60	0.30
FTC (M184I and M184V)	Acute HIV infection at enrollment	TDF and FTC/TDF	4[a]	3.12	(1.03-9.46)	0.05
FTC (M184I and M184V)	Post-randomization	TDF and FTC/TDF	2[b]	3.14	(0.53-18.52)	0.21
FTC (M184I and M184V)	Acute HIV infection at enrollment	FTC/TDF	4[a]	3.72	(1.23-11.23)	0.02
FTC (M184I and	Post-randomization	FTC/TDF	2[c]	3.91	(0.66-	0.13

M184V)					23.07)	
TDF (KR65 and K70E)	Acute HIV infection at enrollment	TDF and FTC/TDF	2[d]	3.39	(0.46-25.05)	0.23
TDF (KR65 and K70E)	Post-randomization	TDF and FTC/TDF	1[e]	0.83	(0.04-18.79)	0.91
TDF (KR65 and K70E)	Acute HIV infection at enrollment	TDF	1[f]	3.50	(0.17-70.94)	0.42
TDF (KR65 and K70E)	Post-randomization	TDF	0	--	--	--

[a] iPrEx, Partners PrEP, TDF2, and VOICE
[b] FEM-PrEP, Partners PrEP, and VOICE
[c] FEM-PrEP and VOICE
[d] Partners PrEP and TDF2
[e] TDF2
[f] Partners PrEP
Note: Evidence will be downgraded in GRADE for imprecision (due to few numbers of absolute events)

Figure 9. Forest plot for proportion of drug resistance among seroconverters experiencing acute HIV infection at enrolment

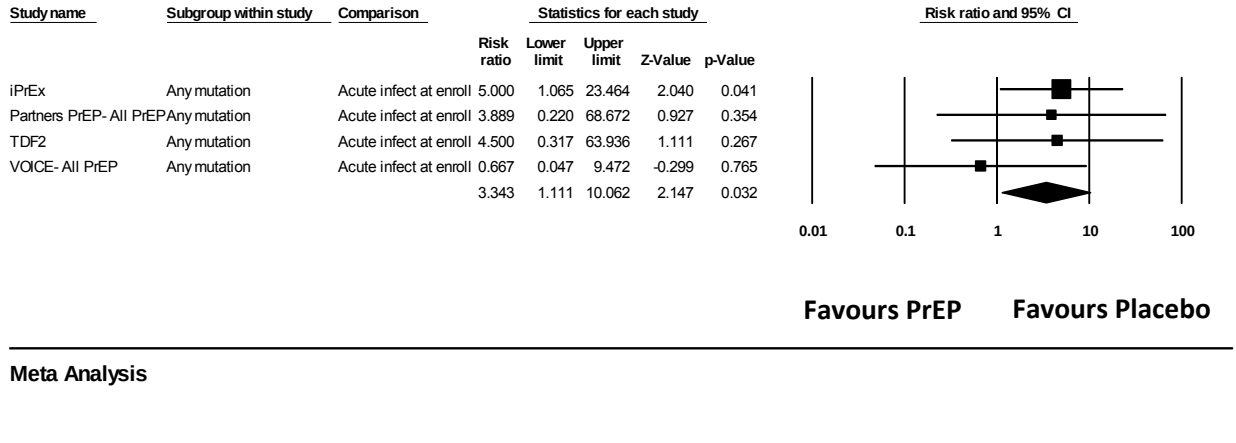
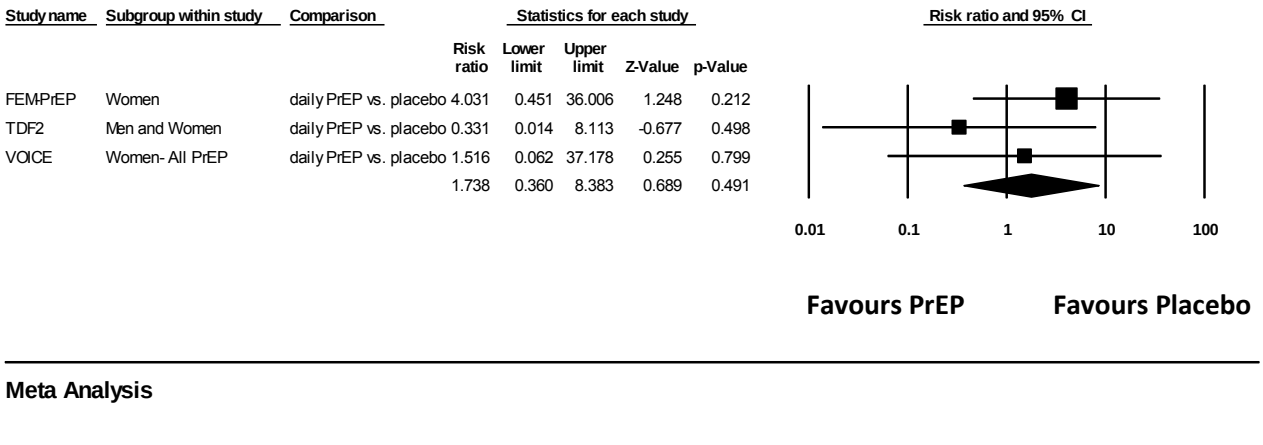


Figure 10. Forest plot for proportion of drug resistant HIV infection among all participants



Hormonal Contraception Effectiveness: Meta-analysis Results

Table 10. Summary of results for PrEP and hormonal contraception effectiveness

Study	Comparison	Adjusted HR	p-value
FEM-PrEP	Risk of pregnancy comparing PrEP to placebo *(adjusted for contraceptive method, site, and age)*	1.2 (0.9 to 1.8)	0.20
Partners PrEP – Combined Oral Contraceptives (COCs)	Risk of pregnancy comparing COCs to no contraception among PrEP group	0.96 (0.58-1.58)	0.87
	Risk of pregnancy comparing COCs to no contraception among placebo group	0.55 (0.26-1.19)	0.13
	P-value for difference in HRs by arm		**0.24**
Partners PrEP – Injectables	Risk of pregnancy comparing injectables to no contraception among PrEP group	0.26 (0.16-0.41)	<0.0001
	Risk of pregnancy comparing injectables to no contraception among placebo group	0.19 (0.10-0.37)	<0.0001
	P-value for difference in HRs by arm		**0.47**

Table 11. Summary of pregnancies rates in studies reporting contraceptive effectiveness

Study	Contraceptive Method	PrEP Pregnancies	PrEP person-years	Placebo Pregnancies	Placebo person-years	Rate ratio[1]	SE[1]
FEM-PrEP	Any method	69	602.9	48	620.7	1.48	0.19
	COCs	60	171.1	43	153.9	1.26	0.20
	Injectables	9	402.3	5	448.2	2.01	0.56
Partners PrEP	Any method	67	924.2	28	508.1	1.32	0.23
	COCs	37	209.3	11	108.7	1.75	0.34
	Implants	1	150.6	0	79.7	1.59	1.63
	Injectables	29	564.3	17	319.7	0.97	0.32

[1]Rate ratios and standard errors calculated using CMA v3.0

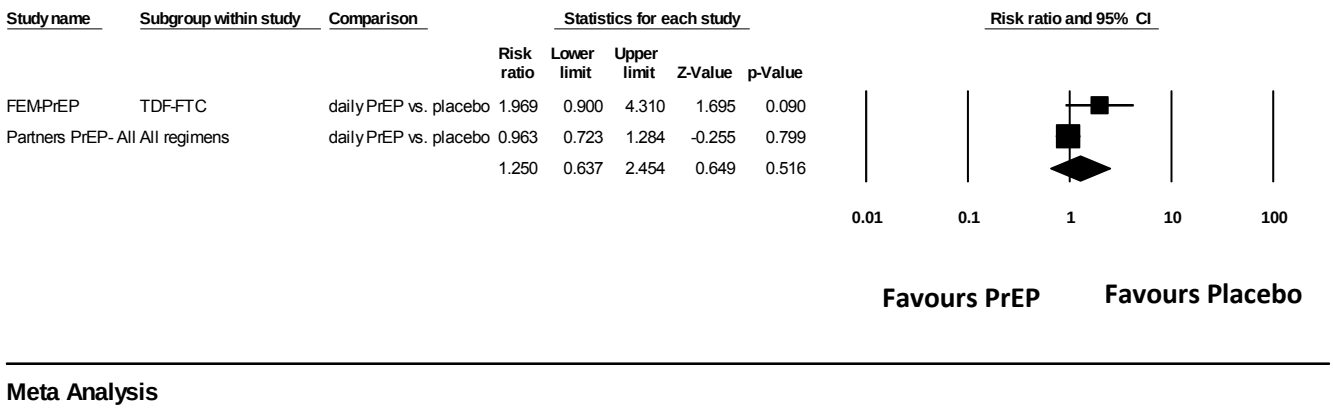
Any Pregnancy-related Adverse Event: Meta-Analysis Results

Table 12: Meta-analysis results for effect of PrEP on pregnancy-related adverse events

Analysis	Number of studies	Risk Ratio (95% CI)	p-value	
RCTs comparing PrEP to placebo				
Overall[1,2,3]	2	1.25 (0.64-2.45)	0.52	64.5
Adherence				
Low	1	1.96 (0.90-4.3)	0.09	n/a
High	1	0.96 (0.72-1.28)	0.80	n/a
Drug Regimen				
TDF	1	0.77 (0.55-1.10)	0.15	n/a
TDF-FTC	2	1.35 (0.93-1.95)	0.11	16.7
Observational studies				
Partners PrEP OLE	After unmasking, frequency of pregnancy loss was 37.5% for FTC/TDF and 36.7%for TDF alone (difference, 0.8%; 95%CI, −16.8%to 18.5%; P = .92).			

[1] Evidence will be downgraded in GRADE for imprecision (due to few numbers of absolute events)
[2] For the FEM-PrEP study, authors note the higher pregnancy-related adverse event rate in the FTC/TDF group (P = 0.04), but also note there were more pregnancies in this group as compared with the placebo group (IR=11.2 per 100 person-years vs. 7.5 per 100 person-years, respectively).
[3] Both trials tested participants for pregnancy at monthly study visits. Therefore, participants were mostly only receiving PrEP for up to the initial 6 weeks of their pregnancy.

Figure 11. Forest plot for effect of PrEP on adverse pregnancy events



Condom Use: Summary of study results

Table 13: Summary of changes on condom use across PrEP studies

Study	Behavioral Measure	Outcome
RCTs: Comparisons between PrEP and placebo groups		
Fem-PrEP	Sex acts without a condom used	Modest but significant reduction (mean reduction= 0.46; P<0.001) comparing last follow-up visit to 7 days prior to enrollment.
iPrEx	Percent of receptive anal partners with which condoms used	Baseline: 50.38% in TDF-FTC; 51.04% in placebo Follow-up (week 132) : 73.98% in TDF-FTC: 83.64% in placebo Wald test treatment by visit interaction: p=0.36.
Partners PrEP	Having sex without a condom with HIV-positive partners in prior month	Baseline: 27% Follow-up (12 months): 13% Follow-up (24 months): 9% (similar across study groups)
TDF2	Protected sex episodes with main/ most recent casual partner	Similar at enrollment (p=0.66) and remained stable over time TDF-FTC: 81.4% [range, 76.6 to 86.4] Placebo: 79.2% [range, 71.6 to 87.6]
West Africa PrEP Study	Condom use last sex	Screening: 52% 12-month follow-up: 95% (for acts in past 7 days)
RCTs: Comparisons between PrEP and no PrEP		
CDC Safety Study	Unprotected Anal Sex (UAS) Unprotected anal sex with HIV positive/ unknown status partner (UASPU)	•Decrease from baseline: (57%) to months 3–9 (48%, P = 0.001) and months 12–24 (52%, P = 0.03). Change in proportion similar between immediate vs. delayed arms (P=0.15) •No statistical difference in UAS episodes between immediate vs. delayed arms during months 3–9 (P = 0.10) and no significant change when delayed group initiated study drug (P = 0.42) •Mean UASPU remained stable or decreased during follow-up [2.02 at baseline vs. 1.51 during months 3–9(P = 0.22) and 1.37 during months 12–24 (P = 0.05)]
Project PrEPare	Male-to-male unprotected anal sex acts	•No significant differences among the 3 treatment groups across visits. •Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
PROUD	Incident STIs (unprotected sex proxy)	Proportion with confirmed rectal chlamydia/gonorrhea) was similar in immediate (29%) and delayed (27%) (P=0.50) arms.
Observational studies: Comparisons between pre/post PrEP use		
iPrEx OLE	Non-condom receptive anal intercourse Syphilis incidence (proxy for unprotected sex)	•Decreased from 34% (377/1115) to 25% (232/926) among PrEP recipients (p=0·006), and from 27% (101/369) to 20% (61/304) among non-recipients (p=0·03). •Decreases in non-condom receptive anal intercourse, non-condom insertive anal intercourse, were similar across groups (p=0·95 and p=0·56) •Syphilis incidence was similar among PrEP recipients and non-recipients (7·2 infections per 100 patient-years vs 5·4 infections per 100 patient-years, HR 1·35, 95 CI 0·83–2·19).
Partners PrEP OLE	Unprotected sex	•Trend toward decreasing frequency of unprotected sex with study partner during study before unmasking, and after unmasking no significant changes in the immediate level (p=0·66) or trend (p=0·25) of unprotected sex •Significant increase in frequency of unprotected sex over time with outside partners (p=0·04). Consequence of this change in trend was a small difference in the estimated vs counterfactual annual average total frequency of unprotected sex acts

Number of Sexual Partners: Summary of Study Results

Table 14: Summary of changes in number of sexual partners across PrEP studies

Study	Behavioral Measure	Outcome
RCTs: Comparisons between PrEP and placebo groups		
Bangkok TDF Study	Sex with more than 1 partner	Enrollment: 522 (22%) Follow-up Month 72: 43 (6%) P value (for all): p< 0.0001
Fem-PrEP	Number of sexual partners	Modest but significant reductions (mean reduction= 0.14; P<0.001) comparing last follow-up visit to 7 days before enrollment.
iPrEx	Mean number of receptive anal partners	Baseline: FTC-TDF: 12.21 (SE=0.81); Placebo: 11.21 (SE=0.81) Follow-up (132 weeks): FTC-TDF: 3.47 (SE=0.81); Placebo: 5.71 (SE=1.59) Wald test of the treatment by visit interaction: p=0.97
IAVI Kenya Study	Median number of sexual partners in past month	Increased from 3 [IQR 2–4] at baseline to 4 [IQR 2–8] at month 4 during the trial, primarily due to an increase of 3 [IQR 1.5–4] to 5 [IQR 2–12] at Kilifi.
IAVI Uganda Study	Median number of sexual partners in past month	Median number remained at 1 [IQR: 1-1] during the trial.
Partners PrEP	Outside sexual partnerships at any point during follow-up	TDF: 468/1584 (29.7%), p=0.74 vs. placebo FTC/TDF: 469/1579 (29.9%), p=0.67 vs. placebo Placebo: 459/1584 (29.1%)
TDF2	Number of sexual partners	Declined similarly in both groups during the course of the study
West Africa PrEP study	Number of sexual partners in past 30 days	Screening: 12 sex acts per week, avg. of 21 partners Follow-up: 15 sex acts per week, avg. of 14 sexual partners
RCTs: Comparisons between PrEP and no PrEP		
CDC Safety Study	Mean number of male sex partners in past 3 months	•Decreased significantly from 7.25 at baseline to 6.02 during months 3–9 and 5.71 during months 12–24 (P <0.001). Declines were similar between the immediate vs. delayed arms during months 3–9 (P value for interaction = 0.67) •Mean number did not differ in months 12–24 vs. months 3–9 with initiation of study drug in delayed arm [incident rate ratio (IRR) = 0.93, P = 0.22] or drug continuation in immediate arm (IRR = 0.96, P = 0.56). •Mean number of positive or unknown HIV-status partners declined from 4.17 at baseline to 3.51 during months 3–9 (P = 0.04) and 3.37 during months 12–24 (P = 0.01).
PROUD	Number of anal sex partners in last 90 days (IQR)	Baseline: Immediate arm: 10.5 (5-20); Delayed arm: 10 (4-20) Month 12: Immediate arm: 10 (3-24); Delayed arm: 8 (3-15)
Observational studies: Comparisons between pre/post PrEP use		
Bangkok TDF OLE	Number of opposite sex sexual partners in past 3 months	0 partners: RCT: 0 699 (29.1) Demo: 383 (48.7) 1 partner: RCT: 1184 (49.2) Demo: 317 (40.3) >1 partners: RCT: 552 (21.7) Demo: 87 (11.1)
iPrEx OLE	Number of sexual partners	Numbers of sexual partners were much the same in the each groups (p=0·64)
Partners PrEP OLE	Members of sero-discordant couples reporting outside sexual partnerships	Before unmasking, 12·4% of visits (4124 of 33 198, representing 794 individuals) had sex outside the primary partnership recorded compared with 15·2% (3480 of 22 934, representing 721 individuals) after unmasking.

GRADE Profile

oral PrEP (containing tenofovir) for preventing HIV infection among people at substantial risk of HIV infection

Patient or population: People at substantial risk of HIV infection
Settings:
Intervention: Oral PrEP (containing tenofovir)

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Oral PrEP (containing tenofovir)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
HIV Infection: PrEP vs. Placebo (Adherence >70%)	**Study population**		**RR 0.30** (0.21 to 0.45)	6150 (3 studies)	⊕⊕⊕⊕ **high**	
	35 per 1000	**10 per 1000** (7 to 16)				
HIV Infection: PrEP vs. Placebo (Adherence 40-70%)	**Study population**		**RR 0.55** (0.39 to 0.76)	4912 (2 studies)	⊕⊕⊕⊕ **high**	
	39 per 1000	**22 per 1000** (15 to 30)				
HIV Infection: PrEP vs. Placebo (Adherence <40%)	**Study population**		**RR 0.95** (0.74 to 1.23)	5033 (2 studies)	⊕⊕⊕⊕ **high**	
	47 per 1000	**44 per 1000** (35 to 58)				
HIV infection: PrEP vs. no PrEP	**Study population**		**RR 0.15** (0.05 to 0.46)	720 (2 studies)	⊕⊕⊕⊕ **high**	
	62 per 1000	**9 per 1000** (3 to 29)				
Any Adverse Event	**Study population**		**RR 1.01** (0.99 to 1.03)	17230 (10 studies)	⊕⊕⊕⊕ **high**	
	782 per 1000	**790 per 1000** (775 to 806)				
Any Grade 3 or 4 Adverse Event	**Study population**		**RR 1.02** (0.92 to 1.13)	16738 (11 studies)	⊕⊕⊕⊕ **high**	
	119 per 1000	**121 per 1000** (109 to 134)				
Drug resistance- Acute infection at enrollment	**Study population**		**RR 3.34** (1.11 to 10.06)	42 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	59 per 1000	**196 per 1000** (65 to 592)				
Drug resistance- Seroconversion post-enrollment	**Study population**		**RR 2.27** (0.48 to 10.6)	274 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	17 per 1000	**38 per 1000** (8 to 178)				
Drug resistance- Overall risk	**Study population**		**RR 1.74** (0.36 to 8.38)	6249 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	1 per 1000	**1 per 1000** (0 to 6)				
Contraception Effectiveness-FEM-PrEP	**78 per 1000**	**93 per 1000** (71 to 136)	**aHR= 1.20 (0.9-1.8)**	1216 (1 study)	⊕⊕⊕⊖ **moderate**[1]	
Contraception Effectiveness- Partners PrEP COCs	**102 per 1000**	aHR (COCs vs. no contraception) for PrEP: **0.96 (0.58-1.58)**	p-value (PrEP vs. placebo): 0.24	317 (1 study)	⊕⊕⊕⊖ **moderate**[1]	
Contraception Effectiveness- Partners PrEP Injectables	**53 per 1000**	aHR (Injectables vs. no contraception) for PrEP: **0.26 (0.16-0.41)**	p-value (PrEP vs. placebo): 0.47	883 (1 study)	⊕⊕⊕⊖ **moderate**[1]	
Adverse Pregnancy Event	**Study population**		**RR 1.25** (0.64 to 2.45)	413 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	327 per 1000	**408 per 1000** (209 to 800)				
Condom Use	**Study population**		Not estimable	(8 studies)	⊕⊕⊕⊕ **high**	
	Not estimable	Not estimable				
Number of sexual partners	**Study population**		Not estimable	(10 studies)	⊕⊕⊕⊕ **high**	
	Not estimable	Not estimable				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding**

risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Total number of events was less than 300; therefore, evidence was downgraded for imprecision.

Comment: Results for condom use and number of partners are reported in tables 13 and 14 of the systematic review report. Because measurements differed across studies, it was not possible to generate a pooled effect size.

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When to start antiretroviral therapy for children and adolescents?

A causal modelling analysis from Africa and Europe

The paediatric team of the IeDEA Southern Africa, IeDEA West Africa and COHERE collaborations[1]

Confidential analysis report to inform WHO guideline revisions in 2015

Cape Town, May 2015

1)Background

Despite considerable progress towards reducing new HIV infections in children, the burden of paediatric HIV in sub-Saharan Africa remains considerable, with an estimated 260,000 newly infected children in 2012 [1]. Antiretroviral therapy (ART) for children and adolescents in resource-limited settings has been shown to be feasible and has increased in recent years, with good outcomes, however coverage remains well below that of adults [2,3].

Criteria for ART initiation in children have varied over time and in different settings [4-8]. To date, there have been very few randomised controlled trials (RCT) that address the question of when to start ART in children in developing countries. Early ART initiation may reduce morbidity and mortality but could increase the risk of toxicity, complications due to non-adherence, and early development of drug resistance.[9-13]

- The CHER trial showed a 76% (95% CI: 49%-89%) reduction in mortality in infants, enrolled at age 6-12 weeks, for immediate ART initiation versus deferring ART when the CD4 percentage was lower than 25% [14].

- The PREDICT Trial enrolled Cambodian and Thai children and showed that for children aged 1-12 years with CD4 15-24%, there was no difference in mortality between the immediate (start irrespective of CD4 count or clinical criteria) and deferred (initiate treatment when CD4 drops to <15% or child has CDC Stage C event) treatment arms [15]. The trial did however show better height gain for children who start ART immediately. However, the authors suggested

[1] Analysis done in Cape Town by Michael Schomaker and Mary-Ann Davies with input and support from Valeriane Leroy, Geneviève Chêne, and Dorthe Raben

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that the study was underpowered to detect differences due to the lower than expected event rate.

Prior to 2008, WHO guidelines initiation criteria were largely based on the 12-month risk of disease progression in untreated children according to CD4 count or percent [4,5]. This was estimated from collaborative cohort studies such as the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) and the Cross Continents Collaboration for Kids (3Cs4kids) study [16-18]. In 2008, WHO revised ART initiation criteria in the guidelines to immediate ART for all infants <12 months of age based on the CHER results [19]. The 2010 WHO guidelines further expanded universal ART to all children <2 years of age and raised the CD4 thresholds for initiation in children aged 2-5 years of age to 750 cells/mm^3 and 25% [6]. These changes were, however, based on the risk of rapid disease progression in children 1-5 years of age, and not on RCT evidence. Most recently, the WHO 2013 guidelines have extended the recommendation of universal ART irrespective of disease severity to all children <5 years of age. [8] This was mainly motivated by potential programmatic advantages; but also a recent IeDEA-SA causal modelling analysis supported this change [20].

The evidence for the optimal timing of ART initiation in children aged 5-10 years is limited. Apart from the PREDICT trial (which was conducted in the wider age range of 1-12 years) only programmatic considerations are speculated on, but there is little knowledge regarding various clinical outcomes. There is even less evidence for adolescents (>10 years) and current guidelines are based on programmatic considerations with respect to harmonizing treatment initiation criteria in children and adults.

In light of these limitations, we are going to conduct a causal modelling analysis, comparing the effect of different treatment initiation criteria on death and growth response, for children aged 5-16 years (children who present before their 16th birthday). Adolescents aged 16-19 years will not be included as data management from different databases would have been required and this turned out to be unfeasible.

1) Data

The analysis is based on data collected from IeDEA Southern Africa (IeDEA-SA), IeDEA West Africa (IeDEA-WA), and the COHERE collaboration.

Funded by the National Institutes of Allergy and Infectious Diseases (NIAID) and the National Institute of Child Health (NICHD) the IeDEA initiative established regional centres for the collection and harmonization of data in North America, Caribbean and Central and South America, Asia and Australia, West Africa, East Africa, Central Africa and Southern Africa, thus creating an international research consortium. The regional cohorts of IeDEA have been described in detail elsewhere [21-23]. The IeDEA consortium addresses unique and evolving research questions in HIV/AIDS that are unanswerable by single cohorts. IeDEA develops and implements methodology to effectively pool the collected data, thus providing a cost effective means of generating large data

sets to address high priority research questions. Combination of data collected under various protocols tends to be difficult and not as efficient as the collection of pre-determined and standardized data elements. By developing a pro-active mechanism for the collection of key variables, IeDEA enhances the quality, cost effectiveness and speed of HIV/AIDS research. The main criterion for clinics to participate in the IeDEA-SA Collaboration is that a clinic treats people with HIV, and prospectively and electronically collects clinical data.

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) was formed in 2005 to pool and harmonize existing longitudinal data on HIV-positive persons collected across Europe to answer key research questions that, in the era of potent combination antiretroviral therapy (cART), could not be addressed adequately by individual cohorts. COHERE uses the HIV Cohorts Data Exchange Protocol (HICDEP), a standardized and validated method of data structure and transfer, to compile data from 40 cohorts of HIV-infected people residing in Europe, representing ~300,000 HIV-positive persons, and over 2 million person-years of follow-up. Mergers of data for approved projects are conducted annually. COHERE compiles data on clinical characteristics, antiretroviral therapy and other medications, HIV seroconversion, opportunistic infections, and laboratory results (CD4-positive T-lymphocyte counts, CD8-positive lymphocytes, viral load, virological and serological tests for other infections, and HIV resistance tests) and socio demographic data. COHERE projects have thus far focused on long-term prognosis, rare outcomes and variations across patient groups, settings and health systems.

To answer the question of timing of initiation of antiretroviral therapy for children, all cohorts which collected and contributed pre- and post-ART data of children and adolescents to the above mentioned collaborations, were considered: Lighthouse Trust Clinic, in Malawi; McCord Hospital, Harriet Shezi Clinic, Khayelitsha ART Programme, Hlabisa HIV Treatment and Care Programme, and Rahima Moosa Mother and Child Hospital (RM) in South Africa; Newlands Clinic in Zimbabwe; Hôpital Charles De Gaulle in Burkina Faso; Centre de Prise en Charge Enfant, Centre Hospitalier Universitaire de Yopougon, Centre Hospitalier Universitaire de Cocody, and Centre MTCT-Plus in Côte d'Ivoire; Korle Bu Teaching Hospital in Ghana; Hôpital Albert Royer in Sénégal; the Collaborative HIV Pediatric Study in the UK; the Advancing Gender Equity and Human Rights in the Global Response to HIV/AIDS network; the Cohorts of the Spanish Paediatric HIV Network; and the French Perinatal Cohort.

		Age 1-5		Age 5-10		Age 10-16	
Cohort	Region	Freq.	%	Freq.	Percent	Freq.	Percent
ATHENA	E	61	0.7	42	0.57	27	0.59
CEPREF	WA	314	3.62	324	4.4	145	3.18
CHIPS	E	298	3.44	283	3.85	193	4.24
CHUC	WA	186	2.15	151	2.05	88	1.93
CHUCDG	WA	91	1.05	85	1.16	50	1.1

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CHUY	WA	278	3.21	215	2.92	124	2.72
CORISPE-cat	E	9	0.1	4	0.05	4	0.09
CoRISpeS-Madrid	E	15	0.17	10	0.14	7	0.15
EPF	E	17	0.2	17	0.23	4	0.09
HARRIETSHEZI	SA	2,073	23.92	1,519	20.64	666	14.63
HLABISA	SA	1,112	12.83	1,039	14.12	855	18.78
KBTH	WA	396	4.57	291	3.95	98	2.15
KHAYELITSHA	SA	584	6.74	305	4.15	138	3.03
LIGHTHOUSE	SA	733	8.46	817	11.1	663	14.56
MCCORD	SA	766	8.84	832	11.31	534	11.73
MTCTP	WA	46	0.53	46	0.63	12	0.26
NEWLANDS	SA	448	5.17	572	7.77	655	14.39
RAHIMAMOOSA	SA	1,032	11.91	669	9.09	218	4.79
ROYER	WA	206	2.38	137	1.86	72	1.58
Total		8,665	100	7,358	100	4,553	100

We included data on all age groups in the descriptive analysis and evaluated the effect of different ART treatment strategies in the two older age groups, i.e. in children aged 5-10 years and children aged 10-16 years. The main analysis was done separately in each age group because measurements of CD4%, weight for age z-score, and BMI for age z-score, are not available for all age groups; therefore, the statistical approach to determine the effect of different ART delivery strategies differed slightly between the age groups, see below.

Methods

We used g-computation [20,24,25] to determine mortality and growth differences for different ART initiation strategies in the children from our database. We chose g-computation because it allows adjustment for time-varying confounders affected by prior treatment[2]; in our data these are CD4 count, CD4%, and WHO/CDC stage (approximated by weight for age z-scores [WAZ] and BMI for age z-scores [BMIAZ] - depending on the age group) which influence both ART initiation and our outcome measures (death/growth). In more detail, we regard the following variables as time-varying confounders affected by prior treatment:

- Age 5-10: CD4 count, CD4%, WHO/CDC stage
- Age 10-16: CD4 count, WHO/CDC stage

Since we don't have regular measurements on WHO stage, we use WAZ to approximate clinically severe events. The justification is that most severe events in the African context relate to a child's WAZ, e.g. tuberculosis and persistent diarrhoea[20,26-28]. For children>10 we have no WAZ but use

[2] Traditional multivariate regression techniques may yield biased treatment effect estimates.

BMI for age z-score instead. This approach has limitations, but may be the best possible option given the data availability.

Our primary study aim is to compare mortality and height outcomes for different CD4 and WAZ based treatment initiation criteria:

- Age 5-10:
  - i) Start ART immediately, irrespective of CD4 count
  - ii) Start ART if CD4 count <500 cells/mm^3 or WAZ<-2 [~WHO 2013]
  - iii) Start ART if CD4 count <350 cells/mm^3 or WAZ<-2 [~WHO 2010]
  - iv) Start ART if CD4 count <200 cells/mm^3 or WAZ<-2 [~WHO 2006]
  - v) No ART

- Age 10-16:
  - i) Start ART immediately, irrespective of CD4 count
  - ii) Start ART if CD4 count <500 cells/mm^3 [~WHO 2013]
  - iii) Start ART if CD4 count <350 cells/mm^3 [~WHO 2010]
  - iv) Start ART if CD4 count <200 cells/mm^3 [~WHO 2006]
  - v) No ART

We use g-computation to estimate (simulate) the outcomes that had been observed for all children in the database had they been treated, likely contrary to the fact, with respect to one of the treatment strategies i) to v). The implementation will follow the algorithm described in Westreich et al. and Schomaker et al. [29,30]. Missing baseline data will be imputed. Missing follow-up data will be carried forward. Children were defined as being lost to follow-up (LTFU), and censored, if at the time of database closure they had no contact with their health care facility for at least 12 months since their last recorded visit.

We therefore emulate the following trials: HIV positive and ART-naïve children, aged 5-10 years (or 10-16 years), presenting at a health care facility for the first time, are randomly assigned one of the treatment strategies (i)-(v), according to the definitions above. Each of the five arms is therefore differing by the CD4/WAZ thresholds used to determine the timing of ART initiation. Assuming full adherence to the regime, no administrative censoring, no loss to follow-up, and no grace period between ART eligibility and ART initiation, we can estimate the cumulative mortality at time t (t=1,…, 60 months after first visit) for each of the regimes as well as the growth (mean HAZ) of those children who survived until time t. In a sub-study, we evaluate the outcomes of those children who present at health care facilities with CD4 count > 500 cells/mm^3.

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The estimated cumulative mortality and growth response will be summarized in figures by means of smoothed trajectories.

2) Results

In total 8665 children aged 1-5, 7358 children aged 5-10, and 4553 adolescents aged 10-16 were contained in the database. Children in Europe presented with higher CD4 count/% and better WAZ/HAZ compared to African children. Children in West Africa presented with higher HAZ but lower WAZ compared to Southern Africa. Older children presented with lower CD4 values while comparisons between WAZ and BMIAZ between age groups is difficult due to unavailability of these measurements in some of the age groups (Table 1). Among the 5-10 year olds (10-16 year olds) 46% (58%) presented with a CD4 count<500 cells/mm^3, 26% (14%) presented with a CD4 count>500 cells/mm^3, and for 28% (28%) no data was available at the first visit; this corresponds to 1903 (615) patients presenting with a CD4 count > 500 cells/mm^3 and 2086 (1281) patients with missing CD4 cell count (note that for the g-computation analysis missing baseline data is imputed though).

The shape of height trajectories was similar when comparing the regions, but overall HAZ values were higher in Europe. The height gain was highest in children aged 1-5 years, and lowest for children presenting at ages 5-10 years (Figure 1).

In the analysis of data from children aged 5-10 the median follow-up time was 982 days (366; 1827). Mortality was estimated to be lower when starting ART earlier (Figure 2). After 5 years of follow-up the difference to immediate ART was 3.3% (2.4%; 5.0%) for “no ART”, 0.5% (0.2%; 0.8%) for “<200”, 0.3% (0.1%; 0.5%) for “<350”, and 0.1% (-0.1%; 0.3%) for “<500” (Figure 3). These differences were partly more pronounced in children who present with a CD4 count of >500 cells/mm^3 (Figure 4, Figure 5), i.e. the differences were estimated as 1.7% (0.9%; 2.6%) for “no ART”, 0.6% (0.2%; 1.0%) for “<200”, 0.6% (0.1%; 0.8%) for “<350”, and 0.4% (0.02%; 0.6%) for “<500” (Figure 5).

Similarly, the earlier ART is initiated the higher the mean HAZ of those children who survive (Figure 6). Comparing immediate ART initiation with delayed ART initiation highlights the better growth response associated with the former strategy (Figure 7). As for the mortality analysis, differences between strategies are more pronounced when focusing on those children who present with a CD4 count of >500 cells/mm^3 (Figure 8, Figure 9).

The comparison of the different intervention strategies is consistent over the three regions. Mortality was lowest and mean HAZ the highest for children included in the European cohorts. Children in West Africa at higher mortality than children from Southern Africa, but children in West Africa presented with a higher mean HAZ than Southern African children (data not shown).

In the analysis of data from the adolescents, i.e. children aged 10-16 years, the median follow-up time was 656 days (217; 1538). The results were overall similar to the results for children aged 5-10, but differences between treatment strategies are less clear pronounced. Mortality was estimated to be

higher when starting ART very late (Figure 10). After 4 years of follow-up the difference to immediate ART was 3.1% (2.4%; 4.8%) for “no ART”, 0.6% (0.2%; 1.1%) for “<200”, -0.1% (-0.2%; 0.6%) for “<350”, and 0.1% (-0.3%; 0.4%) for “<500” (Figure 11). These differences were similar when focusing on those children who present with a CD4 count of >500 cells/mm^3, but given the smaller absolute numbers of patients confidence interval were wide (Figure 12, Figure 13).

The earlier ART is initiated the higher the mean HAZ of those children who survive (Figure 14). As for the mortality analysis, differences between strategies are more pronounced when focusing on those children who present with a CD4 count of >500 cells/mm^3 (Figure 16, Figure 17); however, because of the rather small absolute numbers confidence intervals are rather wide. Results were similar for the different regions, though, again, data was sparse in Europe.

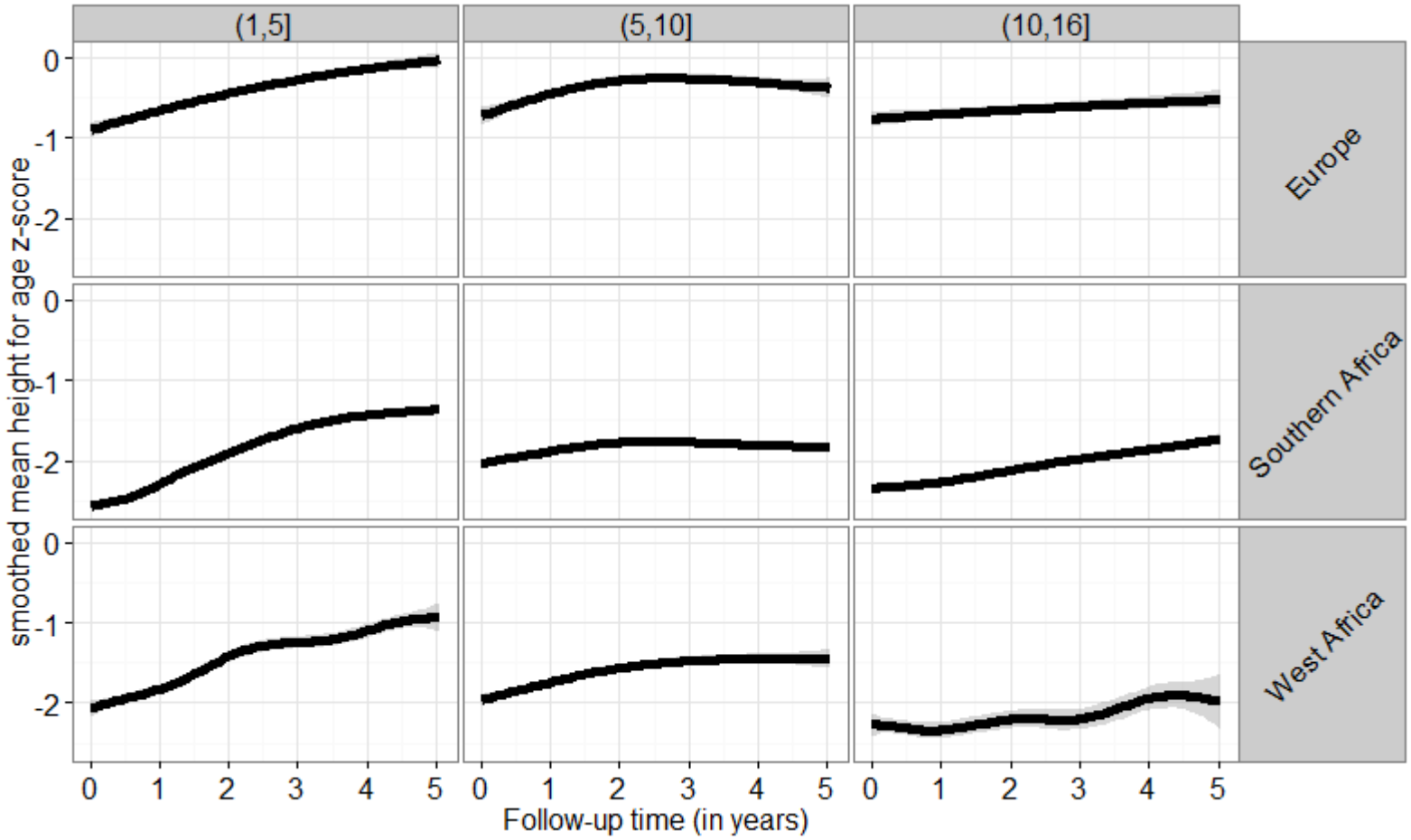
Table 1: Characteristics at first visit (available data [n (%)] + percentages per category for categorical variables and Median (first; third quartile) for continuous variables)

	Europe	Southern Africa	West Africa	1-5 years	5-10 years	10-16 years	Total
Sex	991 (100 %)	16206 (99.85 %)	3355 (100 %)	8656 (99.9 %)	7352 (99.92 %)	4544 (99.8 %)	20552 (99.88 %)
male	468 (47.23 %)	7888 (48.67 %)	1708 (50.91 %)	4419 (51.05 %)	3644 (49.56 %)	2001 (44.04 %)	10064 (48.97 %)
Age	991 (100 %)	16230 (100 %)	3355 (100 %)	8665 (100 %)	7358 (100 %)	4553 (100 %)	20576 (100 %)
Median (1st;3rd qrt)	6.08 (3.18 ; 9.73)	5.99 (2.98 ; 9.64)	5.51 (2.9 ; 8.78)	2.56 (1.7 ; 3.74)	7.19 (6.06 ; 8.46)	12.42 (11.15 ; 14.04)	5.94 (2.98 ; 9.48)
Age category	991 (100 %)	16230 (100 %)	3355 (100 %)				20576 (100 %)
1 to 5	400 (40.36 %)	6748 (41.58 %)	1517 (45.22 %)				8665 (42.11 %)
5 to 10	356 (35.92 %)	5753 (35.45 %)	1249 (37.23 %)				7358 (35.76 %)
10 to 16	235 (23.71 %)	3729 (22.98 %)	589 (17.56 %)				4553 (22.13 %)
CD4 count	835 (84.26 %)	11077 (68.25 %)	2651 (79.02 %)	6019 (69.46 %)	5272 (71.65 %)	3272 (71.86 %)	14563 (70.78 %)
Median (1st;3rd qrt)	555 (298.5 ; 879)	421 (200 ; 725)	489 (198 ; 841)	676 (394 ; 1037)	373 (172 ; 630.25)	237.5 (87.75 ; 424.5)	440 (205 ; 757)
CD4%	799 (80.63 %)	9668 (59.57 %)	2012 (59.97 %)	5471 (63.14 %)	4515 (61.36 %)	2493 (54.76 %)	12479 (60.65 %)
Median (1st;3rd qrt)	20 (13 ; 27)	15.2 (9 ; 22.7)	15 (8 ; 22)	17 (11 ; 23.8)	15.2 (8 ; 23)	12.8 (6 ; 20.21)	15.7 (9 ; 23)
WAZ	615 (62.06 %)[3]	8189 (50.46 %)[1]	2002 (59.67 %)[1]	5956 (68.74 %)	4850 (65.91 %)		10806 (52.52 %)[1]
Median (1st;3rd qrt)	-0.07 (-0.87 ; 0.69)	-1.46 (-2.49 ; -0.6)	-1.94 (-3.34 ; -0.98)	-1.46 (-2.66 ; -0.5)	-1.47 (-2.48 ; -0.62)		-1.46 (-2.57 ; -0.56)
HAZ	767 (77.4 %)	8545 (52.65 %)	2125 (63.34 %)	4834 (55.79 %)	4178 (56.78 %)	2425 (53.26 %)	11437 (55.58 %)
Median (1st;3rd qrt)	-0.65 (-1.44 ; 0.21)	-2.24 (-3.17 ; -1.29)	-1.98 (-2.94 ; -0.97)	-2.37 (-3.43 ; -1.25)	-1.81 (-2.71 ; -0.94)	-2.12 (-3.01 ; -1.21)	-2.08 (-3.07 ; -1.1)
BMIAZ	474 (47.83 %)[1]	4905 (30.22 %)[1]	1125 (33.53 %)[1]		4116 (55.94 %)	2388 (52.45 %)	6504 (31.61 %)1
Median (1st;3rd qrt)	0.24 (-0.46 ;	-0.56 (-1.45 ;	-1.4 (-2.72 ; -		-0.42 (-1.3 ; 0.32	-1.02 (-2.08 ; -	-0.62 (-1.61 ;

[3] Note that WAZ is not calculated for children >10 years, and BMIAZ is not calculated for children<5 years; thus, reported percentages seem small

	0.94)	0.21)	0.43)		)	0.15)	0.19)
ART started	991 (100 %)	16230 (100 %)	3355 (100 %)	8665 (100 %)	7358 (100 %)	4553 (100 %)	20576 (100 %)
ever	803 (81.03 %)	10289 (63.39 %)	2031 (60.54 %)	5602 (64.65 %)	4723 (64.19 %)	2798 (61.45 %)	13123 (63.78 %)

Figure 1: Smoothed mean HAZ trajectories for different age groups and regions. Descriptive summary of the raw data.



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a) Age group: 5-10 years

Figure 2: Estimated mortality for different treatment strategies

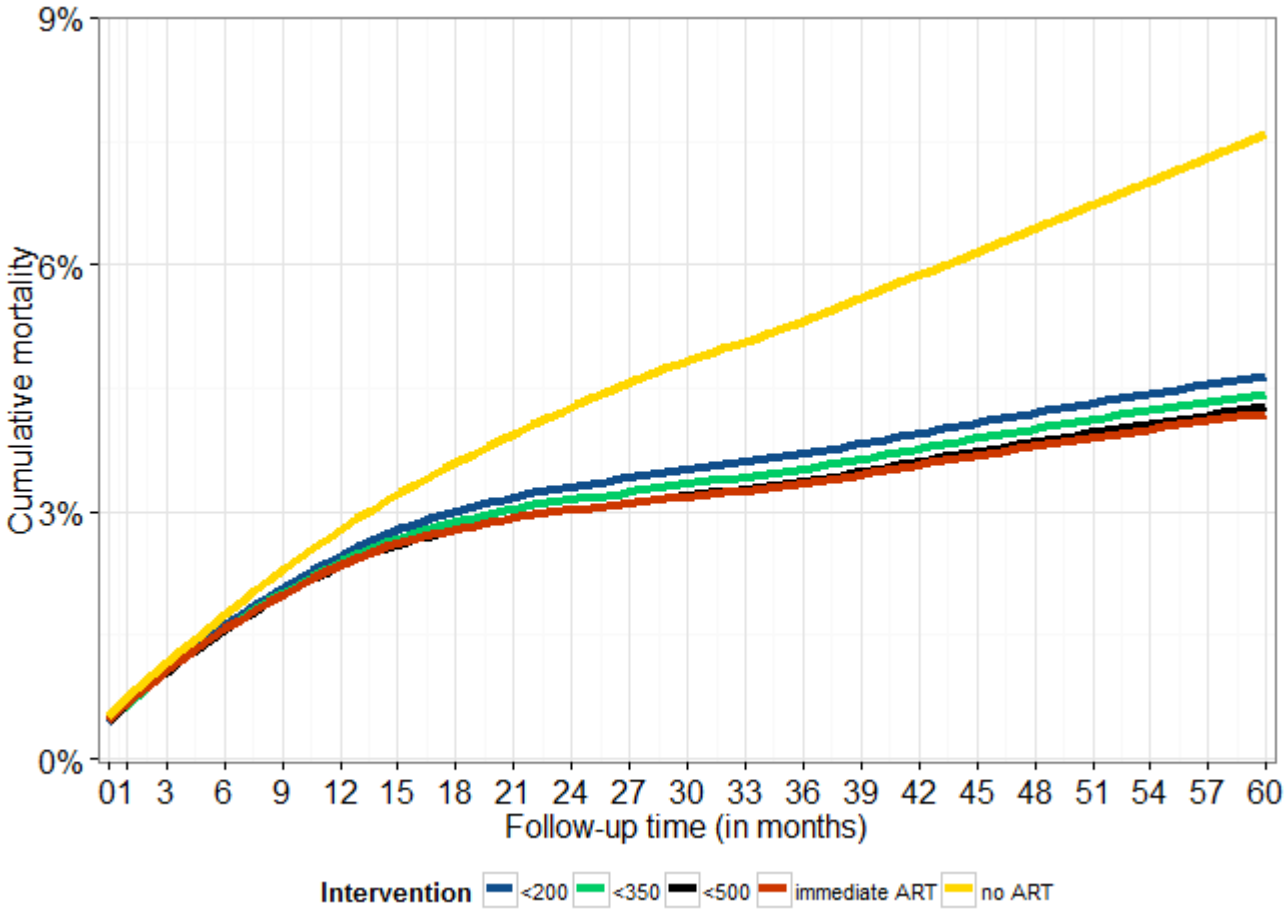

Figure 3: Estimated mortality differences of treatment strategies to `immediate ART initiation'.

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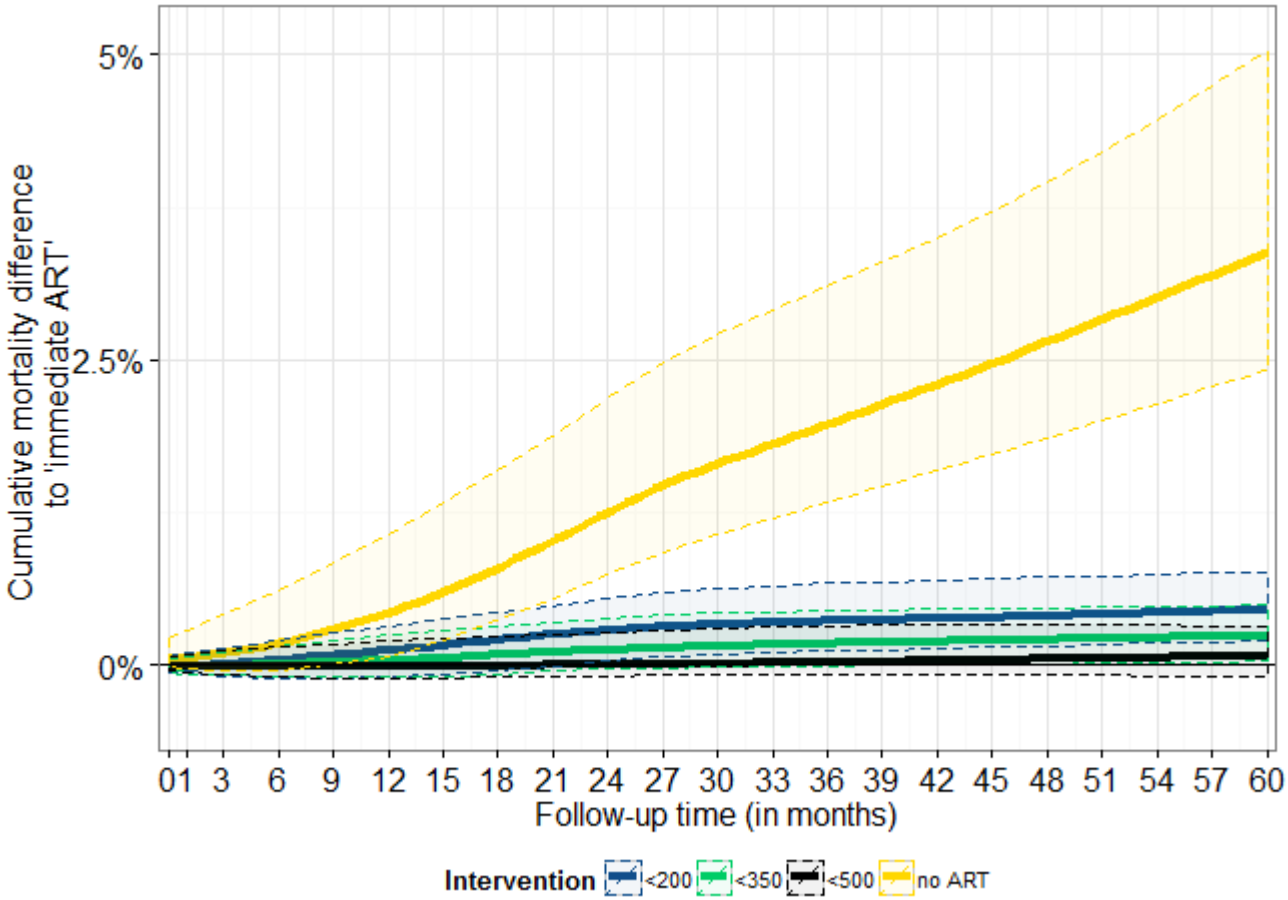


Figure 4: Estimated mortality for different treatment strategies – restricted to children who present with CD4 count > 500 cells/mm^3

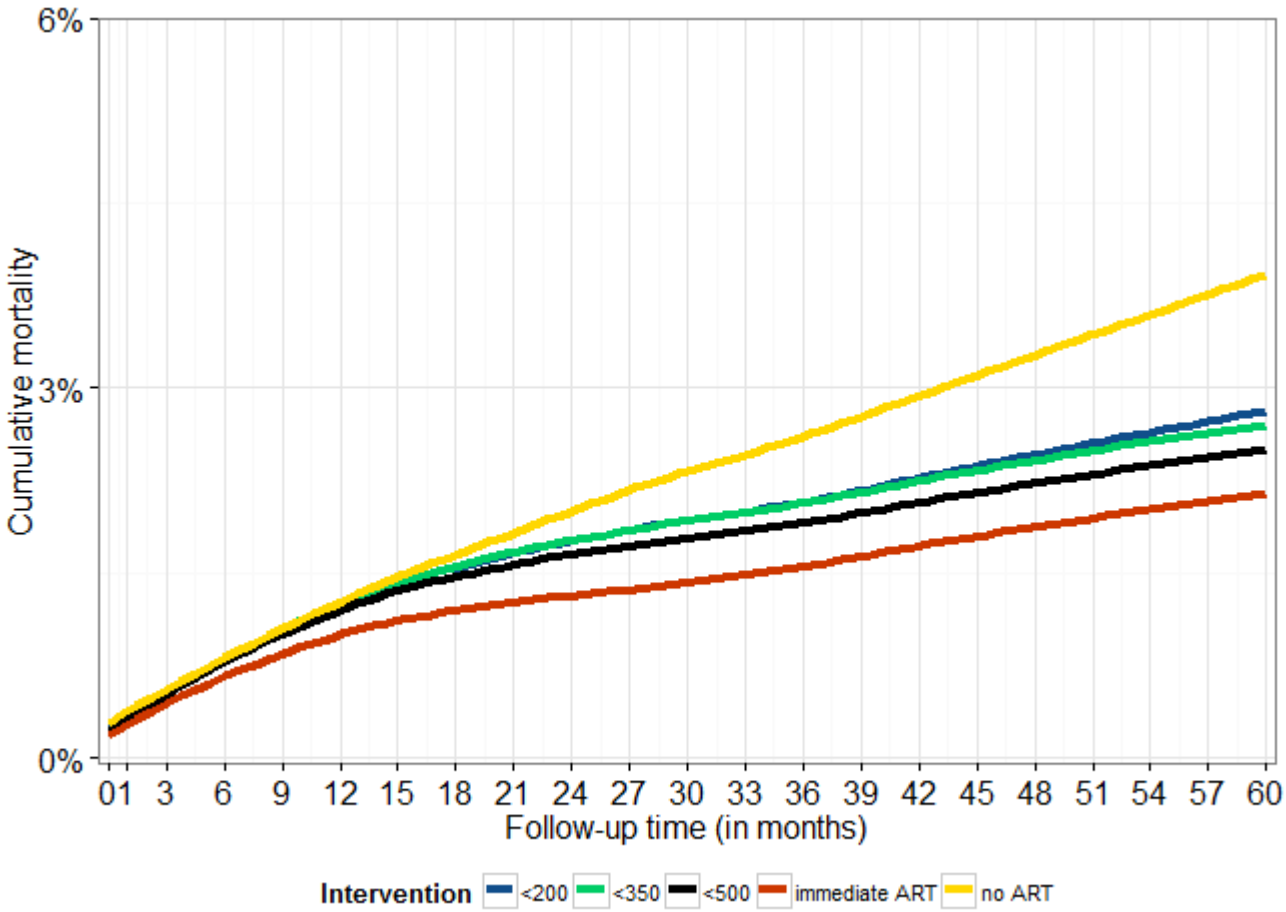


Figure 5: Estimated differences of treatment strategies to `immediate ART initiation' – restricted to children who present with CD4 count > 500 cells/mm^3

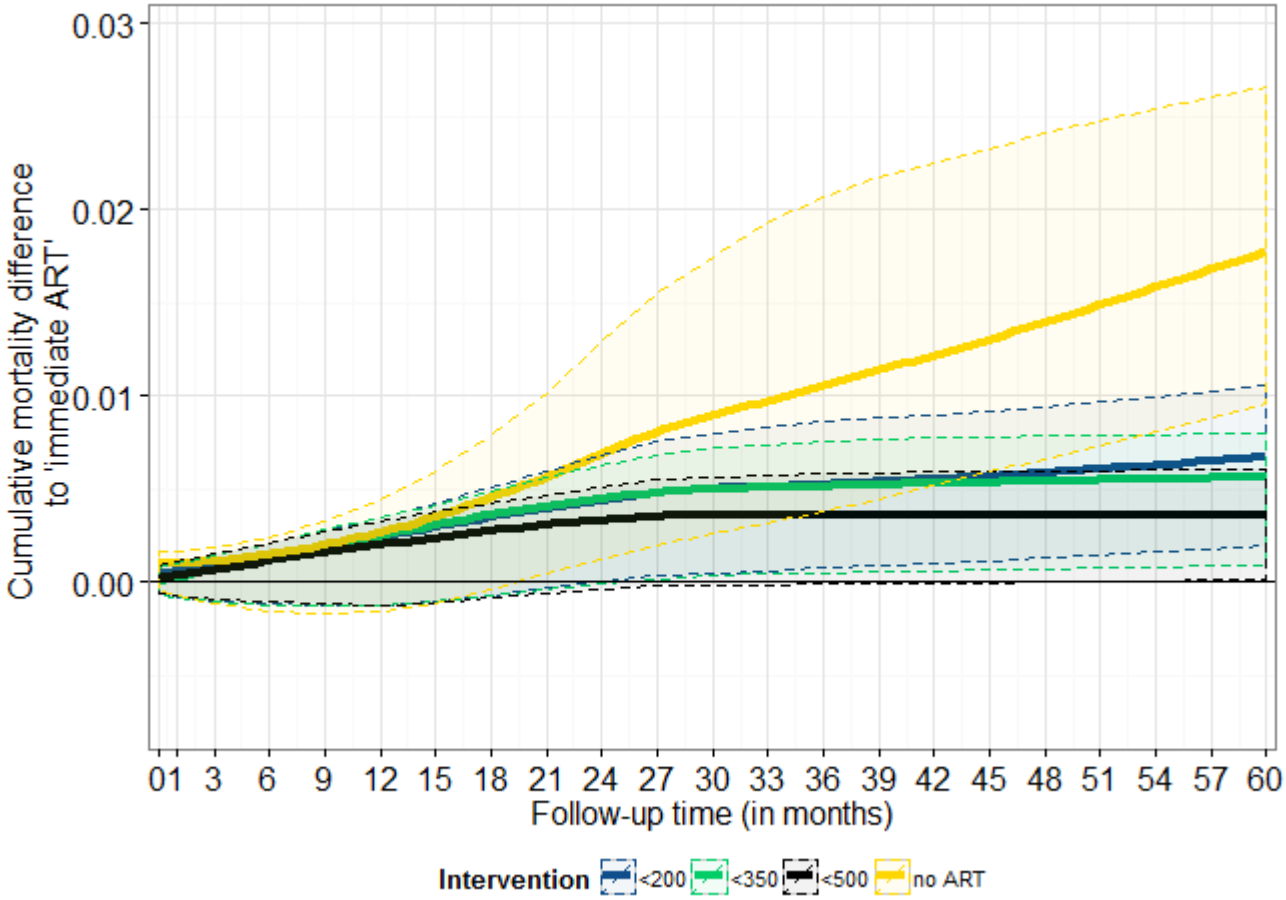


Figure 6: Estimated mean HAZ for different treatment strategies

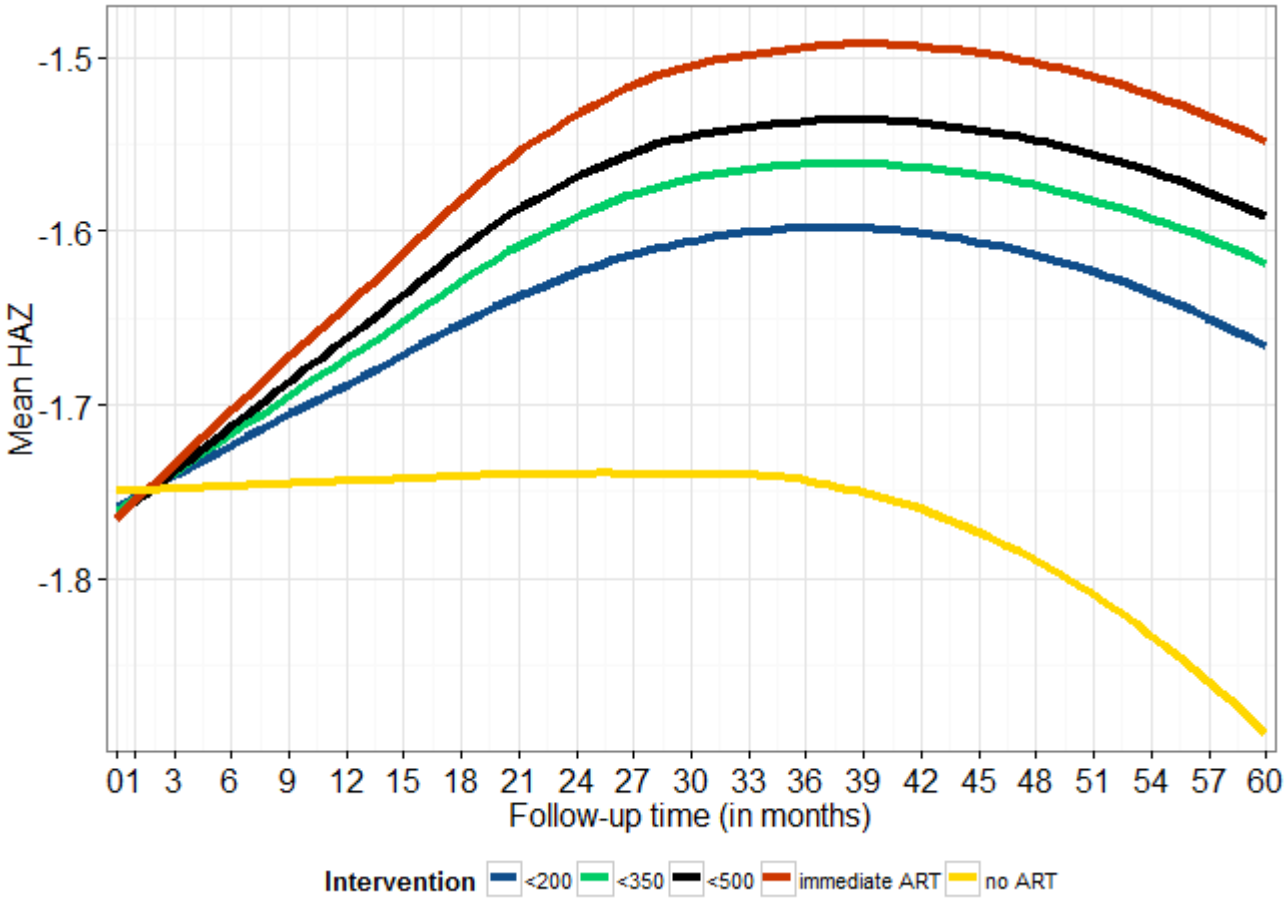


Figure 7: Estimated mean HAZ difference compared to immediate ART initiation

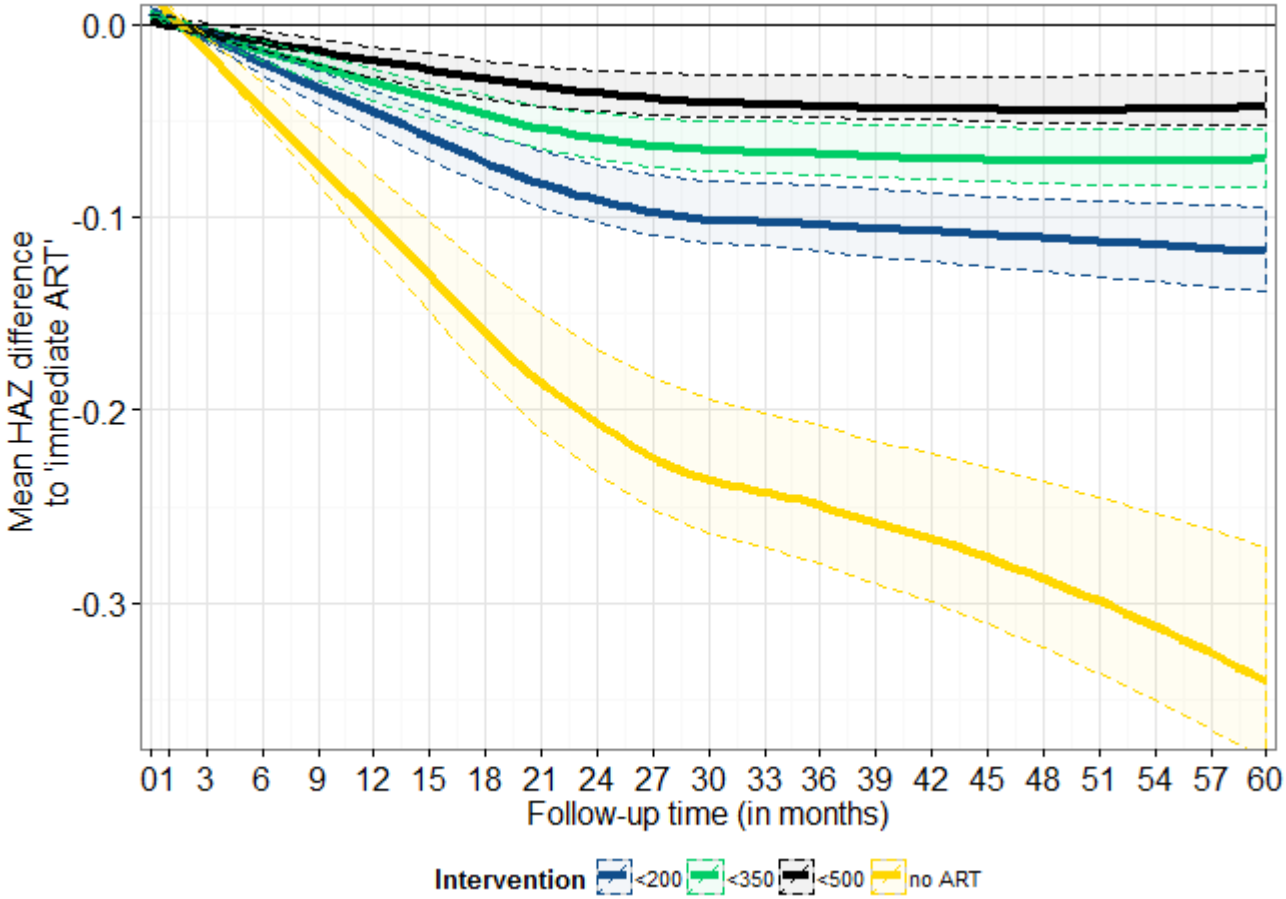


Figure 8: Estimated mean HAZ for different treatment strategies initiation' – restricted to children who present with CD4 count > 500 cells/mm^3

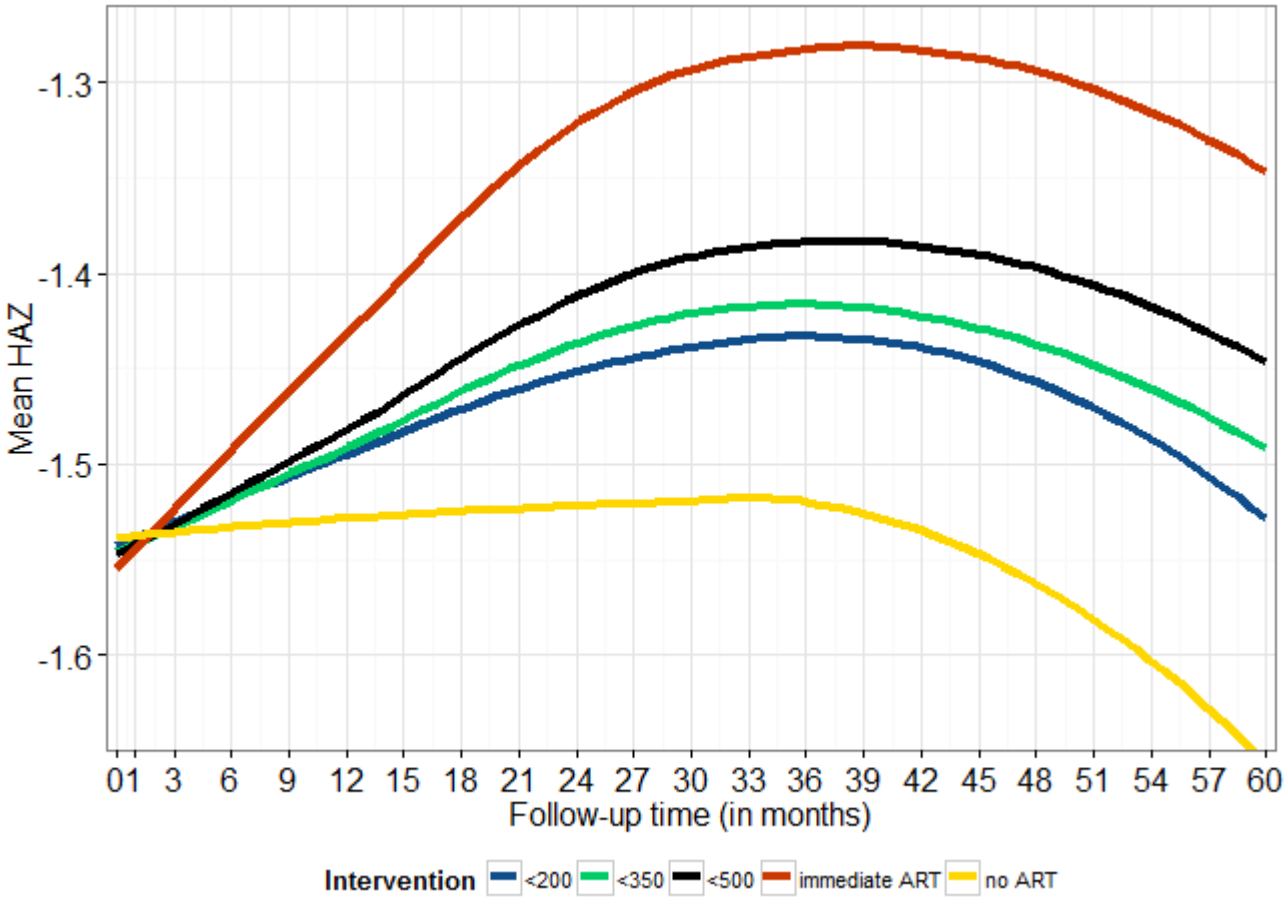
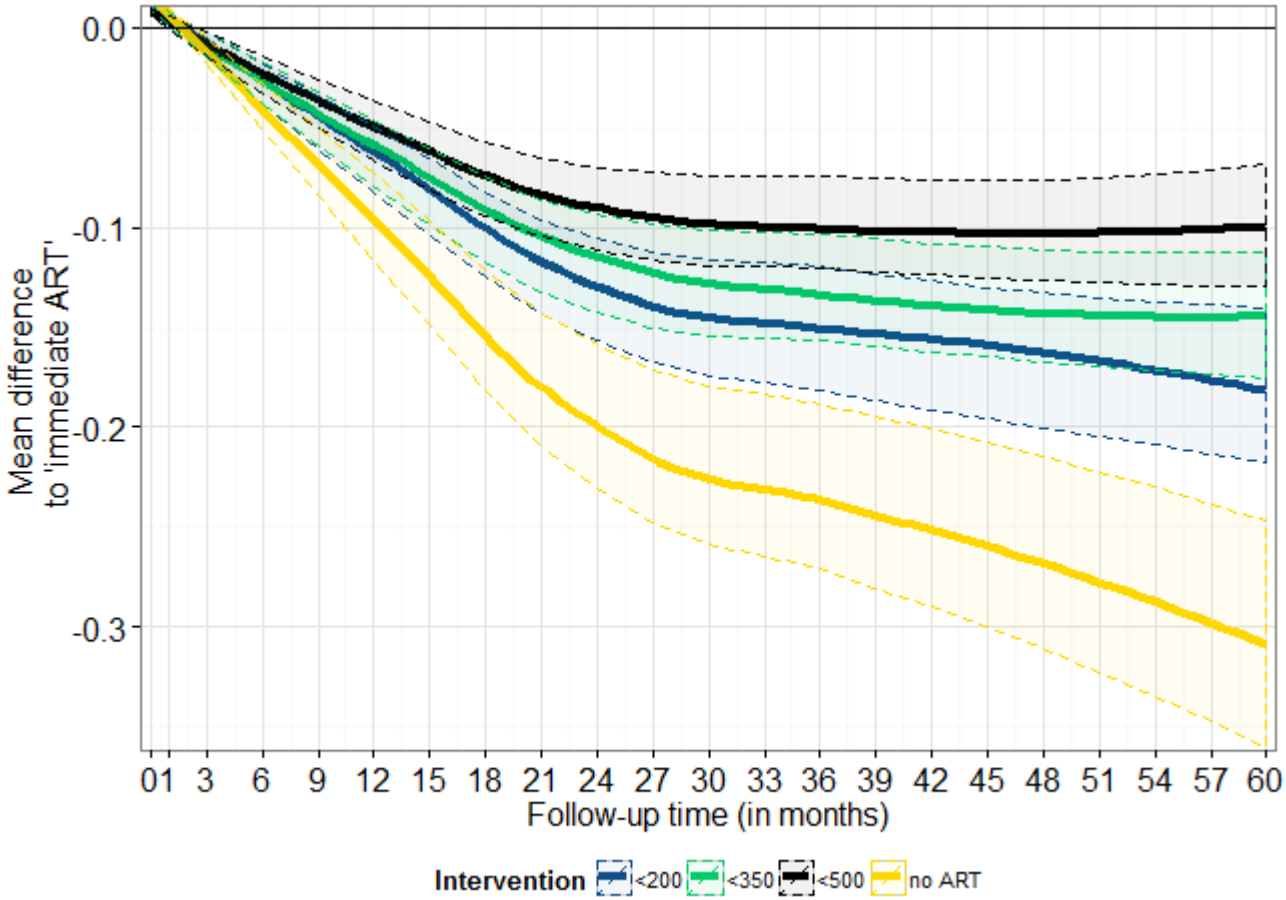


Figure 9: Estimated mean HAZ difference compared to immediate ART initiation – restricted to children who present with CD4 count > 500 cells/mm^3



b) Age group: 10-16 years

Figure 10: Estimated mortality for different treatment strategies

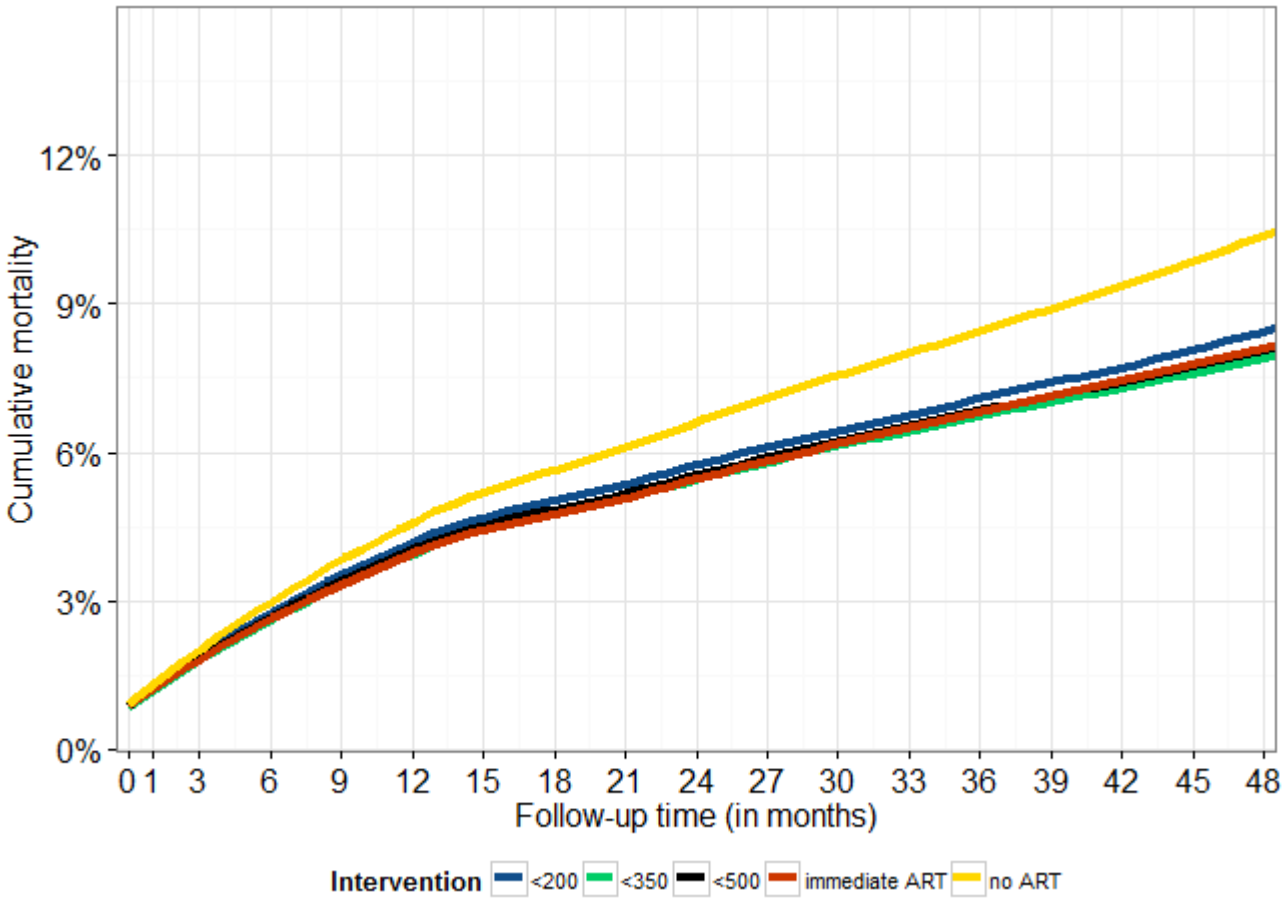


Figure 11: Estimated mortality differences of treatment strategies to `immediate ART initiation'.

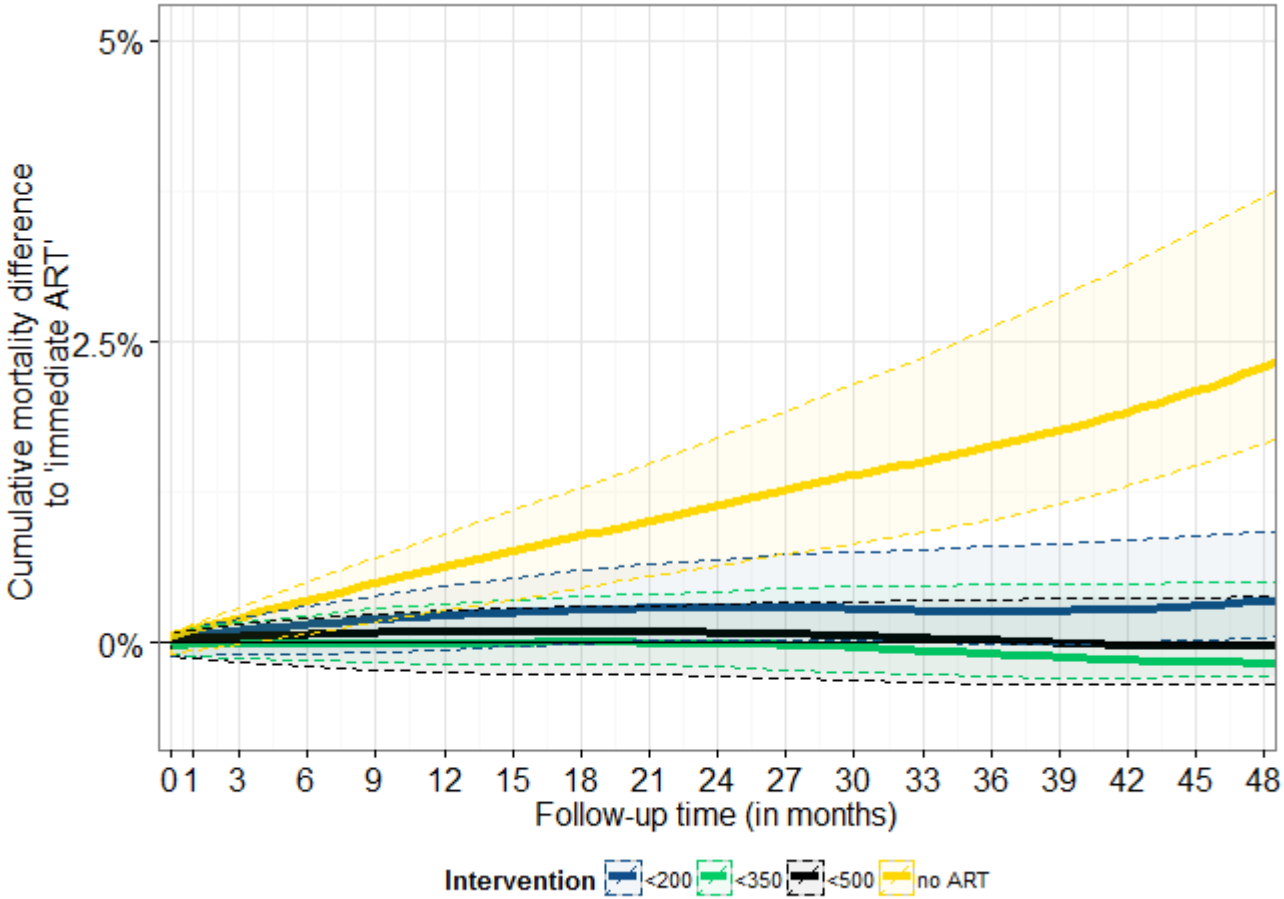


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Figure 12: Estimated mortality for different treatment strategies – restricted to children who present with CD4 count > 500 cells/mm^3

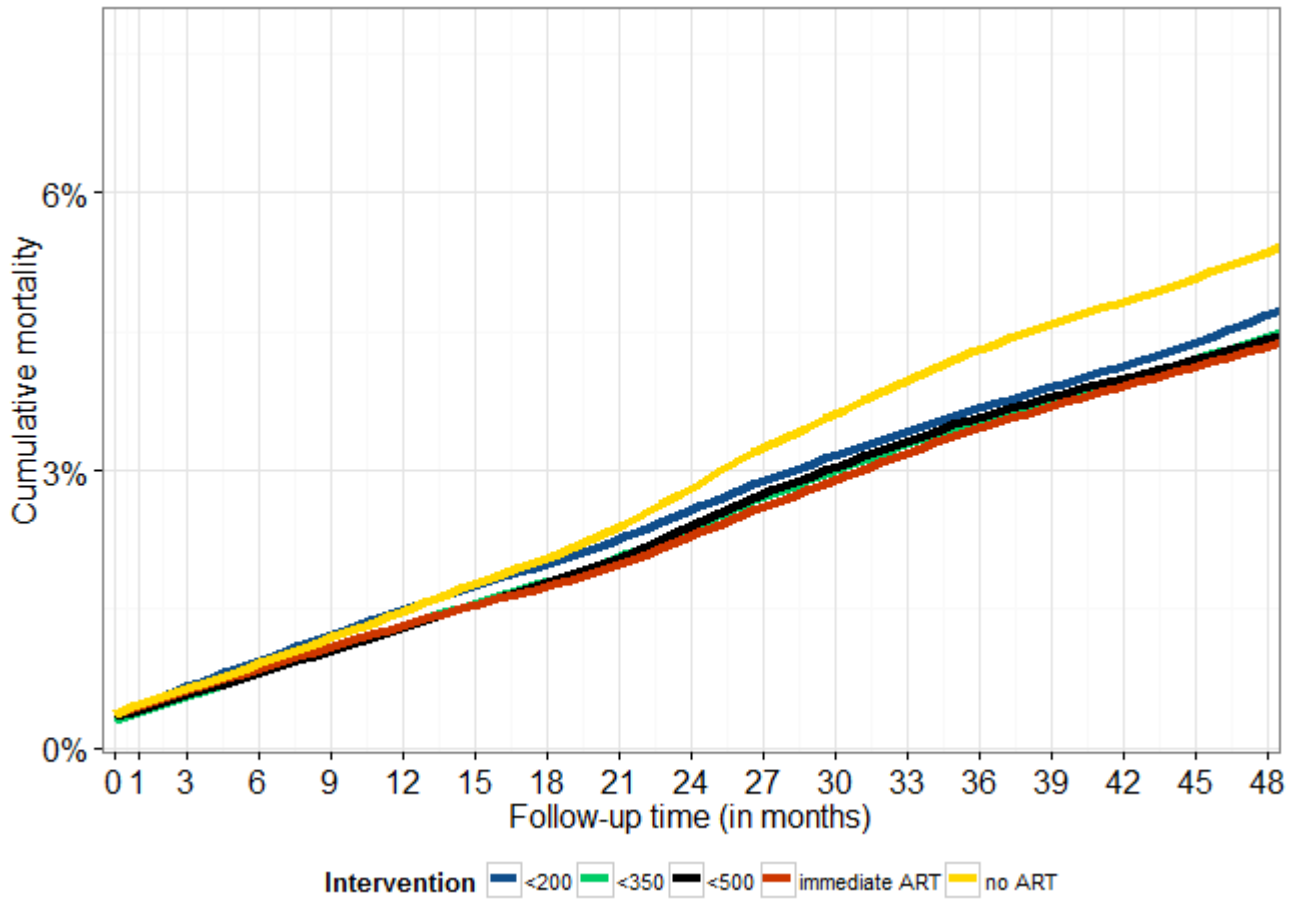

Figure 13: Estimated differences of treatment strategies to `immediate ART initiation' – restricted to children who present with CD4 count > 500 cells/mm^3

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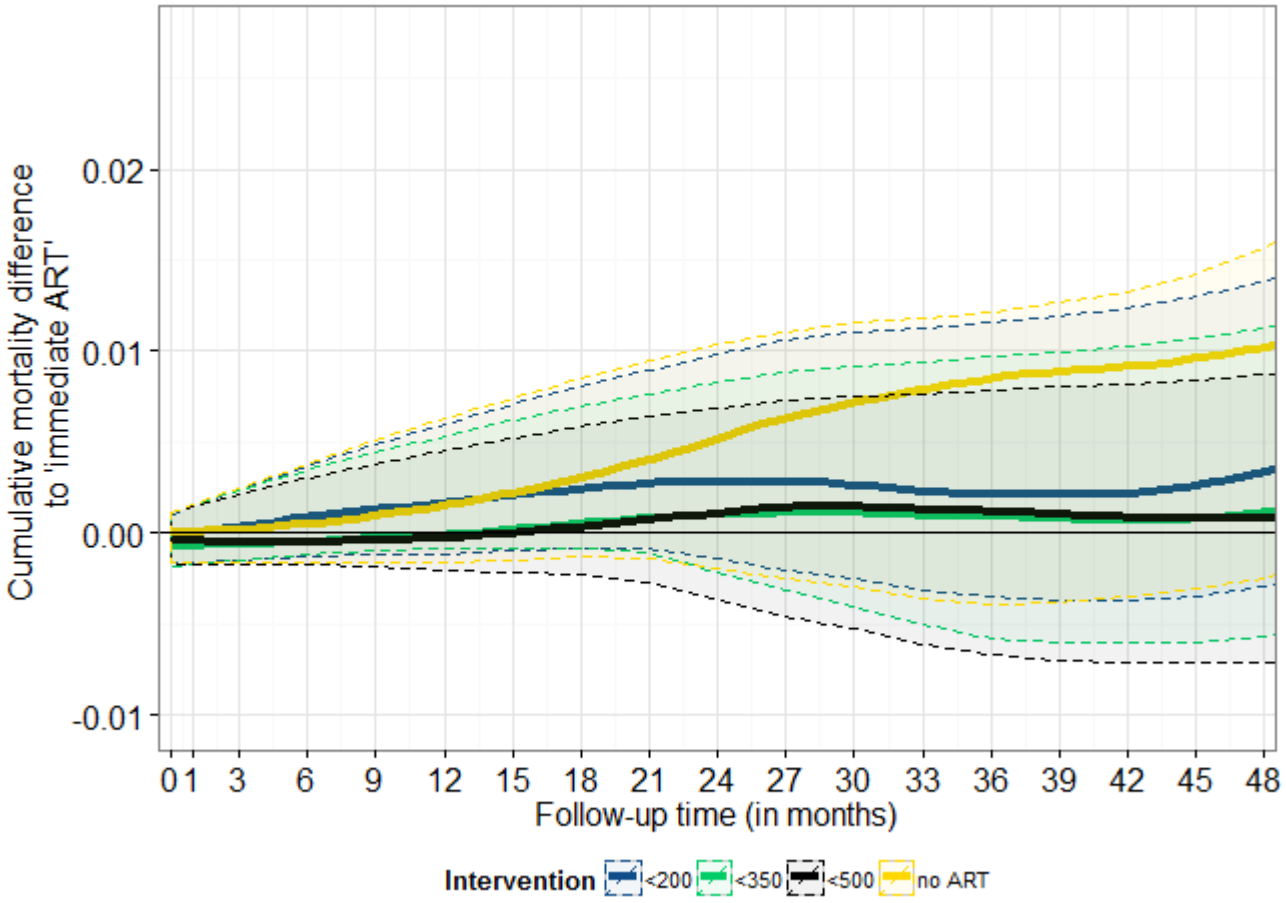

Figure 14: Estimated mean HAZ for different treatment strategies

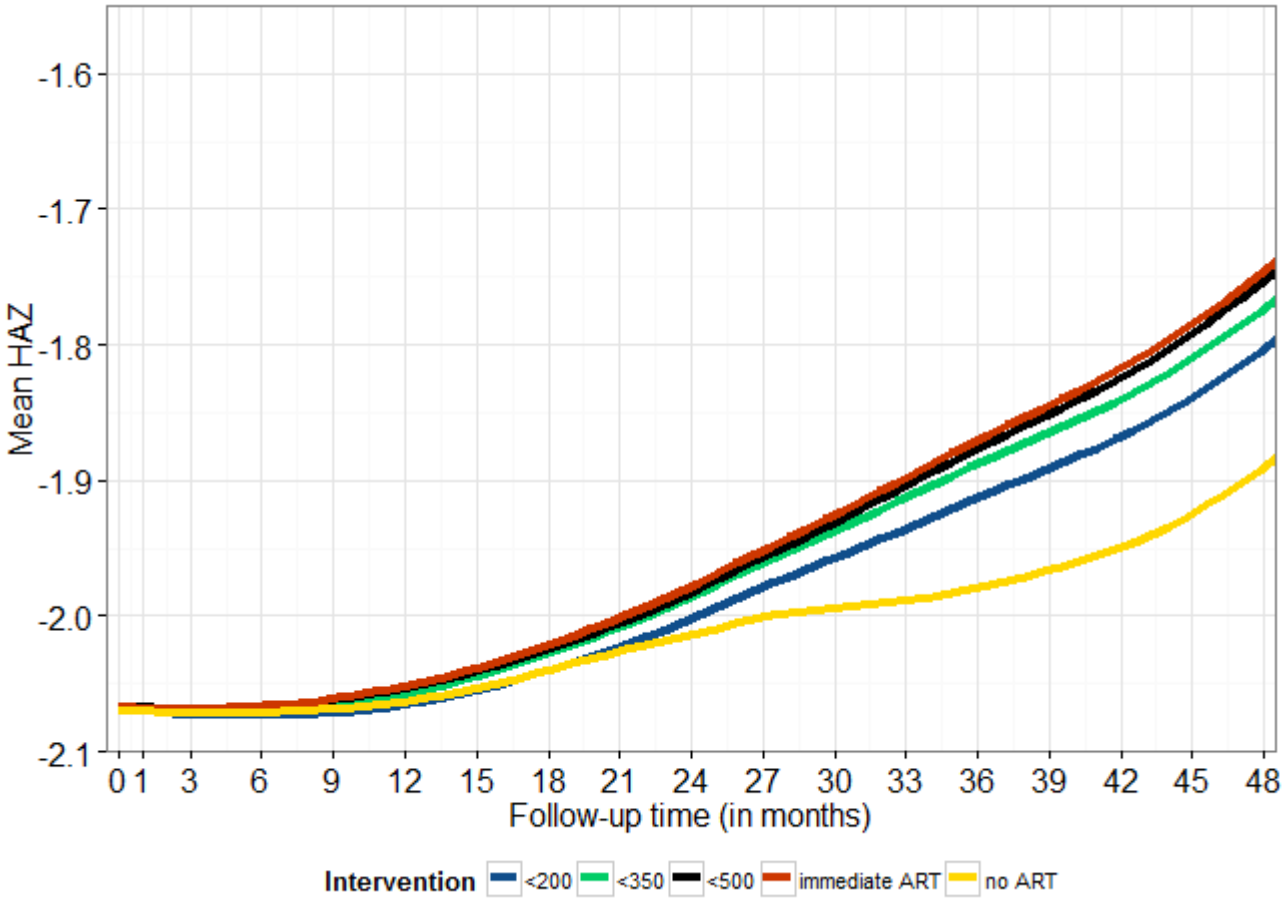

Figure 15: Estimated mean HAZ difference compared to immediate ART initiation

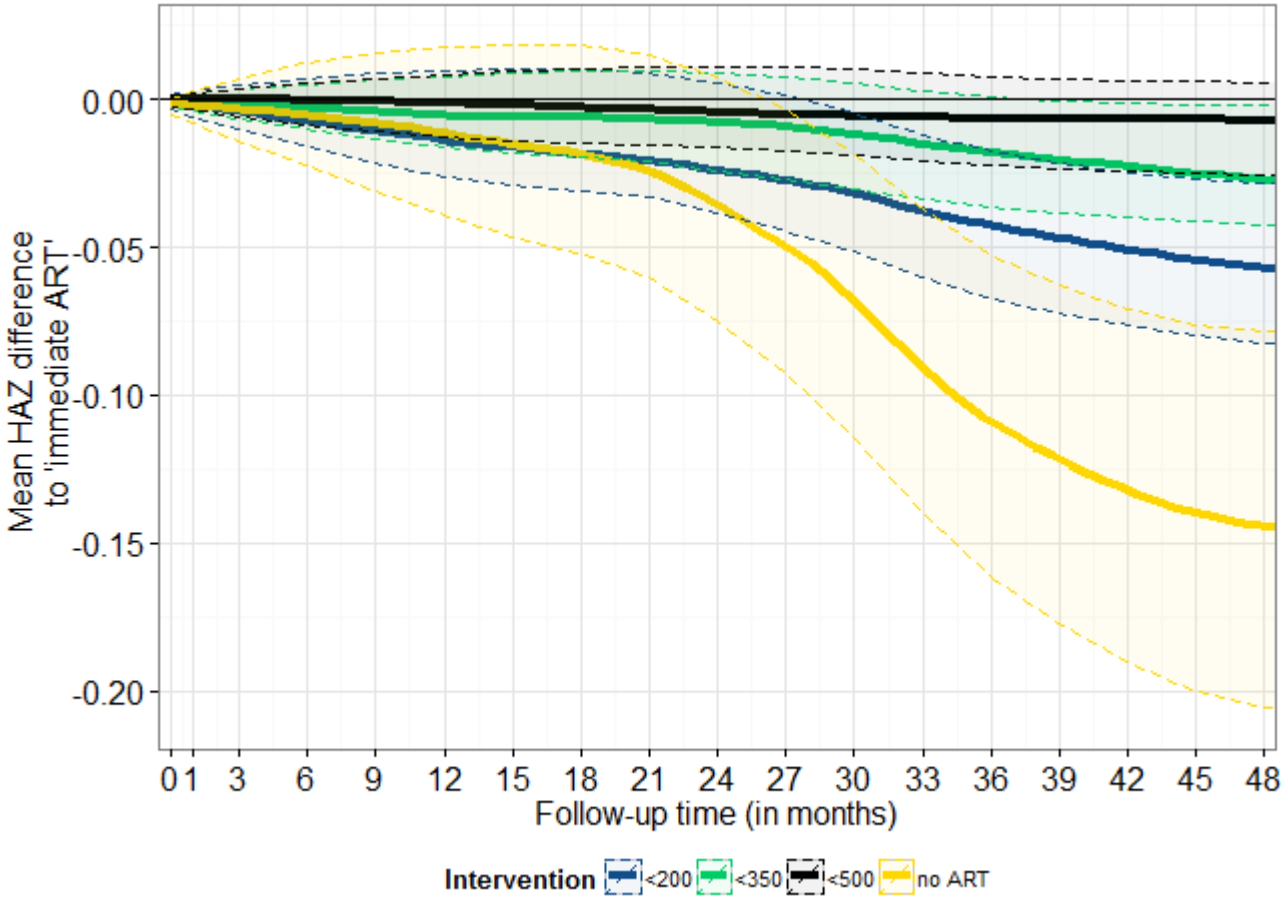

Figure 16: Estimated mean HAZ for different treatment strategies initiation' – restricted to children who present with CD4 count > 500 cells/mm^3

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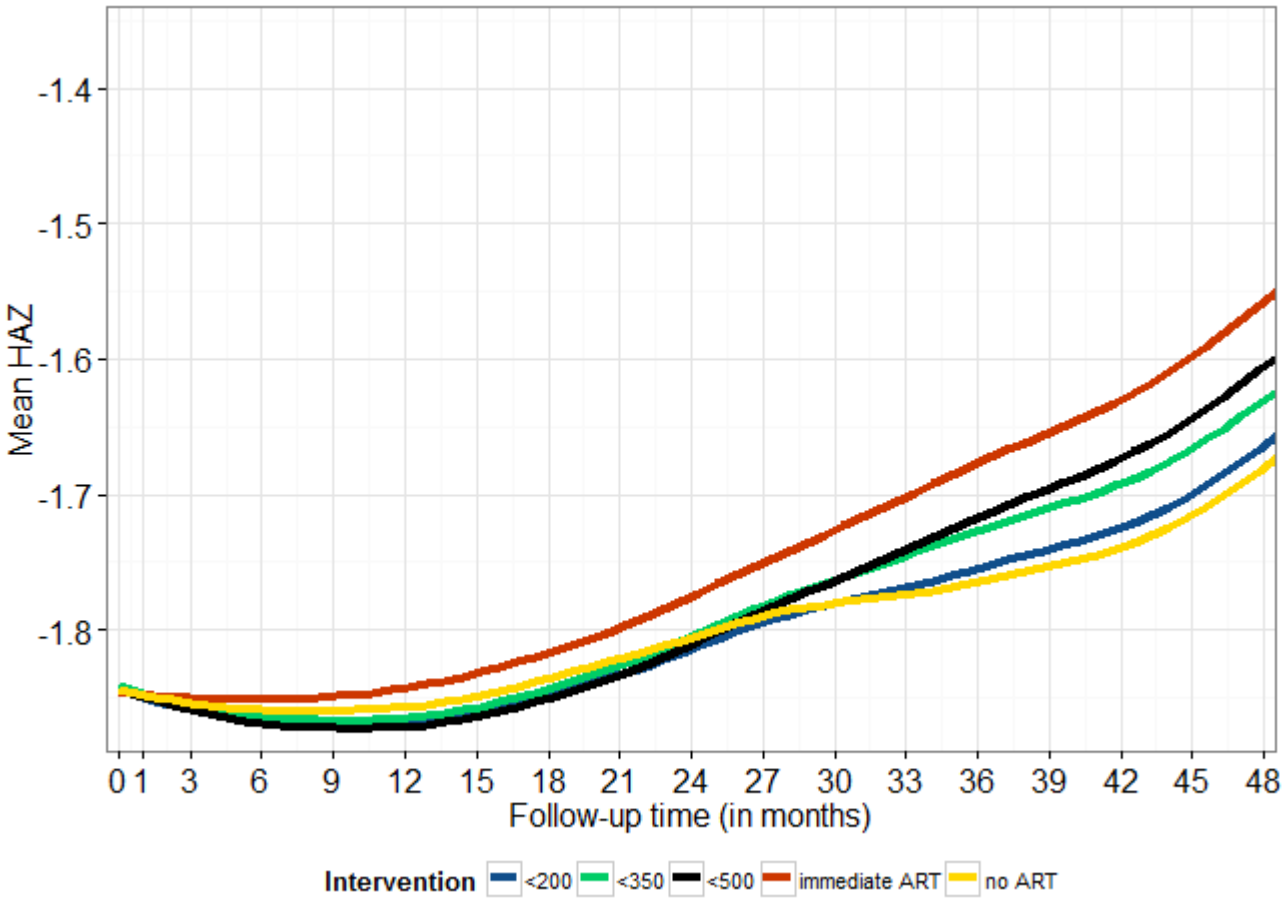
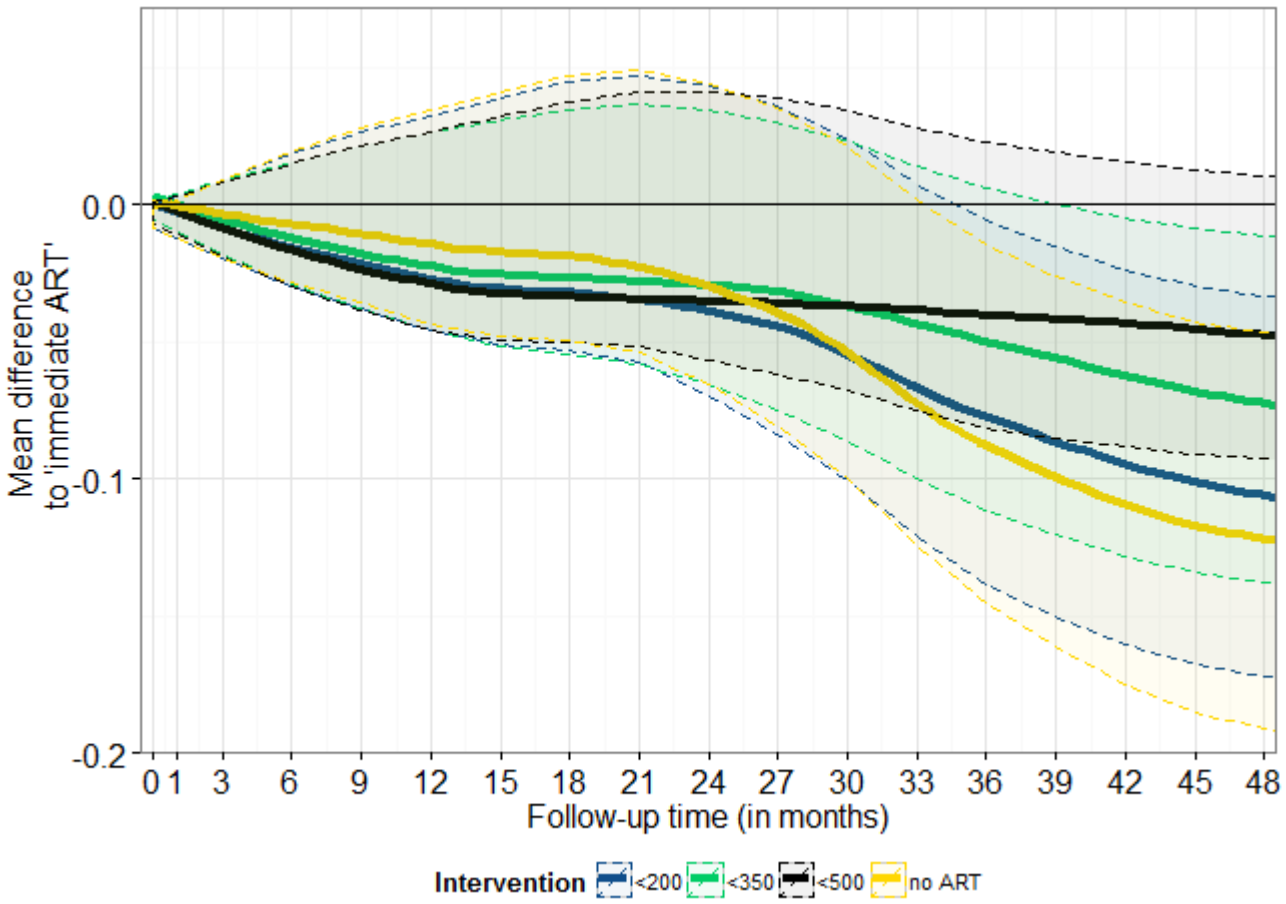


Figure 17: Estimated mean HAZ difference compared to immediate ART initiation – restricted to children who present with CD4 count > 500 cells/mm^3



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3) Discussion

The above analyses suggest that in general earlier treatment initiation yields lower mortality and better growth outcomes. The differences between immediate ART initiation and delaying until CD4 count < 500 cells/mm^3 (or WAZ <-2 for children aged 5-10) when evaluating mortality were however small or non-existent. Nevertheless, if the subgroup of children who present with CD4 count > 500 cells/mm^3 is considered, differences with respect to both mortality and growth response are more clearly pronounced, in particular for the 5-10 year olds. In general, for children aged 5-10 the differences between immediate ART initiation and delayed ART initiation is more clearly pronounced than for adolescents. The general conclusions could be confirmed in all regions, but data from Europe was sparse and results should be primarily interpreted as outcomes from urban and peri-urban African populations.

The analyses have been conducted in a careful manner, but there remain some limitations: while assumptions that could be checked (imputation, natural course scenario [30,31], model assumptions, others) indicate reasonable to good behaviour of the g-computation algorithm, there are assumptions that cannot be checked: in particular informative censoring, e.g. if sicker children are more likely to be censored (and/or defined to be lost to follow-up), could be a potential source of bias. Therefore, mortality estimates should be interpreted with caution. It may also be possible that due to the unavailability of WHO staging data our proxy measures (WAZ, BMIAZ) do not capture all information related to clinically severe events; some unmeasured confounding could therefore persist and affect our results. Moreover, follow-up in our analyses is restricted to 5 years. It could be possible that if there are benefits of delaying treatment these would only be observed at later follow-up times. For example, although treatment failures, toxicity issues, and drug resistance may occur earlier in children who start ART earlier, their long term negative effects may not be seen immediately.

It is important to bear in mind that the different age groups represent different groups of patients: the 5-10 year old children comprise mostly long term survivors whose immune system may be strongly affected by HIV infection; therefore the overall height gain for older children may not be as strong as for younger children, as also suggested by the descriptive summaries. However, because they have been living with HIV for a long time immediate ART initiation could potentially be of benefit, especially when considering the target group of children presenting with CD4 count > 500 cells/mm^3, see Figures 4,5,8,9. As indicated above, benefits of immediate ART initiation are not as clearly pronounced for the group of adolescents. Comparing the shape of the height trajectories for all 3 age groups suggests that the growth response of these children is –on average- better than the response from the 5-10 year olds, but worse than that of the 1-5 years olds; one interpretation of this points towards the heterogeneity of this group: some children may be long term survivors, but many others may be newly infected. Therefore the treatment strategy may depend on length/mode of infection and this could be part of the consideration of when to start treatment in adolescents.

There are also other considerations: changing existing structures in a health care system is a difficult and complex task. The differences estimated by causal modelling do not necessarily reflect all factors which affect population outcomes; for example, treating more children implies the need for more resources such as trained health care workers and doctors. If they are not available it may be possible that expanding treatment eligibility to all children happens at the cost of early infant diagnosis or treatment of the sickest children. If this is the case, immediate ART could potentially lead to worse outcomes than those estimated by the causal modelling.

4) Conclusion

For children aged 5-10, the above analyses show in general a trend towards lower mortality and better growth outcomes for earlier treatment initiation. The differences between immediate ART initiation and delaying until CD4 count < 500 cells/mm^3 (or WAZ <-2) were however not present when evaluating mortality. However, if the subgroup of children who present with CD4 count > 500 cells/mm^3 is considered, differences for both growth and mortality are pronounced more clearly.

For children aged 10-16 differences between different treatment strategies were less clearly pronounced. The clearest differences could be seen when evaluating the growth response in children who present with CD4 count > 500 cells/mm^3. However, given the smaller sample size confidence intervals were larger compared to the other age group. Given these considerations, as well as the mixed pool of patients in this age group, we recommend being cautious about the interpretation of the results for the adolescents.

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Priorities for HIV Care in Sub-Saharan Africa: A Population Perspective

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22 May 2015

1. Executive Summary

The provision of antiretroviral therapy (ART) has dramatically reduced HIV-related mortality in generalised HIV epidemic settings. However, over a decade since the introduction of ART, mortality rates among HIV positive adults remain three to six times higher than those not infected with HIV.

Understanding the HIV care experience, if any, among persons dying from HIV are crucial for identifying gaps in HIV care and providing direction for programs to improve, but direct population-wide data on this are sparse in high-prevalence HIV epidemic settings. In this report, we consult empirical data and mathematical modelling to estimate and project the relationship of the HIV care experience and mortality among people living with HIV.

Addressing the "When to start ART" question, we use models to simulate the potential impact of immediate ART initiation (irrespective of CD4 cell count) on HIV mortality and transmission.

Key Conclusions on the Care Cascade:

- Based on empirical data and model inference, in generalised epidemic settings, the majority of HIV-related deaths occur among adults who are **never engaged** with or **disengaged** from the HIV care system at the time of death.

- In settings with mature ART programmes presently, between **45% and 60% of all HIV-related deaths** are estimated to occur among adults who have initiated ART. Mortality rates are highest among persons on ART 6 months or less—indicative of **late initiation**—and those who have **disengaged or experienced gaps in ART care**.

- Over the coming decade, an estimated **15–35% of HIV deaths** in the will occur **among adults never linked to care**, assuming current patterns of HIV testing and linkage continue.

- Focusing on improvements in patient monitoring and care for those o**n ART for at least six months** could only affect a relatively **smaller proportion (10–30%) of deaths** occurring among patients who are stable on ART.

- **Persons disengaged** from ART (following ART initiation) have a **very high mortality rate**. The contribution of this group to overall HIV-related deaths is projected to **increase** in the coming decade and amount to **20–35% of HIV-related deaths** if current levels of disengagement and return to care persist.

- Clinic-based indicators derived from outcomes of patients who enter care is insufficient for evaluating the overall effectiveness of HIV care and treatment programmes.

- Population level data, particularly population surveillance of deaths, would help to decrease uncertainty in model-based inferences.

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Key Conclusions on 'When to Start':

- Poor retention in pre-ART care results in **missed opportunities** to initiate patients onto ART, who are subsequently lost and may return to care too late or not at all. **Immediate ART initiation** for all patients linking to HIV care is predicted to result in **6–14% fewer HIV-related deaths over the next decade than there would be if ART initiation policy remained as is**. The vast majority of that impact is due to this strategy initiating more people on ART in a timely manner rather any direct therapeutic or prevention benefits conferred by a change in eligibility from the current guidelines.

2. Introduction

Antiretroviral therapy (ART) has substantially reduced HIV-related mortality in generalised HIV epidemic settings in sub-Saharan Africa. Over the decade since ART has been available, the life expectancy for all adults has increased by around ten years in general population cohorts under demographic surveillance in eastern and southern Africa (Reniers *et al* CROI 2015). However, HIV-positive adults still experience 3 to 6-times higher mortality rates compared to those who are not infected with HIV in settings with mature HIV programmes (Reniers *et al*. AIDS 2014). Understanding the sources and reasons for excess HIV-related mortality in settings where ART is available is essential for prioritising interventions towards the points in the HIV care and treatment system where this remaining HIV-related morbidity and mortality can be reduced most effectively.

This report describes which stages of HIV care give rise to the greatest share of HIV-related deaths based on observational studies that link mortality among HIV-positive adults to previous HIV care and treatment experience and mathematical modelling. We used mathematical modelling to project how the distribution of mortality across care stages will evolve in the future and evaluate the effects on mortality of one potential modification in ART programmes - to change the eligibility criteria for ART initiation so ART initiation is immediate and does not require a CD4 count

3. Empirical evidence from mortality surveillance

Directly observed information about the previous HIV care experience among adults suffering HIV-related mortality are sparse due to limited availability of vital registration and other mortality surveillance in generalised HIV epidemic settings.

We rely on two data sources to review empirical estimates of the HIV care experience among persons dying from HIV in settings with mature ART programmes in sub-Saharan Africa:

- General population cohort studies among populations under demographic and HIV surveillance in the ALPHA network, and
- Individually linked vital registration and HIV care and treatment data from the Western Cape, South Africa.

General population cohort studies from the ALPHA Network

The ALPHA Network (http://alpha.lshtm.ac.uk/) consists of general population cohort studies in which a geographically defined population is under routine demographic surveillance—recording all births, deaths, and migrations in the population—and regular home-based population-wide HIV serosurveillance. Some sites are able to link demographic and HIV surveillance information to patient data from local HIV care and treatment facilities, furnishing population-wide estimates of HIV

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prevalence, mortality among HIV-negative and HIV-positive adults, and by stages of HIV care. Analysis for this report consists of data from four of these cohort studies (Table 3.1, Figure 3.1).

Table 3.1: ALPHA network sites included in this analysis

Study site	Country	Adults (15+ y) under surveillance, 2013	Dates of HIV surveillance	HIV prevalence at last sero-survey	% of HIV positive ever started ART, 2012
Rakai	Uganda	20,055	1998-2012	11%	28%
Masaka	Uganda	9,697	1989-2014	10%	26%
Karonga	Malawi	18,580	2007-2012	6%	41%
uMkhanyakude	S. Africa	39,145	2003-2014	28%	41%

Figure 3.1: Locations of the ALPHA Network general population cohort study sites included in this report.

The mortality rate among HIV-positive adults has declined dramatically in all sites since the availability of ART and continued to decline as programmes have matured (Figure 3.2). In each site, the 2011–'12 mortality rate among HIV-positive adults was around 25 per 1000 PYs, a 3 to 4 fold reduction from peak mortality levels. Deaths among adults on ART have increased as a proportion of all deaths in HIV-positive adults, but in 2012 the majority of deaths occured among adults who had not initiated ART, except uMkhanyakude, in KwaZulu-Natal, South Africa, where about 40% of deaths to people living with HIV occurred in adults who had never initiated ART, 20% in those who had recently initiated, and 40% amongst those having initiated more than six months ago.

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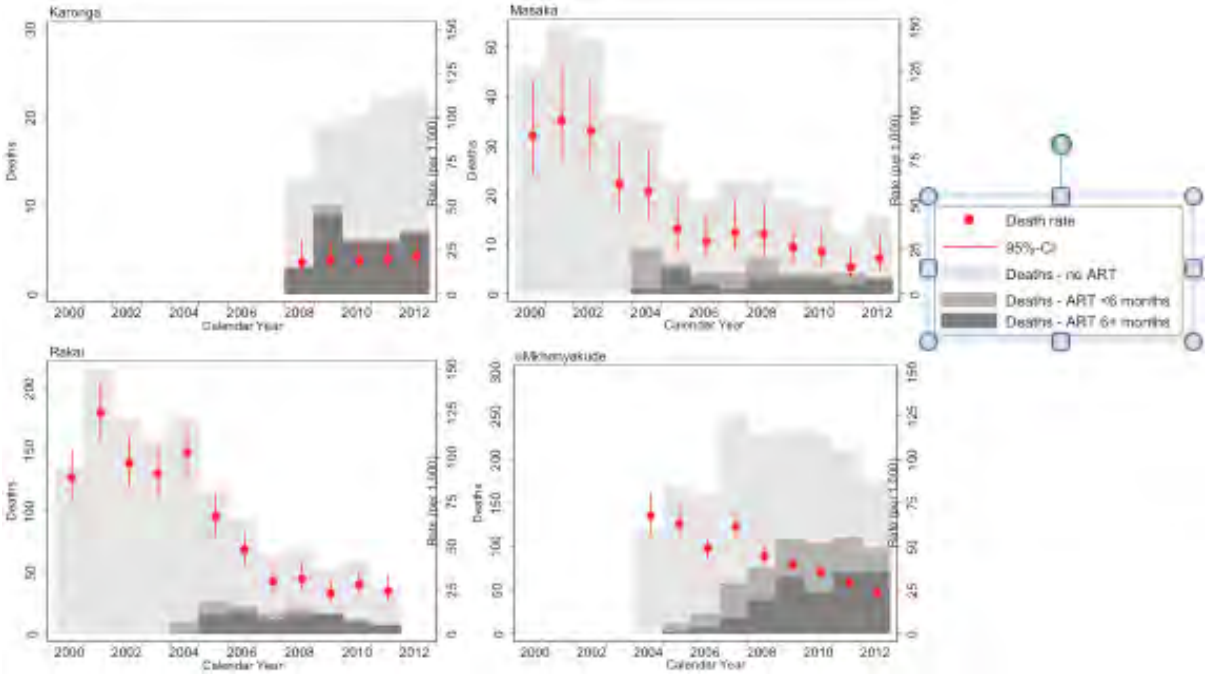

Figure 3.2: Mortality rates among HIV-positive (red dots and 95% CIs), and the number of deaths to known HIV-positive adults by ART experience.

Figure 3.3 stratifies the mortality analysis by the main stages of HIV care. Excess HIV mortality rate is calculated as the difference in mortality between HIV-positive adults compared to HIV-negative counterparts in the same five-year age group. HIV-related mortality rates are highest among adults on ART less than six months and among those who have disengaged from ART care or experienced gaps in receiving HIV treatment. However, these stages represent the smallest proportion of the HIV-positive population in 2009-2012, and so the contribution of these stages to total HIV deaths is relatively small at this time.

The largest proportion of the population is in the ART naïve groups, and mortality among each of these groups—undiagnosed, diagnosed and not in care, and linked to care—is considerably higher than mortality among patients stable on ART for greater than six months. As such, patients not yet on ART still contribute the majority of excess HIV deaths in most sites.

Figure 3.3B summarizes the distribution of excess HIV-related deaths across the care stages in each of the four sites. In most sites, the largest share of HIV-related deaths occur among patients who are not yet in care or undiagnosed—between 20 and 50% of HIV-related deaths.

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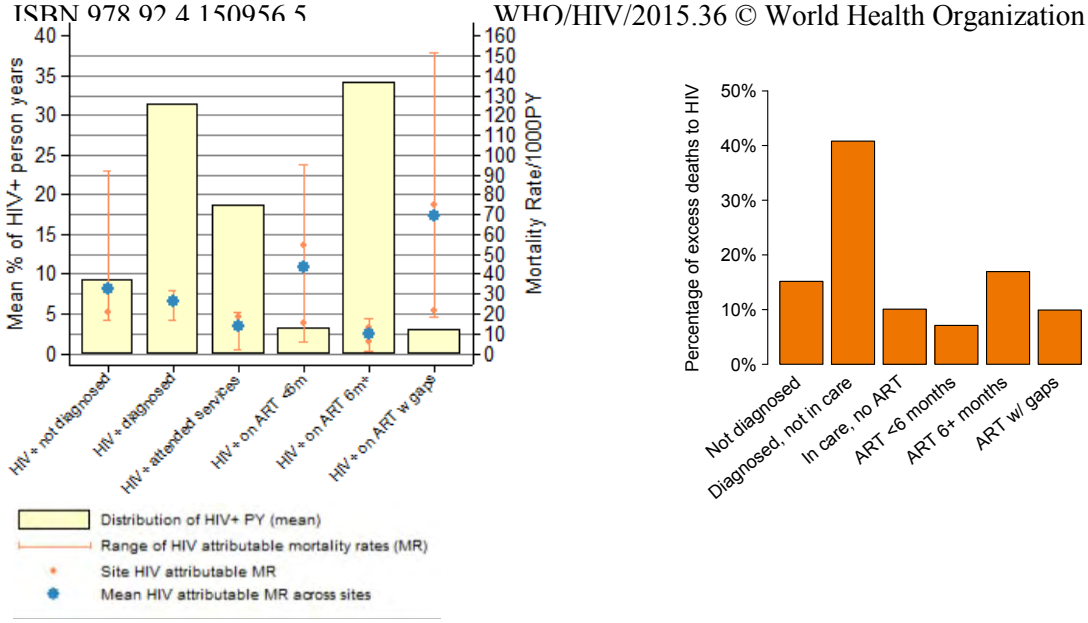

Figure 3.3: HIV-related mortality across stages of care in ALPHA Network sites. (A; left) Distribution of the population in each stage of HIV care (bar height; left axis) and excess HIV mortality rate (blue dots; right axis). (B; right) Distribution of excess deaths across care stages, combining excess mortality rate and person-years in each stage. Data pooled over all sites for period 2009 through 2012 or 2013.

Linked vital registration and HIV care and treatment in Western Cape, South Africa

Boulle and colleagues retrospectively linked HIV-associated adult deaths recorded in the Western Cape vital registration system in 2012 to patient records from HIV care and treatment (Boulle et al. 2014). A total of 38,695 adult deaths were recorded in 2012, of which 3370 were recorded as HIV-associated. Of these, 3161 (94%) were linkable to a unique patient identifier in the medical record system.

Table 3.2 summarise the stage of care reached for the 3161 HIV positive deceased persons. Eight hundred (25%) had no evidence of previous HIV-related care, 1118 (35%) had a CD4 count test but never started ART, and 1243 (39%) had previously been on ART. Among those with a CD4 count, but had never initiating ART, 882 (79%) had a CD4 count below 350 cells/µL and were eligible for ART under guidelines in force at that time, but did not initiate.

Among those patients who did initiate ART, 312 deaths (34%) occurred among those who had been on ART less than 6 months, indicative of late ART initiation attributable to failure of earlier diagnosis and linkage to care. A further 628 deaths occurred among patients who had last received ART more than 6 months before death (326 deaths) or experience a gap in treatment of 3 months or more. Only 303 deaths (9.6%) occurred among patients who had continuously been in care for the previous year—focusing on improvements to care for patients continuously on ART could only have averted a maximum of around 10% of HIV-related deaths in this year.

Table 3.2: Previous HIV care experience among HIV-related adult deaths in Western Cape, 2012.

HIV care experience	Deaths	Percentage
Not diagnosed or not linked to care	800	25.3%
Linked to care, never initiated ART	1,118	35.3%
On ART <6 months	312	9.9%
Lost from ART care or >3 month gap in receiving ART in the past year	628	19.9%

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On ART continuously for >6 months	303	9.6%
Total	**3,161**	**100%**

4. Mathematical models

To supplement directly observed data about previous HIV care experience among those dying from HIV, we generated estimates of HIV-related deaths across stages of HIV care using mathematical models calibrated to HIV epidemic and HIV diagnosis, care, and treatment data from settings with mature ART programmes.

Mathematical models

We used mathematical models representing the HIV epidemic and HIV care and treatment in four countries: Rwanda, Kenya, Malawi, and South Africa. The model for each country was independently developed and calibrated to national level estimates of HIV prevalence and ART coverage and country-specific data about HIV diagnosis, linkage to and retention in care, ART initiation, and disengagement from ART programmes. Table 4.1 describes the settings represented by each of the models and changes in CD4 ART eligibility thresholds.

The models were independently developed and each makes subtly different assumptions about patient behaviours related to HIV care seeking in order to reconcile available data about HIV testing, ART coverage, linkage, and retention in care. Table 4.2 summarises key assumptions for each model. Different model assumptions to some extent reflect the true differences across the four settings, but also highlight that available HIV care cascade indicators can be explained through different underlying assumptions about the factors that determine HIV care seeking, which may affect projections for future epidemic and mortality trends.

Table 4.1: Summary of mathematical models and HIV epidemic in 2015

Model	Country	ART CD4 eligibility†	HIV prevalence††	% HIV+ diagnosed††	% HIV+ on ART††
Bendavid	Rwanda	’03-‘12: <350 ’13-: <500	3%	81%	57%
Olney	Kenya	‘04-‘10: <200 ’11-‘14: <350 ’15-: <500	4%	83%	49%
HIV Synthesis	Malawi	‘04-‘11: <250 ‘11-‘14: <350 ’14-: <500	10%	78%	58%
EMOD	South Africa	‘03-‘10: <200 ’11-‘14: <350 ’15-: <500	17%	76%	50%

† All models additionally allow for ART eligibility based on the presence of WHO Stage 3/4 conditions or opportunistic infections. HIV Synthesis and EMOD additionally incorporate changes to Option B+ for pregnant women.
†† In the year 2015, among all adults age 15+ years.

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Table 4.2: Model assumptions about stages of HIV care and the effects of HIV-related symptoms on accessing care.

	Bendavid — Rwanda	**Olney — Kenya**	**Synthesis Transmission — Malawi**	**EMOD — South Africa**
HIV diagnosis	- 10% of adults will never test. - For remaining 90%, testing rate for HIV+ adults increases over time from 0.21 per year in 2003 to 0.42 per year in 2015.	- 14% of HIV+ adults are tested each year. - Person with WHO Stage 3/4 condition receive a test after a mean of 10 weeks.	- Test rate dependent on gender/ pregnancy, calendar time, and presence of WHO stage 3/4 event. - In 2015, 0.2 per year for non-pregnant, asymptomatic. - Persons with WHO Stage 4 event, test at rate 2.4 per year during 3 month period in which event occurred.	- Routine annual HIV testing increases over time, up to maximum of 80% of adults in 2015. - 60% probability of testing when developing HIV-related symptoms. - 60% of pregnant women receive HIV test via antenatal care.
Linkage to care	- Probability of linking to care increases from 70% in 2003 to 90% in 2015. - 50% of those lost from linkage will return to upon developing an opportunistic infection (OI).	- 90% of newly diagnosed link to care. - Asymptomatic persons return to care rate 0.15 per year. - Previously diagnosed persons with symptoms (WHO 3/4) link/re-link to care at rate 10.1 per year.	- 60% if asymptomatic; 85% if current WHO Stage 3; 95% if current WHO 4/TB. - Asymptomatic previously diagnosed persons return to care at rate 0.2 per year. - Previously diagnosed persons with WHO stage 4 re-link at rate 2.4 per year during 3 month period of event.	- 85% of those testing positive link to CD4-agnostic ART staging (WHO stage, TB, pregnancy, pediatric HIV). - Among those not eligible based on WHO Stage, TB or pregnancy, 85% return for CD4 measurement. - If ART ineligible, individuals link to pre-ART with probability that increases from 46% to 63% in 2015.
Pre-ART care	- Individuals disengage from pre-ART care at a rate of 0.06 per year.	- 90% of linked to care return for CD4 test result after 1 month. - If not ART eligible, 75% return for CD4 test after 1 year.	- All linked persons have CD4 count every 6 months, with 85% probability the scheduled test is performed. - Rate of loss from pre-ART care of 0.16 per year.	- Individuals retained in pre-ART monitoring test for ART eligibility every 6 months. - After each visit, individuals not ART eligible are retained

				in pre-ART with a 75% probability.
ART initiation	- Initiate immediately upon either presenting to care with OIs are initiated at the time of presentation or CD4 test below eligibility threshold.	- Persons with WHO 3/4 conditions when appearing for care initiate ART immediately. - Persons eligibile based on CD4 criteria results initiate ART at rate 2.5 per year.	- Eligible persons (based on CD4, WHO Stage 4, pregnancy Option B+) initiate at rate 1.8 per year before 2011 and 1.2 per year after 2011.	- 75% of persons determined eligible link to ART care and initiate ART after a delay of between immediate and 4 months.
Mortality on ART (in year 2015)	- On ART <6 mos: 21 per 1000 PYs. - On ART ≥6 mos: 11 per 1000 PYs.	- On ART <6 mos: 58 per 1000 PYs. - On ART ≥6 mos: 14 per 1000 PYs.	- On ART <6 mos: 16 per 1000 PYs. - On ART ≥6 mos: 11 per 1000 PYs.	- On ART <6 mos: 73 per 1000 PYs. - On ART ≥6 mos: 12 per 1000 PYs.
Retention on ART	- Persons on ART disengage at rate 0.01 per year. - 25% of those who who are lost spontaneously return to care within 2 years. - 50% of those lost return to care upon developing an OI.	- In first year on ART, disengage at rate 0.05 per year. - After first year, disengage at rate 0.02 per year. - Assume not to reinitiate ART.	- Rate of interruption of ART is 0.04 per year during first 2 years. - Rate of interruption 0.02 per year after 2 years. - Rates doubled for persons experiencing drug toxicity.	- ART disengagement rate is 0.033 per year. - Of those disengaging from ART, 25% are permanently lost , whereas the remaining 75% can resume ART later.

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Sources of HIV-related mortality

Figure 4.1 illustrates the HIV mortality rate (number of HIV-related deaths per 1000 HIV-positive adults) over the period 2003 through 2025 if the 2015 ART eligibility and patterns of accessing HIV care continue. Overlaid are the trends in the percentage of all HIV-positive adults who are diagnosed and the percentage of HIV-positive adults who are on ART (henceforth 'ART coverage').

Between 2004 and 2015, HIV-related deaths per 1000 HIV-positive adults declined by 66% in Rwanda, 48% in Kenya, 69% in Malawi, and 44% in South Africa, as ART was scaled-up.

Figure 4.1 illustrates the share of HIV-related mortality that occurs among persons who have not initiated ART (red) compared to those who have initiated ART (blue). The fraction of HIV deaths occurring among ART experienced adults increases as care programmes scaled-up, but in 2015 still a large fraction—40% to 60% of HIV deaths—are estimated to be among persons who never initiated ART (Figure 4.2). This includes an estimated 20–30% of HIV deaths occurring among undiagnosed persons and 25%–45% of deaths among persons who were either never diagnosed or never linked to care. These patterns are consistent with the independent empirical findings in Section 3.

Figure 4.3 compares the distribution of the HIV-positive adults across a finer classification of care stages (top panel) with the distribution of HIV related deaths (bottom panel). This illustrates large differences in HIV mortality rates across care stages (Figure 4.4).

To date, persons who have disengaged from ART have contributed a modest amount to all HIV-related deaths (purple section of Figure 4.3, bottom panel), but this proportion of HIV deaths coming from this population is expected to grow substantially, contributing between 20% and 35% of all HIV deaths in the coming decade. This accords with the findings from the Western Cape, where deaths among persons disengaged from care are already becoming dominant.

Between 30% and 50% of HIV deaths are projected to occur among persons who never initiated ART, in the absence of improvements in diagnosis, linkage to care, and ART initiation.

In contrast, adults stable on ART (for >6 months) are projected to comprise the largest share of all HIV-positive adults—around 60% of all HIV-positive adults— but they contribute a much smaller proportion of HIV-related deaths (between 17% and 30%) because they have by far the lowest estimated mortality rate (between 7 and 15 per 1000 PYs).

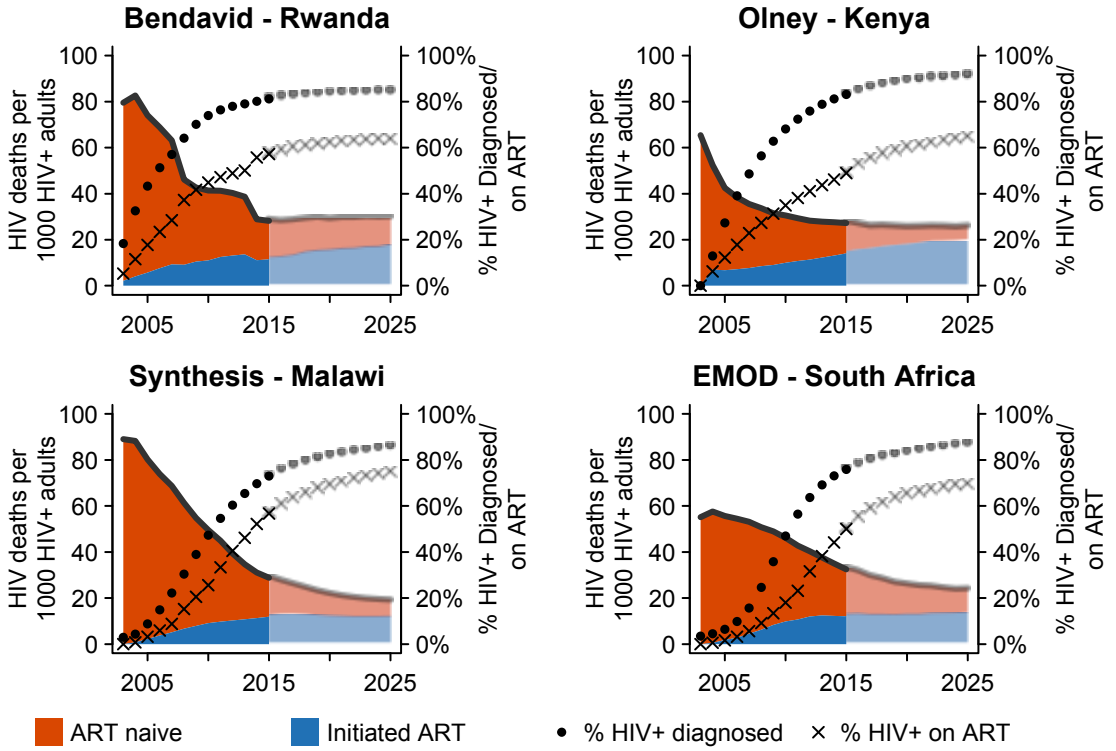

Figure 4.1: Number of HIV-related deaths per 1000 HIV-positive adults (left axis). Shading illustrates the proportion of deaths to HIV-positive adults who never initiated ART (red) and ever initiated ART (blue). Overlaid dots and crosses indicate the percentage of HIV-positive adults who are diagnosed and on ART, respectively (right axis).

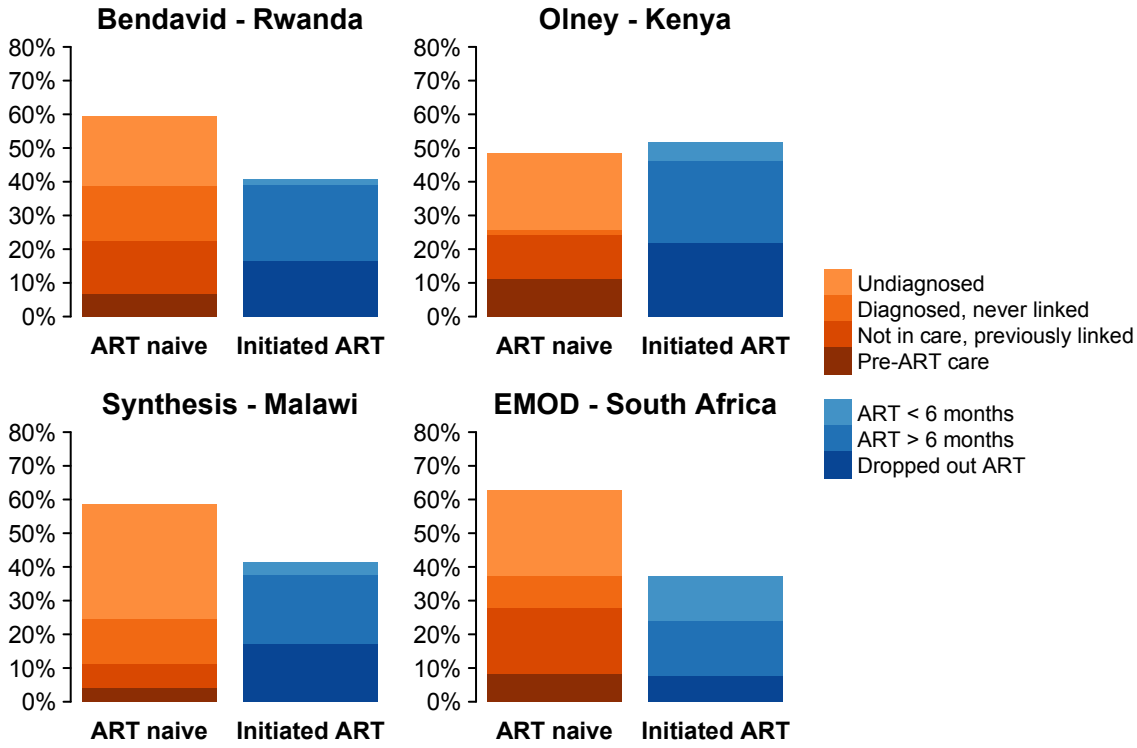

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Figure 4.2: Distribution of HIV-related deaths occurring in the year 2015 across stages of HIV care.

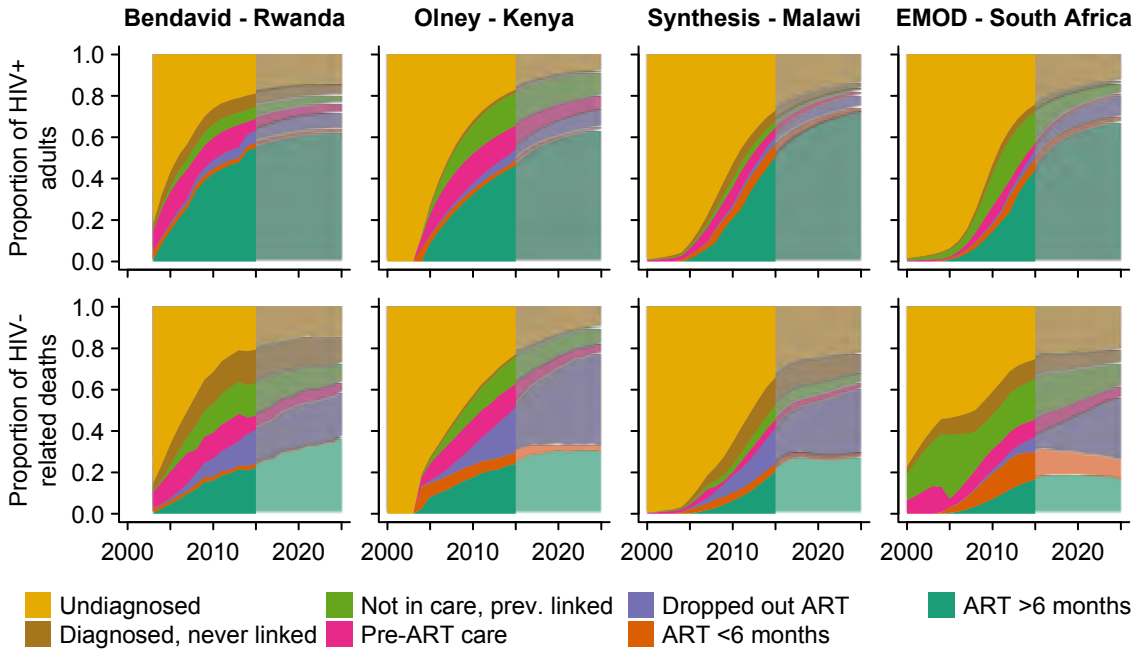

Figure 4.3: (Top) Distribution of HIV-positive adults across HIV care stages over time. (Bottom) Distribution of HIV-related deaths across HIV care stages. Translucent sections illustrate projections for HIV mortality over the decade from 2016 through 2025, assuming a continuation of current ART eligibility (CD4 <500) and patterns of accessing care.

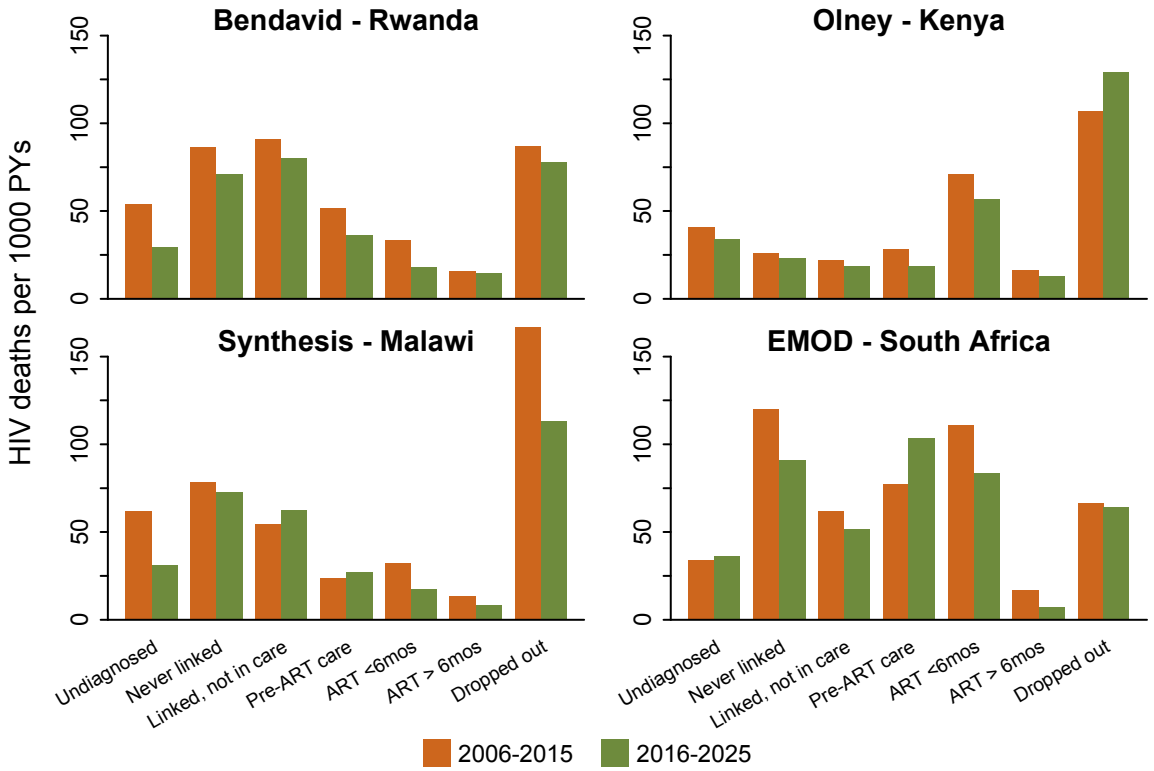

Figure 4.4: Excess HIV-related mortality rate in each stage of care over the periods 2006–2015 and 2016–2025.

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5. 'When to Start ART' – The Pragmatic benefits of immediate ART initiation

Data from Western Cape and estimates from mathematical models illustrate a substantial contribution to HIV-related deaths occurring among persons who were at one point linked to care and subsequently lost or return very late. Models estimated that between 10% and 30% of HIV deaths in 2015 occurred among persons who had at one point been linked to care but never initiated ART. Over the next decade this group will account for between 9% and 22% of HIV-related deaths if current guidelines continue in the absence of strategies that relink HIV+ persons to ART (Table 5.1).

Table 5.1: Projected percentage of HIV-related deaths among persons ever linked to care but did not initiate ART over 2016–2025.

Rwanda	Kenya	Malawi	South Africa
18%	15%	9%	22%

While direct therapeutic benefits of earlier ART initiation (above CD4 >500) could be modest and the population-wide HIV prevention benefits are still being evaluated in trials, an un-quantified potential benefit of immediate ART initiation irrespective of CD4 count are those derived from preventing the losses that occur among patients in pre-ART care.

Strictly, the extent to which immediate ART would ameliorate the mortality resulting from losses incurred during pre-ART care depends on the retention of these same patients on ART compared to pre-ART. Although data is lacking on this precise point, results from the RapIT trial in Johannesburg were very positive about the effectiveness of same-day ART initiation as a strategy for improving retention in care: among ART eligible patients, 98% initiated ART within 90 days of those randomised to receive point-of-care CD4 eligibility assessment and same-day ART initiation if eligible, compared to only 72% randomised to standard clinic initiation procedures (Rosen *et al*. CROI 2015); and clinic attendance after ART initiation and viral suppression after 6 months were the same among both arms.

The effect of immediate ART initiation on HIV mortality

We used models for Kenya, Malawi, and South Africa to investigate how a strategy in which all patients presenting for HIV care are immediately initiated onto ART would affect HIV-related mortality over the ten-year period 2016 through 2025.

Model simulations assume that HIV-positive patients linking to care initiate ART immediately instead of being referred for CD4 testing, and assume that such patients are retained on ART similarly to patients eligible under current guidelines (although data on this point is currently lacking). These simulations do not assume any other changes to HIV testing, linkage to care resulting from immediate ART eligibility.

Figure 5.1 illustrates the estimated percentage reduction in HIV-related deaths over the decade 2016–2025 resulting from immediate ART initiation. Immediate ART averted 9% of HIV related deaths in Kenya, 6% in Malawi, and 14% in South Africa. (Note that these values are less than the values given in Table 5.1 as some of the deaths that would have occurred among those disengaging following linkage in Table 5.1 would not be averted by immediate ART initiation.)

Over the period 2015-2025, the vast majority of that benefit comes from initiation of more people on ART and them starting earlier (Figure 5.2). Over the longer-term, the additional benefit of reduced transmission may become an important factor as well.

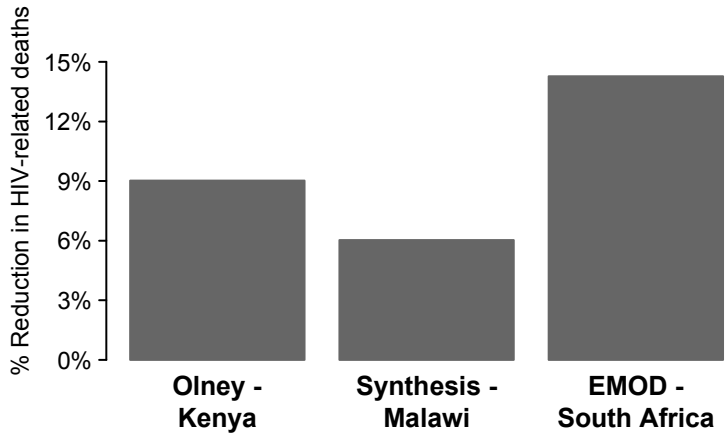

Figure 5.1: The percentage reduction in HIV-related deaths over the period 2016 through 2025 associated with immediate ART initiation irrespective of CD4 cell count compared to continuing CD4 <500 eligibility criteria. Other than immediate ART initiation for patients linking to care, simulations do not assume any other changes to HIV testing, linkage to care resulting from immediate ART eligibility. Each of the models also incorporate effects of reduced HIV transmission. Olney and Synthesis assume modest reductions in the risk of HIV-related morbidity or mortality for persons initiating ART with CD4 >500 (which is already very low in the absence of ART), while EMOD assumes no immediate therapeutic benefit of immediate ART initiation.

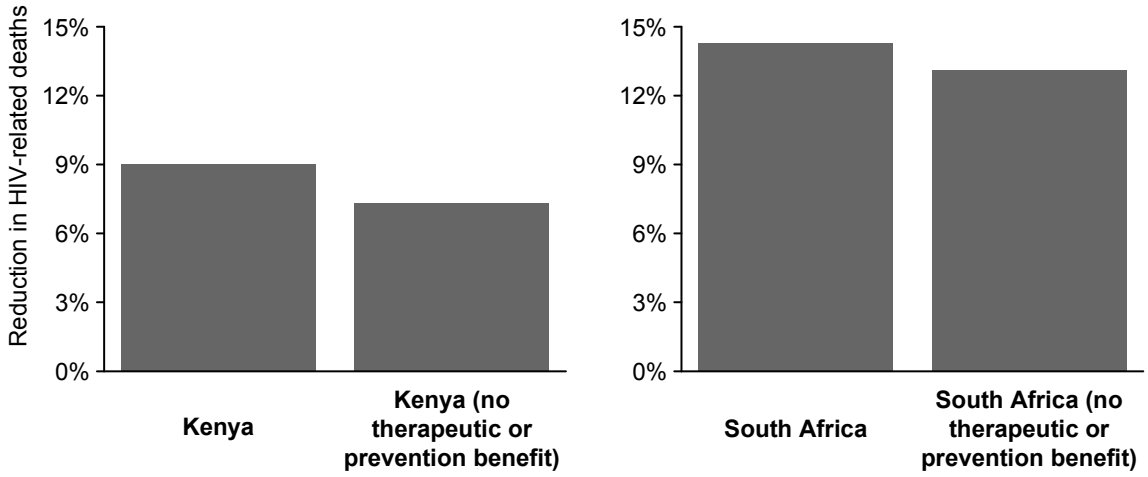

Figure 5.2: The effect of immediate ART initiation on HIV-related mortality during 2016–2025 assuming no therapeutic benefit from earlier ART initiation (i.e. untreated persons with CD4 >500 experience the same mortality as those on ART) and no prevention benefit (i.e. the same number of new infections occur each year irrespective of treatment policy).

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6. Defining priorities for improving HIV care

HIV programmes should commit resources to where they are expected to generate greatest health gains in the population (i.e. so that resources are used 'cost-effectively'). This will require combining information about where HIV deaths are occurring, described in sections 3 and 4 of this report, with accumulating evidence about which interventions can effectively reduce HIV deaths and the costs of these interventions.

With good data on programs and the estimates of the cost and impact of a range of interventions, it is possible to provide further evaluation of different options for strengthening the care cascade.

We calibrated a mathematical model to a longitudinal dataset from the Academic Model Providing Access To Healthcare (AMPATH) program in Western Kenya. These data describe the routes into care, losses, and clinical outcomes. We simulated the cost and impact of interventions acting at different stages of HIV care, including improvements to diagnosis, linkage to care, retention and adherence on ART, and immediate ART eligibility and universal test-and-treat. We quantified impact in health in terms of DALYs averted over a period 2010-2030, incorporating reduced death and morbidity from HIV infection, and any reductions in numbers newly infected.

We found that no individual intervention on the cascade is expected to avert more than 10% of DALYs (Figure 1). This small impact is because any single intervention is confounded by other weaknesses in the cascade. The changes to better retain patients on ART and to remove the pre-ART stage of the cascade by initiating ART for any HIV-positive person as soon as they are diagnosed, give greater impact than any other single intervention.

However, a combination of interventions (including improved testing and linkage, together with pre-ART and ART outreach strategies) was estimated to generate a much larger impact and it is likely (based on provisional estimates of cost) to avert DALYs cost-effectively. The combination of HIV care interventions was estimated to generate a similar level of health gains as a radical expansion to 'Universal test and treat' over this time frame but at substantially lower cost. Switching to a policy of immediate ART initiation in addition to this combination of 'cascade interventions' would lead to even larger health gains.

These results show that moving to a UTT strategy with a leaky cascade would not maximize health benefits in a resource-limited setting, whereas a combination of interventions that strengthen the cascade including a move to immediate ART initiation could generate substantial health gains cost-effectively.

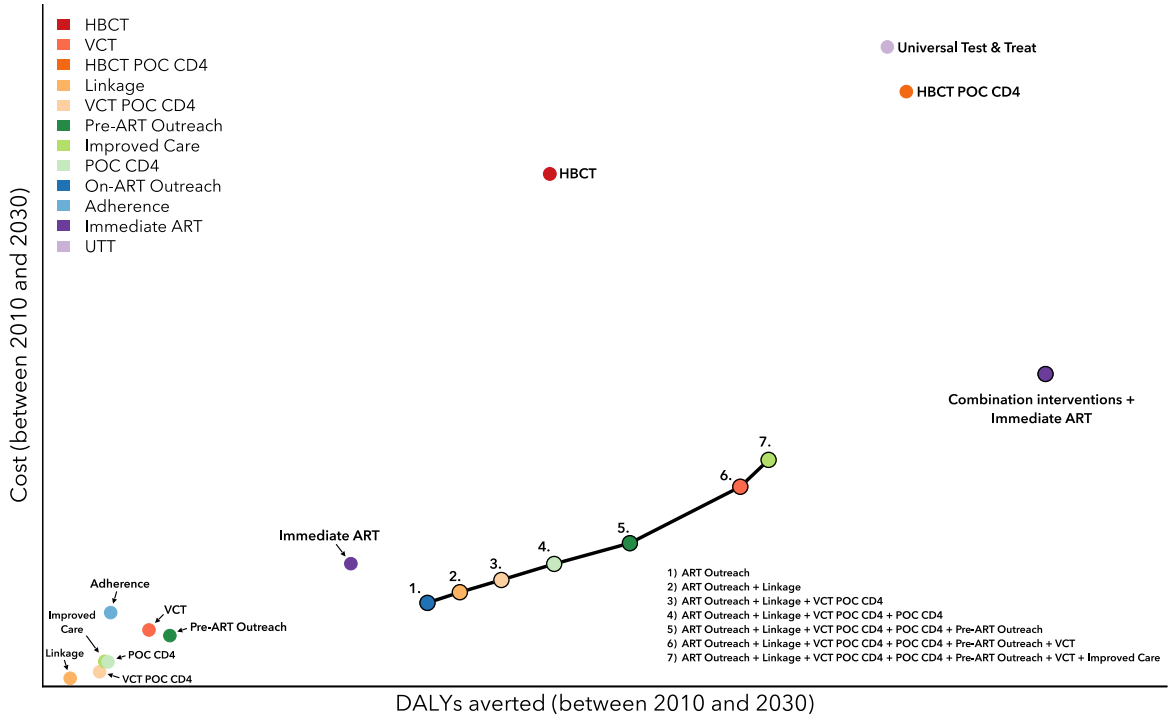

Figure 6.1. DALYs averted and additional cost of care for individual interventions between 2010 and 2030. Cost is estimated by calculating the additional cost of care relative to baseline between 2010 and 2030, and impact through calculating the number of disability-adjusted life-years (DALYs) averted relative to baseline in the same period. Points linked together indicate combinations of interventions (listed within the figure), otherwise interventions applied individually. The interventions are: Home-based counselling and testing (**HBCT**) of 90% of the population every 4 years, with patients more likely to link to care if previously diagnosed; Enhanced voluntary counselling and testing (**VCT**) that increases the rate of testing through VCT by 25%; Home-based counselling and testing with point-of-care CD4 testing (**HBCT POC CD4**) is the same as HBCT but with the addition of POC CD4 testing which increases rate of linkage to care; The **linkage** intervention reduces the risk of not linking to care by 50%; **VCT POC CD4** provides POC CD4 testing for all persons testing through VCT, increasing the chance they link to care; **Pre-ART Outreach** returns 20% of patients that have been lost from pre-ART care every year; **Improved Care** reduces the risk of being lost from pre-ART care by 50%; **POC CD4** provides point-of-care CD4 testing to all persons in pre-ART care; **On-ART Outreach** returns 40% of patients lost from ART care every year; **Adherence** reduces the risk of not adhering to ART and failing to achieve viral suppression by 50%; **Immediate ART** removes pre-ART care, providing immediate treatment for all individuals entering care; Universal test and treat (**UTT**) combines immediate ART with HBCT.

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7. Conclusions

Understanding the sources of HIV mortality in settings where ART is widely available is essential for assessing what interventions could be implemented to further reduce HIV mortality and morbidity and maximise the investments in HIV care and treatment. As ART coverage reaches high levels in many settings in sub-Saharan Africa, the majority of HIV-positive adults are on ART. However, adults on ART for six months or more are responsible for a relatively smaller proportion of HIV-related deaths because mortality rates are much higher among persons who are not actively engaged in care. The implication of this is that interventions focused on diagnosing, linking and retaining patients in care and on ART may generate greater health benefits than interventions focused on improving care for patients stably on ART.

Using models, we estimated that immediate ART initiation irrespective of CD4 cell count could reduce HIV deaths by 6–15% over the next decade compared to the current guidelines of initiation at CD4 <500. This results not from any assumption about better ART outcomes if patients start at CD4 cell counts>500, but from the reduced risk of patient disengagement that can occur in pre-ART care. The 'pragmatic benefits' should be considered when weighing the potential benefits of different ART eligibility policies and other interventions to improve HIV care.

Identifying priorities for improving HIV care requires combing information about where the weaknesses are that give rise to HIV mortality and morbidity, the main focus of this report, with additional information about what interventions can effectively ameliorate these health losses. In reality, both the weakness in care and the available interventions will be specific to local settings, and analyses such as that described in Section 6 provides an opportunity to define priorities within local contexts. The general principle is that a comprehensive approach to priority setting must consider health losses to HIV across the entire population, not just those most apparent who are engaged in care.

A substantial limitation in preparing this report was lack of comprehensive data about HIV mortality and the care experiences among those dying from HIV. We were able to assemble data from four sites in eastern and southern Africa and the vital registration system in South Africa, all in settings with relatively mature ART programmes. No data were available from lower ART coverage settings, and in these settings even data about HIV diagnosis and care were too meagre to generate model-based inferences about sources of mortality.

This report highlights that a substantial share of HIV-related mortality occurs among persons who are not in care, and this is anticipated to continue into the future. Monitoring ART programmes using clinical indicators, such as (1) viral suppression among persons on ART, (2) mortality among patients on ART, and (3) active outreach to assess mortality among ART patients lost-to-follow-up provide an incomplete picture of the population-level effectiveness of ART programmes. Population-wide surveillance of mortality and access to care should be integral to comprehensive strategies for monitoring and evaluating HIV care and treatment programmes.

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Preliminary report of the community-led consultation for who 2015 consolidated treatment guidelines update

Acceptability of Early Initiation of Antiretroviral Therapy (ART) and Viral Load Monitoring:

Values and Preferences of Service Users and Providers

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1. Background

The World Health Organization (WHO) is in the process of updating the 2015 Consolidated Guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection.

The guiding principles of the ARV guidelines include respecting human rights and therefore in making any recommendation it is vital that the views and impact on an individual to consider starting treatment are considered. Whilst the evidence on the benefits and harms of initiating and maintaining ART to achieve viral suppression is expanding there is less known on the challenges and impact on people living with HIV. In the context of global priorities to scale up treatment for people living with HIV, the values and preferences from end users and service providers on decisions about when and how to begin treatment, and the implications of viral load monitoring on treatment adherence and management, are of critical importance in the development of global policy on these issues.

2. Aim and Objectives

The aim of this project was to understand and document the values and preferences of people living with HIV, care givers and service providers towards key emerging interventions in the care pathway:

- Earlier initiation of antiretroviral therapy (ART) at a higher CD4 count
- Measurement of viral load to monitor and manage HIV, and support treatment adherence and engagement in care

The key *objective* of this project was to determine the acceptability, challenges and facilitators of earlier initiation of ART and viral load monitoring among community members living with HIV (users or potential users of services) and providers. Attention was focused on specific groups (adolescents, adults and caregivers, as well as key populations including sex workers, PWIDs and MSM). The *sub-objectives* were:

1. To provide a narrative description of the acceptability of earlier initiation ART and monitoring viral suppression for people living with HIV and service providers.
2. To explore challenges and facilitators of initiating ART and enabling individual choice.
3. To articulate suggested strategies and perceived preferences to support treatment initiation and adherence.

4. To explore understanding of viral load and the impact of viral load monitoring on adherence and engagement in care.
5. To review the terminology of initiating treatment and messaging required to better enable individual choice.

3. Methodology

3.1 General Approach

The community consultation process involved workshops that engaged groups in focused discussions using preset guides. Workshops were held in eight countries (Zambia, Kenya, India, Indonesia, Portugal, Ukraine, Peru and Zimbabwe), targeting different population groups to ensure a diversity of perspectives from both concentrated and generalized epidemic settings. Workshops were led by regional and country networks of people living with HIV, namely: AIDS Healthcare Foundation Ukraine (AHF); Asia Pacific Network of People Living with HIV (APN+); African Community Advisory Board (AFROCAB); European AIDS Treatment Group (EATG); Grupo Português de Activistas sobre Tratamentos de VIH/SIDA (GAT); the International Community of Women Living with HIV/AIDS (ICW); and Asociacion Via Libre. Technical support was provided by Pangaea Global AIDS/Pangaea Zimbabwe AIDS Trust, working with the program leads of the networks in each of the countries to develop tools and support the consultation process. Table 1 provides an overview the sub-groups consulted in each of the participating countries.

Table 1: List of sub-groups by country

COUNTRY	Generalized Settings			Concentrated Epidemics -Key Populations			Service Providers
	Adolescents/ Young People	Adults	Parents / caregivers	People who use drugs (PWIDs)[5]	Sex Workers	MSM/ TG	
India		X			X		X
Indonesia			X			X	X
Kenya		X				X	X
Peru	X					X	X
Portugal		X		X		X[7]	
Ukraine		X		X			X
Zambia	X	X	X				
Zimbabwe	X		X		X		
Total	**3**	**5**	**3**	**3**	**2**	**4**	**4**

3.2 Workshop Tools

A variety of tools were develop by Pangaea, in consultation with the networks and WHO, to support the process including:

- Community Consultation Workshop Manual: this document described the purpose and procedures of the workshops
- Participant information guide and consent form: This was used to explain the purpose of the workshops to participants, and to gather verbal or written consent prior to the start of the discussion for each participant
- Pre-workshops survey: To collect demographic information on group members with no specific identifying information (e.g. name) of individual participants
- Workshop Facilitation guide: Used by facilitators to guide the discussion among participants, listing topics of interests and general questions to aid the flow and discussion of issues

- Data Reporting Tool: Used by the country coordinator, facilitator and note-takers to record information systematically to aid in the analysis and documentation.

Country Leads and their selected facilitators and note-takers were substantially involved in co-developing the discussion guides through webinars and reviewing and commenting on drafts via email. Once final tools were agreed, country teams participated in a half-day virtual training workshop led by Pangaea on the workshop documents.

3.3 Workshop reporting, country debriefs and data analysis

Country teams conducted the workshops between the 8th and 19th of May, 2015. Following the workshops, each country team participated in a debrief session with Pangaea to discuss the emerging themes; Pangaea also provided support to teams in filling in their Data Reporting Tools. Completed Data Reporting Tools were then sent to Pangaea.

Thematic analysis of data was conducted by Pangaea, including review of all Data Reporting Tools to understand themes that emerged and analyse where findings were consistent or divergent across sub-populations and regions. Findings were compiled into thematic summaries across the two areas of interest ("test and treat" and "viral load monitoring"). These summaries were shared with the country teams and WHO for feedback to ensure that themes matched with workshop findings from the perspective of country leads and network members. The feedback was integrated into the thematic summaries and shared again for final consensus and approval by country leads. These summaries are presented as findings below.

4. Findings

4.1 Participant Demographics

Three workshops were held per country with 8-12 participants per workshop, for a total of 24 workshops (see Table 1): three workshops were held with adolescents; five with adults living with HIV; three with parents/caregivers of children living with HIV; three with people who use drugs; two with sex workers; four MSM and transgender groups; and four with service providers.

A total of 280 individuals participated in the consultation workshops: 206 representing different groups of people living with HIV, and 74 service providers. Table 2 shows the demographic breakdown of participants by gender, age, region and sub-population.

Among PLHIV, approximately 80% were currently on ART; just under half had started at CD4 <350 and had been on ART for over four years. Nine participants (7%) had begun ART at CD4 regardless of CD4 count or at CD4 <500. Having received a viral load test varied greatly by region: over 90% of participants from Europe and Latin America had received a least one viral load test, while only 55% of African and 64% of Asian participants had received one. Most (70%) who reporting receiving a viral test were receiving them every six months.

Types of service providers who participated in workshops varied by region. In Africa, 90% of service providers were from primary health care facilities, while the majority from Asia (86%) and Europe (67%) were from community-based organizations or facilities providing specialized care; in Latin America the majority were from tertiary institutions.

Table 2: Basic Demographic Information on Workshop Participants

	PLHIV		Service Providers		TOTAL
	#	%	#	%	#
GENDER					
Male	110	53	22	29	**132**
Female	90	44	52	71	**142**
Transgender	6	3	0	0	**6**
TOTAL	**206**	**100**	**74**	**100**	**280**
AGE					
15 to 24 years	43	27	0	0	**43**
25-34 years	54	33	20	27	**74**
35-44 years	68	42	37	50	**105**
45+	41	25	17	23	**58**
TOTAL	**206**	**127**	**74**	**100**	**280**
REGION					
Africa	62	30	35	47	**97**
Asia	76	37	14	19	**90**
South and Central America	17	8	13	18	**30**
Europe	51	25	12	16	**63**
TOTAL	**206**	**100**	**74**	**100**	**280**
SUBPOPULATIONS					
Adults with HIV	97	47	-		**97**
Adolescents	32	16	-		**32**
MSM	24	12	-		**24**
Sex Workers	23	11	-		**23**
IDU	30	15	-		**30**
TOTAL	**206**	**100**			**206**

4.2 Thematic Summaries: Earlier Initiation of ART

What follows are highlights and detailed summaries of the key themes that emerged from the analysis by "Earlier Initiation of ART" and "Viral Load Monitoring".

Highlights of Key Themes: Earlier Initiation of ART

- Overall for community participants living with HIV (PLHIV) and service providers, **early initiation of treatment is acceptable** and the health benefits are well understood.
- It was uniformly noted that a **collaborative decision** between service provider and client/care-giver is optimal. The **right to decide when to start treatment** must rest with the client, and the ultimate decision must be client-driven.
- Treatment initiation at any time must **include comprehensive and accurate information**, and the **right to informed choice** about starting treatment and staying in care.
- **Full understanding and readiness** of clients initiated on ART is required otherwise they **are likely default** – this was uniformly noted.
- **Motivation to initiate treatment was often described as being driven by the desire to regain and maintain health, and a strong will to live. For those initiating treatment early, this motivation may be less strong. Other challenges such as stigma, lack of disclosure and**

confronting side effects, may be harder to overcome when illness is not driving the choice to initiate treatment.

- While motivating PLHIV to **start treatment may be relatively "easy"** to do, **staying on and adhering to treatment over the long terms is challenging**.
- **Stigma and discrimination** were uniformly raised as **fundamental concerns** constraining treatment access, affecting quality of services and infringing on the ability of clients to adhere to and stay on treatment. **Regardless of sub-group, the majority of participants described experiences** of discrimination and stigmatization when accessing services.
- To **promote ongoing engagement in care and adherence**, it is critical that all clients have: access to adequate and **consistent supplies of free/affordable** ARVs; a facility that is easily **accessible and convenient**; concern and support from **providers who are trained and are sensitive** to the needs of PLHIV (including key population groups); provider and/or community **adherence support**; facilities that actively work to enhance adherence; national programs and facilities that **reduce structural barriers;** facilities that **specifically serve or are dedicated to PLHIV** and/or key populations and that have built in systems and spaces that help **ensure privacy and confidentiality**.
- Ideas on the terminology of "Test and Treat" vs "Test and Offer" were mixed across population groups and regions with no clear preference emerging.
    - **Test and Treat**" a) implied **lack of choice**; b) focused primarily on biomedical aspects of health without paying attention to other considerations c) sometimes **associated with coercion** or forced treatment; d) and primarily on prevention to those who are not infected, **rather than the protection of PLHIV**.
    - **"Test and Offer"**: a) was seen as "too soft" by providers and some PLHIV (especially advocates); b) because it wouldn't encourage early treatment initiation c) and it would **lose information of the benefits or urgency to start treatment**. While **"Test and Offer" was seen as more palatable** by some participants and in some cases conveyed the message that client's right to choose was respected.

<u>Highlights of regional and sub group differences: Earlier Initiation of ART</u>

- The main regional difference was related to **treatment access**. For those in the African region, having access to treatment was a major concern. **Moving towards treating everyone was welcomed as an advocacy platform for increasing treatment access across the region.**
- Woman, especially pregnant women, felt that they **had limited control over decisions** on starting treatment.
- Women were also particularly concerned about **loss to confidentiality** when starting treatment.
- Key populations living with HIV experience '**double' stigma and discrimination.**
- Key populations require **specialized services and support** that are responsive to their needs that can help alleviate or change social norms that negatively impact on the health and their rights.
- Adolescents and young people voiced **being left out of decisions about treatment altogether**, often being made without their knowledge of their own status or what the treatment is for. This was highlighted as a major barrier for adherence.
- **Supportive and sensitive health providers, peer support** and sharing experiences especially during transition to adult services is critical for adherence for adolescents.
- Parents and caregivers felt that facilities had **insufficient numbers of and trained staff** to adequately provide the care and support the treatment needs of their children.
- **Psychosocial support for parents and caregivers** is required especially to support disclosure to the child.
- Service providers face **particular challenges** when initiating and maintaining treatment among certain populations

- For service providers to effectively support people living with HIV to engage with care, initiate and maintain treatment they require: a) **national guidelines** that support the strategic use of ART while also supporting the right of people living with HIV to decide when and how to begin treatment; b) consistent **training** and capacity building particularly for key populations, children and adolescents; c) consistent **supplies of drugs** and commodities, d) and the decentralization of services.

Detailed Summary of Key Themes: Earlier Initiation of ART

1. **Overall for community participants living with HIV (PLHIV) and service providers, early initiation of treatment is acceptable and the health benefits are well understood.**
    - Participants felt that optimally clients should have access to treatment and be encouraged to take it up as soon as they were ready to do so, but that full information and improved treatment literacy were paramount, as was the fact that the ultimate decision to start needed to rest with the client.

2. **It was uniformly noted that a collaborative decision between service provider and client/care-giver is optimal. The right to decide when to start treatment must rest with the client, and the ultimate decision must be client-driven.**

- **"Shared decision-making**" between providers and clients and an ideal balance of individual rights of PLHIV and the responsibilities of the health care provider was emphasised.

  "People should have time to accept their HIV diagnosis/status, and obtain enough information from their provider, and then decide to start treatment." (Adult PLHIV, Ukraine).

  "*Counsellors at PSI subtly persuaded me to start treatment. I didn't feel coerced but gently persuaded. By the end of it, it was my choice as their advice was convincing*" (SW, Zimbabwe)

    - Across groups and regions, it was noted that there is **no real mechanism to uphold HIV clients' rights**: in many cases, rights are not known, and clients may not even know if their rights are being violated.

  "*Having rights does not guarantee them in real life. We have rights, but so what? There is nowhere to turn when the rights are violated.*" (PWID, Ukraine).

    - Providers play a critical role in **persuading, supporting and encouraging initiation** of treatment at the right time
    - Support and encouragement to start treatment should ideally come from providers based on national treatment guidelines, results from diagnostic tests and/or clinical signs, **but it must be done in such a way that ensures the rights of clients to informed choice** with ultimate decisions resting with the client or the client's care-givers (in the case of children).

3. **Stigma and discrimination were raised as fundamental concerns constraining treatment access, affecting quality of services and infringing on client's ability to adhere to and stay on treatment. Participants, regardless of sub-group, described experiences of discrimination and stigmatization when accessing services.**

"…all other patients have a room to wait from, we are made to wait in a shelter by the roadside" (Adult PLHIV, Zambia);

"I was chided by a staff for not bringing a pen to sign the register…they wore gloves even for checking my temperature…I was emotionally hurt and pitied myself for being HIV positive (SW, India);

"My doctor said I was rotten, that I was paying for my wrong behavior of the past" (PWID, Portugal).

- In addition to stigma and discrimination at the facility-level, **clients also described reluctance to disclose to partners and family members for fear of being shunned or even expelled from their homes,** clearly posting a barrier to treatment initiation and adherence.

"After I disclosed, I was given my own cup and plate, my family would no longer eat with me." (Adolescent, Zimbabwe)

"Many women fear Option B+ because if their husband finds out their status, they will be kicked out and maybe even lose their children." (Service Provider, Zambia)

- Scale-up of early treatment must take into consideration and these issues at the level of service provision and implementation.

4. **Treatment initiation at any time must include comprehensive and accurate information, and the right to informed choice about starting treatment and staying in care.**

   "*Information is critical, if there isn't information you don't stay on treatment, each person adheres when they want.*" (PWID, Portugal)

   - Clients **need comprehensive information** from service providers not only about the health **benefits** of starting and staying on treatment for life, but also about the **potential challenges** including side-effects, and the **implications of non-adherence** once treatment is begun.

   "*Treatment literacy and adherence counselling should be made mandatory before initiation of treatment…ART is lifelong and not and emergency*." (Adult PLHIV, Kenya);

   "*When I started taking my drugs, I did not know what they were for. I thought that they were just like pain killers and could be taken only for a period of time. I did not understand why they had to be taking for life so I took them for two years then I stopped. A while after stopping I got so sick…"* (MSM, Kenya)

   - **Service Providers have a critical role to play in providing information**, support, and empathy for challenges faced with side-effects and other treatment challenges; most participants noted a lack of concern of side-effects given by many providers.

5. **Full understanding and readiness of client initiated on ARVs is required otherwise they are likely default – this was uniformly noted.**
   - Particularly for promotion of immediate treatment on the day of diagnosis, during pregnancy, or while the patient is still well, needs to be balanced or promoted along-side client-readiness.
   - This includes **emotional readiness** and disclosure to partners, family and friends were important enablers for successful and informed decisions to starting treatment as well as cope with the HIV diagnosis, fear of HIV-related stigma, fear of refection or divorce and other challenges to starting and staying on treatment.

6. **Motivation to initiate treatment was often described as being driven by the desire to regain health and a strong will to live. For those initiating treatment early, this motivation may be less strong. Other challenges such as stigma, lack of disclosure and confronting side effects, may be harder to overcome when illness is not driving the choice to initiate treatment.**

- Motivation to initiate and tolerate side effects/treatment challenges was most high among participants who had started treatment because of low CD4 count or illness, or because they had seen a loved one die or vastly improve upon starting treatment

"*You don't have a choice, you will be so sick that to you, treatment is the only option*" (SW, Zimbabwe*)*.

- For those initiating treatment early (e.g. when they feel well), it may be harder to overcome when illness is not driving the choice to initiate treatment. **High levels of treatment literacy and understanding of the benefits of early treatment will be required**

"*The doctor was clear. I knew treatment was hard, but the alternative was worse.*" (Adult PLHIV, Portugal);

"*I insisted, I threw up a lot, but I wanted to be healthy for my* son." (Adult PLHIV, Zambia)

7. **While motivating PLHIV to start treatment may be relatively "easy" to do, staying on and adhering to treatment over the long terms is challenging.**
   - Particularly for **certain groups** like pregnant women, children, adolescents and key populations. Additionally for those clients' whose choice to start treatment felt pressured, or if they did not fully understand the implications of life-long treatment and were not made aware of potential clinical or other side effects.
   - Service providers noted that **pregnant women** are often highly motivated to start treatment as a way to prevent transmission to their child, but that they often default after delivery and/or breastfeeding.

"*Many pregnant women on Option B+ keep the drugs at home and do not take them because they are given mandatory and without extensive treatment preparedness.*" (Service Provider, Kenya)

8. **To promote ongoing engagement in care and adherence, it is critical that clients have access to:**
   - **Adequate and consistent supplies of free/affordable ARVs**. It was also noted that treating everyone in some countrie**s is not realistic due to resources or infrastructure limitations** – in such cases, it was questioned whether moving toward "Test and Treat" made sense.
   - **Facilities that are easily accessible** and that offer services and the collection of medicines during hours that are **convenient** for clients. Many participants experienced the limited hours where services are provided as constraining and ultimately increasing the cost of treatment through multiple trips to the clinic to collect medications.
   - **Concern and support from providers.** PLHIV often expressed frustration about the lack of perceived concern for and support by providers especially around managing side effects, leading some to default on treatment.

"*If you feel worse taking medicines, you don't see the point of continuing and if you don't know the advantages or how to manage them, it's harder to understand why it's important*" (PWID, Portugal)

- Access to a facilities with **trained service providers who are sensitive to the needs of PLHIV** and key populations was considered important. NGO service providers were seen as having a stronger capacity to provide quality services, including the comprehensive support required (such as through information sharing, counselling and other psycho-social services).

- **Provider and/or community adherence support** is an important and often overlooked component of support when initiating treatment, and for ensuring those who are initiation early stay on treatment over time. This is particularly important if a client is started at a time when they are still feeling well.

"There is a need for psychosocial support for people who are to be started on treatment when they are well because traditionally people take medicine when they are sick…treatment support group therapy sessions should be encouraged as this is a safe space for coping and adhering to treatment." (Adult PLHIV, Kenya)

- **Facilities that actively work to enhance adherence** through adherence counselling, pill counts, table boxes with reminders or time-set beeps, use of mobile phones/tablets – and referrals to and from NGOs/CBOs - were seen as being effective in helping clients stay on treatment
- Facilities that are **specifically serve or dedicated to PLHIV and/or key populations** were seen as having **built in systems and spaces that help ensure privacy and confidentiality** are maintained
- **It is also critical that national programs and facilities reduce structural barriers to treatment initiation and retention**, such as costs of diagnostic tests, drug-stock outs, long waiting times at clinics and/or pharmacies, as well as limited hours. Such barriers inconvenience clients and often result in economic burdens (such as lost time at work, costs of multiple clinic trips) that interrupt care and treatment.

9. **Ideas on the terminology of "Test and Treat" vs "Test and Offer" were mixed across population groups and regions.**
   - Some felt that terminology of "**Test and Treat":** a) **implied lack of choice;** b) focused primarily on **biomedical aspects** of health without paying attention to other considerations such as time needed to cope with the HIV diagnosis, fear of HIV-related stigma, fear of refection or divorce and other challenges to starting and staying on treatment c) sometimes **associated with coercion** or forced treatment; d) and primarily on prevention to those who are not infected, **rather than the protection of PLHIV**.

"*Starting someone on the same day they are diagnosed (test and treat) doesn't give good results. ART is lifelong and therefore one should be prepared through treatment literacy and psychosocial support. Stop making treatment an emergency*!" (Adult living with HIV, Kenya)

"Test and treat is not proper. It is like you test and then you are put before the fact you must start treatment. It's like you have no choice, even if you do not believe." (Adult living with HIV, Ukraine)

"Test and treat sounds like you are forced to it." (PWID, Portugal)

"Test is the patient's initiative, treat is the doctor's initiative…. but it's not your decision to start treatment" (PWID Ukraine)

- Others felt the language of **"Test and Offer"**: a) was **"too soft";** b) wouldn't encourage early treatment initiation c) would lose information of the benefits or urgency to start treatment.

"*Sometimes people do not want to start ART…people do not believe their diagnosis. Often they start ART and quit it. We need to convince and to talk to them, but a patient has the right to refuse*." (Service Provider, Ukraine)

"Test and Offer would give the impression that they can refuse treatment which would not benefit any child." (Parents and caregiver, Zambia)

- "**Test and Offer"** on the whole was seen as **more palatable** and in some cases, conveying the message that right to choose was respected.

"*People should be given choices and allowed to be ready to take ARVs, and if they don't choose to take them, they should be left alone*" (Service Provider, Kenya).

"Test and offer gives more space to the client to prepare themselves to start treatment with fulfilled knowledge on their current condition. It is more soft and acceptable for every group especially with the ones who are not well informed about HIV and AIDS" (MSM, Indonesia)

"In test and offer, there is a choice for the patient, it is more psychologically acceptable and more person friendly" (Adults living with HIV, Ukraine)

"It is important that WHO offers "test and offer" instead of "test and treat" as it ensures that the package is not only medical, but that non-medical aspects of health and HIV are also included and prioritized." (Service Provider, Kenya)

<u>Specific themes for regions and sub populations: Earlier Initiation on ART</u>

Regional

10. **The main regional difference was treatment access. For those in the African region this was a major concern. Moving towards treating everyone was welcomed as an advocacy platform for increasing treatment access across the region.**
    - While all participants were invested in ensuring client choice in starting treatment, an over-riding concern in these regions **focused on ensuring access in the first place.**

Women living with HIV

11. **Woman, especially pregnant women felt that they had little control over decisions to start treatment**
    - Pregnant women reported that the decision to start treatment was largely **determined by the health professionals** at the antenatal clinics. Within option B+, it was perceived by a number of participants that little **choice is offered women not to continue** on treatment.
    - Female client's decision to initiate treatment is also **influenced by male partners**, and often women fear abandonment by partners (Service Provider, Kenya)

12. **Women were particularly concerned about loss to confidentiality when starting treatment.**
    - Women living with HIV are particularly concerned about loss of confidentiality with treatment initiation including fear of rejection, divorce and violence.

"*When I found out my status, I was crying every day. I had two small children, it was just difficult to accept that ART is forever, for all your life. It was difficult to make a decision*" (Adult woman, Ukraine)

Key populations (sex workers, MSM, TG, PWIDs) living with HIV

13. **Key populations living with HIV experience 'double' stigma and discrimination**
    - It was clear that all PLHIV faced significant fear of and/or experience of stigma and discrimination at community and facility levels. Among key population groups including sex workers, MSM, PWIDs, and young people, many reported experiences of double discrimination for also being a member of a marginalized and stigmatized group.

14. **Key populations require specialized services and support that are responsive to their needs that can help alleviate or change social norms that negatively impact on the health and their rights**.

*"…in our card there is information (indicated that this person) uses drugs, and many doctors just hate people on OST (opioid substitution therapy) and don't even hide this" (*PWID, Ukraine).

- Special considerations for these groups are paramount, including ensuring training of health care workers to support and respond to their special needs; supporting stand-alone clinics and/or facilities that cater to these special groups and investing in community systems and support activities that can help alleviate or change social norms that negatively impact on the health and rights of these groups.
- Key population groups uniformly **noted a difference between public sector facilities**, and NGO facilities that are specialized in the care of special groups such as sex workers, MSM and PWIDs. In public health facilities, members of key population groups experience negative health worker attitudes, being openly called derogatory names and being ridiculed by nurses. NGO facilities included professionals trained to work with and support these populations.

"Health workers who have been sensitized treat us well" (MSM, Kenya).

Decisions to start and stay on treatment "was facilitated by the good attitude of my health care worker" (PWID, Ukraine)

Adolescents and young people living with HIV

15. **Adolescents and young people voiced being left out of decision about treatment altogether, often without their knowledge of their own status or what the treatment is for. This was highlighted as a major barrier for adherence.**

"*Most of the time I did not take my medication because I had no understanding of what I was drinking."* (Adolescent, Zimbabwe)

- When speaking of the issue of informed choice about when to start treatment, many young people noted being left out of the decision altogether – given the decision was made between the provider and their care-taker with **little to no consideration of their own wishes.** In many cases, young people were put on treatment without being disclosed to so they did not know what they were taking or why, or the importance of consistent adherence. This was highlighted as a major barrier to adherence by this sub group.

16. **Supportive and sensitive health providers, peers support and sharing experiences, especially during transition to adult services is critical for adherence among adolescents.**

- In the case of young people who **were made aware of their status**, supportive and sensitive health care providers at pediatric clinics were critical to their staying on treatment; however their experiences changed once moving to the adults clinics.
- Peer support and knowing about **other people's positive experiences** were critical to staying on treatment.

"*Knowing that my peer became a doctor makes me feel that I can also become one.*" (Adolescent, Zimbabwe)

Parents and caregivers of children living with HIV

17. **Parents and caregivers felt that facilities had insufficient numbers of and trained staff to adequately provide care and support the treatment needs of their children.**

- Parents and caregivers generally noted that facilities are understaffed and are not adequately trained to support the special and needs of children; they are not perceived as being "child-friendly"; service providers were sometimes able to deal with side-effects; and they did not understand issues of care-giver consent.

18. **Additional support for parents and caregivers is required especially around disclosure to the child.**
    - Caregivers expressed **fears of disclosing to their child**, particularly about how the child contracted the virus. Mothers, especially indicated lack of disclosure to children was sometimes due to needed to keep the information from their partner for fear of being left or kicked out of the marriage.
    - The **emotional stress on caregivers is immense**, indicating a need for improved support for them to attend to the care and treatment needs. Support from pastors, peers, child support groups, immediate family and other relatives were cited as critical enablers for seeking care and supporting treatment for the child/children in their care.

"I am always crying because I see my child's health deteriorating" (Parents/Caregivers, Zimbabwe)

Service Providers

19. **Service providers face particular challenges when initiating and maintaining treatment among certain populations.**
    - It was noted that **supporting individuals who use drugs** or alcohol to start and stay on treatment poses special challenges due to treatment interactions (e.g. TB drugs and methadone), lack of stability and high drop-out rates.
    - Service providers also expressed challenges in **initiating children on ART if parents are not ready**, and they expressed frustration that there are no laws or policies to support children who need to be on ART when their parents are in denial of or otherwise unsupportive of treatment
    - It was felt that pregnant women were "easy" to initiate but that **real challenges exist in support women to continue** with treatment after delivery.

"*Something needs to be done on how Option B+ is implemented, otherwise, most of the children will continue to be infected as most mothers to not adhere to treatment because of poor preparation and initiation*" (Service Providers, Kenya)

20. **For service providers to effectively support people living with HIV to engage with care, initiate and maintain treatment they require:**
    - **National guidelines** that support the strategic use of ART and support the right of people living with HIV to decide regarding treatment
    - Consistent training and **capacity building**, especially for initiating children, and better supporting key populations
    - Consistent **supplies of drugs** and commodities
    - Decentralization of services

4.3 Thematic Summaries: Measurement of viral load (VL) to monitor and manage HIV

<u>Highlights of Key Themes: Viral Load Monitoring</u>

- Knowledge about viral load testing/monitoring was high; however **access to VL monitoring was limited in most countries/settings** - with the exception of participants from European countries, most had not received a viral load test.
- It was generally understood that **access to VL monitoring gives clients a measure of understanding, control and motivation to adhere** to and manage their HIV.
- While general knowledge about VL monitoring is high, **literacy on the implications of an undetectable or detectable VL are less well understood**. Misconceptions need to be addressed between providers and clients when delivering a VL result**.**
- Limited machines and high cost of testing, waiting for results and challenges of monitoring those living in rural areas were noted to **constrain access to and effectiveness of VL monitoring.**

Highlights of Regional and sub group difference: Viral Load Monitoring

- Generally, VL monitoring in **Africa and Asia was associated more with addressing suspected clinical failure** whereas in **Europe, it was regarded as part of regular monitoring.**
- In the African region generally, viral load monitoring was not available except **through specialized clinics;** when available, it was reported to be **costly across all countries.**
- **Service providers reported that VL monitoring helped them decongest and reduce traffic at the clinic** by categorizing patients and seeing priority patients (those with High VL) frequently and those with undetectable VL less frequently.
- Service providers had **differing views on the best monitoring** for clients**.** Particularly nurse felt that CD4 was still necessary however physicians **felt VL should be prioritised over CD4.**
- **The timings allocated to attend for viral load sample collection** was noted a challenge for certain populations.
- Parents / caregivers were aware of the importance of viral load in monitoring the children's health and HIV disease; **providing confidence in overseeing their child's treatment. However, most children had not been offered a VL test.**

Detailed Summary of Key Themes: Viral Load Monitoring

1. **Knowledge about viral load testing/monitoring was high; however access to VL monitoring was limited in most countries/settings - with the exception of participants from European countries, most had not received a viral load test**
    1. Participants seemed to understand that viral load and CD4 tests measure different but related aspects of HIV disease

"They are the two most important parameters about my health condition. If I go to an appointment and the doctor states that my viral load is no longer undetectable, I will be very concerned because it means that my treatment is no longer effective, and it will have a consequence; the CD4 will go down" (Adult living with HIV, Portugal)

    2. If VL testing was received in the public sector facilities, it was often due to **suspicion of treatment failure**. In resource constrained settings, VL testing is not used to monitor treatment success as much as to *"monitor clinical failure to make a case for switching to second-line regimens…"*
    3. VL monitoring is available in the private sector, however **costs are prohibitive** for most.
    4. Most national **governments have not moved towards VL** monitoring as part of their HIV treatment guidelines

2. **It was generally understood that access to VL monitoring gives clients a measure of understanding, control and motivation to adhere to and manage their HIV.**
   - Knowledge of one's viral load improves confidence and adherence.

"When you get to know your viral load it gives you the urge to push on regardless of the results. When it is detectable you want to achieve undetectable, and when it gets to undetectable you want to ensure it remains there." (MSM, Kenya)

- In Zimbabwe, young participants noted that by knowing viral load

"I am motivated to take my drugs and stop behaviour although taking drugs is difficult." (Adolescent, Zimbabwe)

"When viral load is undetectable, it gives us confidence and the urge to continue on with treatment." (Adults, Kenya)

3. **While general knowledge about VL monitoring is high, literacy on the implications of an undetectable or detectable VL are less well understood. Misconceptions need to be addressed between providers and clients when delivering a VL result.**
   - While clearly there is substantially less risk of HIV transmission when a person's viral load is undetectable, providers and policy makers must ensure that messaging **continues to promote condom use** and other risk reduction measures.

"Undetectable viral load means that there is less chance of transmitting the virus, therefore there is no need to use condoms." (MSM, Indonesia)

- Service Providers further noted that there are misconceptions among some clients that an undetectable VL means that they have been "cured":

"Some stop taking medication thinking that they have been healed" (Service Provider, Kenya).

*As on*e caregiver noted,

"CD4 monitoring is more important than viral load monitoring as young children are not sexually active, so levels of the virus would not normally increase" (Caregiver, Zambia).

4. **Limited machines and high cost of testing, waiting for results and challenges of monitoring those living in rural areas were noted to constrain access to and effectiveness of VL monitoring.**
   - Waiting for results of VL tests mean that treatment decisions are not made when they need to be made.
   - It is especially difficult to monitor VL for people living in remote areas.

"*Often, when a patient comes from a remote place, he comes for one day and gets the viral load test and goes back home for three months. In a week, we get the results and even see that viral load is detectable, but the patient is gone." (Service Provider, Ukraine)*

- Patients and providers indicated the **potential usefulness of point of care VL** testing to address some of the logistical constraints and challenges**.**

<u>Specific themes for regions and sub populations: Viral Load Monitoring</u>

Regional

5. **Generally, VL monitoring in Africa and Asia was associated more with addressing suspected clinical failure whereas in Europe, it was regarded as part of regular monitoring.**

6. **In the African region generally, viral load monitoring was not available except through specialized clinics; when available, it was reported to be costly across all countries.**
    - Results were not always readily available because of reagents and specimen transport issues.

Service Providers

7. **Service providers reported that VL monitoring helped them decongest and reduce traffic at the clinic by categorizing patients and seeing priority patients (those with High VL) frequently and those with undetectable VL less frequently**.
    - This could be incorporated in the guidelines to assist health facilities find better ways to decongest and prioritize patients "in need".
8. **Service providers had differing views on the best monitoring for clients. Particularly nurses felt that CD4 was still necessary however physicians felt VL should be prioritised over CD4.**

"*There are clients whose viral load are undetectable. These clients do not need to come to the facility monthly. They can come after every three months. This decongests the facility enabling us to give more time to those who still struggling with treatment or have not been initiated on treatment" (Service Provider, Kenya).*

Adolescents, and key populations

9. **The timings allocated to attend for viral load sample collection was noted a challenge for certain populations.**
    - Adolescents indicated that they had challenges in providing blood samples for VL in the mornings as this interfered with school or work**.**
    - Commercial sex workers also reported challenges with timetables for VL testing.
    - Service providers should give special considerations to these groups and possibly vary the times for sample collection.

Parents/ Caregivers

10. **Parents / Caregivers were aware of the importance of viral load in monitoring the children's health and HIV disease; providing confidence in overseeing their child's treatment. However, most children had not been offered a VL test.**

5. Strengths and Limitations

The community consultative process described in this report had many strengths and, like in all inquiries of this nature, certain limitations.

The key strength of our approach was that it was community-led by individuals representing a broad range of people living with HIV across the globe, including key affected populations. Our qualitative approach allowed us to examine issues in detail and depth, without restricting views or responses to a pre-determined set of outcomes. This approach also allowed for country teams to be flexible in how they discussed issues within their groups to tailor the discussion to achieve the highest level of relevance, and to uncover the subtleties and complexities about the issues of interest, that would have been missed with a more quantitative approach. The data presented here is therefore, based on human experience and it fundamentally reflects the lived realities of peoples' lives. This rich information provides invaluable insights on how to tailor global policies based on clinical evidence into interventions that work for people on the ground.

These strengths having been mentioned, it is also important to note that as with any qualitative exploration, there are inherent limitations. The level and depth of information gathered varied to some degree in quality and detail across the different country settings based on the experience level of the individuals conducting the workshops, and those taking notes of the sessions. We put in place measures to limit this variability through the standardisation of data collection and reporting tools, and post workshop debriefs. This consultation process was also limited in scope and time, given resource constraints, and findings may not be fully generalizable to every country, sub-group or individual. However, given the richness of the information we were able to collect and synthesize, and the range of countries and groups consulted, we none-the-less feel that these limitations do not infringe upon the importance or validity of incorporating these values and preferences into the WHO guideline updating process.

Adolescent Africa: A situational analysis of adolescent HIV treatment and care in sub-Saharan Africa

Paediatric Treatment for Africa

September 2014

Abstract

In an effort to contribute to the upcoming WHO update of the consolidated guidelines on HIV/AIDS, the focus of this study was a review of the availability of specialised and appropriate HIV treatment and care services for adolescents in sub-Saharan Africa so as to provide data to address the gap in the previous guidelines. Surveys covered a wide range of themes, including: barriers to treatment and care for HIV-infected adolescents; definitional issues; data and tracking systems; treatment outcomes data collection; clinical presentation and issues; treatment adherence; treatment failure; retention in care and loss to follow-up; adolescent friendliness; as well as service and community integration. Standardized definitions of adolescence and sufficient disaggregation of descriptor data (age, mode of infection, and by key populations) are two critical missing pieces in most settings, and remain a key barrier to the development of youth-friendly HIV services and systems. Having these in place is imperative to enable transitioning protocols to be developed as individuals graduate from paediatric services to adolescent services where these exist, and subsequently adult services. It also will facilitate the tracking of adherence, retention and treatment outcomes in this age group which at present is taking place very inconsistently, if at all. Data recording systems (both paper-based registers and electronic systems) should be in place to address these challenges. A primary finding was that adherence is a major concern for healthcare providers, and should be addressed in the guidelines. Specifically, facilities have minimal protocols for managing non-adherence in this group, determine adherence most often using pill counts, and focus adherence counselling on adherence behaviour rather than drivers of poor adherence. Once treatment failure is confirmed, the tendency at facility level is to counsel adolescents without engagement of family and supporters, and after switching to second-line regimens, ongoing adherence challenges remain the major challenge. There is a need for clear definitions, guidelines or protocols and recommendations around counselling content to help standardize approaches around supporting adherence, transition and retention in adolescents. Further guidance around service integration, and SRH service integration in particular, as well as recommendations around how facilities can best address disclosure-related challenges may be helpful. Looking at a regional breakdown of study results, a common finding across the various themes assessed is that the sub-region furthest behind with regards to having guidelines, processes, services and systems in place for the provision of treatment and care for adolescents is West and Central Africa.

Introduction

The World Health Organisation (WHO) is currently updating its consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection, published in 2013. One notable gap in the 2013 consolidated ARV guidelines was the absence of guidance related to the specific management of adolescent HIV and AIDS. This was in part due to a limited understanding of adolescent HIV treatment, care and service delivery needs. To this end, the WHO has partnered with Paediatric AIDS Treatment for Africa (PATA) to review of the availability of specialised and appropriate HIV treatment and care services for adolescents in sub-Saharan Africa so that the next iteration of the consolidated guidelines can incorporate this guidance.

Due, in part, to the success of previous paediatric HIV treatment efforts, an increasing number of young people are living beyond young childhood into adolescence. This success brings with it novel challenges, including immunological complications, suboptimal antiretroviral therapy (ART) and formulations, and difficulties encountered in the transition from caregiver dependence to a growing independence (Sohn & Hazra, 2013). Globally, it was estimated 2.1 million adolescents (10–19 years old) were living with HIV in 2012. HIV-related deaths among adolescents were estimated to have increased since 2000, making HIV the second leading cause of mortality among this age group worldwide. Ninety percent of 2012 global adolescent HIV-related deaths are estimated to have occurred in Africa, and one of every six deaths among adolescents in 2012 in Africa are estimated to have been due to HIV. Since there are limited empirical data, mortality estimates are based on modelling and should be interpreted with caution. It is becoming increasingly apparent that adolescents are underserved in terms of HIV treatment and care services. This issue is garnering increased attention in the global discourse around HIV and AIDS. Some of the adolescent-specific challenges that are highlighted in the current literature with regards to HIV treatment and care are summarised below.[1]

A key challenge is how adolescence is conceptualised and defined. In some countries, there may not be a recognised period between childhood and adulthood. Where there is such a period, it may be defined in dissimilar ways across different settings or by diverse cultures, and a standard definition may not exist. This gap is more than academic and has service delivery implications – without defining adolescence, it is challenging to provide the necessary support during the transition periods of early and later adolescence. HIV treatment centers are typically either geared towards adult or paediatric populations (UNICEF, 2013). This has two direct effects. First, developmental and transitional needs of adolescents are often not addressed as they are not a recognised sub-population. Second, data are often not collected for or ascribed to this age group. As a result, evidence required to inform policy is limited due to the lack of data, or is hampered by differing age ranges defined as ‘adolescence’. At this stage, it is not clear how many clinics have developed operational guidance corresponding to the WHO definition of the period between 10 and 19 years of age. There is a further challenge in that data disaggregation between perinatally- and behaviourally-infected adolescents is poor, leading to limited conclusions that may be drawn about either population (Sohn & Hazra, 2013).

[1] Please note that challenges related to HIV prevention, testing and disclosure prior to treatment and care are not included as these are beyond the scope of this research.

The specific adherence and retention challenges associated with adolescence are poorly documented (Arrive et al., 2012). Although there are few direct data for adolescents in HIV programs, what evidence there is has generally shown worse treatment outcomes among adolescents than adults (Shroufi et al., 2013), however adolescent-specific service delivery may lead to improved outcomes. A lack of simple treatment options for adolescents (UNAIDS, 2014) could explain this difference to some degree. Appropriate paediatric- and adolescent-adapted or suitable formulations that meet the unique needs of children and adolescents living with HIV, such as flexible dosing across multiple age and weight bands, are often unavailable and sub-optimal products are difficult for clinics and families to transport and store, have complex dosing requirements, may need refrigeration and are often unpalatable (DND*i*, 2013). Complicated treatment regimens and sub-optimal pharmacokinetic impact have detrimental implications for treatment adherence and retention in the continuum of care.

Other challenges that arise in HIV services with increased longevity include the transition from paediatric services to adult-focused care. Adolescents face considerable barriers in accessing HIV treatment, and remaining in care over this transition period. Current HIV diagnosis and care services are primarily aimed at adults, infants and young children and guidelines often tend to exclude HIV-infected adolescents, many of whom are orphans (Shroufi et al., 2013).

Infected youth have unique needs. For example, they have significantly higher risks and rates of depression and attentional deficits (Chernoff et al., 2013). Overall, this population presents with challenges related to mental health. For instance, in a study conducted among 82 Ugandan HIV-infected adolescents almost all of whom were orphans, 51% reported psychological distress and 17% had attempted suicide (Musisi et al., 2009). There is a clear need for clinics to provide age-appropriate counselling as well as for a broader response that builds the capacity of families, communities and institutions to provide supportive social environments for HIV-infected adolescents (Amzel et al., 2013).

The value of sexual and reproductive health (SRH) services in lowering transmission rates has been widely documented. Further, this is important from both a health and reproductive perspective, as well as from a rights-based point of view. Although greater emphasis is now being placed on the integration of SRH and HIV services for adolescents, there is limited data as to whether this is actually occurring in practice, and if so, to what degree.

Adolescent-friendly services have been strongly linked to better treatment outcomes in adolescent patients (Evans et al., 2013). Further, Shroufi et al. (2013) have argued that through adolescent-friendly programming, enrolment rates as well as treatment retention can improve. However, only a small proportion of perinatally-infected adolescents who are long-term survivors have access to ART, and most receive it through limited numbers of specialized treatment and care centres in urban and peri-urban settings (Kasedde et al., 2013). At present however, the extent to which adolescent-friendly services are being provided more widely beyond these specialised centers is not clear. In terms of broad community engagement and its benefits for patient populations and their healthcare, Liberato et al., (2011)

emphasise the point that linkages with community achieve better reach of target population, improved use of resources, increased local competence for and commitment to health action and change, and enhanced community ability to respond to emerging health issues.

In summary, it is clear that the increasing numbers of HIV-infected children who are surviving into adolescence require a targeted approach which takes into account their particular stage of life and the concomitant challenges that transitioning inevitably brings. It is also evident that many of these challenges are not well understood, and that the degree to which these challenges are being addressed remains unclear. This study seeks to explore the availability of specialized and appropriate HIV treatment and care services for adolescents in health facilities in 23 countries in sub-Saharan Africa.

Methodology

Study design and sample

This study utilised a cross-sectional survey design, which included both quantitative and qualitative items. Two hundred and eighteen (218) health facilities from twenty three (23) countries across the four sub-Saharan regions were surveyed. Countries in the sample include: Benin, Burkina Faso, Cameroon, Democratic Republic of Congo, Guinee, Nigeria, Republic of Congo and Senegal (West/ Central Africa); Burundi, Ethiopia, Kenya, Rwanda, Tanzania and Uganda (East Africa); and Angola, Botswana, Lesotho, Malawi, Namibia, South Africa, Swaziland, Zambia and Zimbabwe (Southern Africa)(Figure 1). The largest number of facilities were from Nigeria (n=44 facilities), Kenya (n=35 facilities) and South Africa (n=18 facilities).

The sample was drawn primarily from PATA network health facilities, with additional responses sought from other networks (South Saharan Social Development Organization, Elizabeth Glaser Paediatric AIDS Foundation and Clinton Health Access Initiative) to gain additional representation. These additional networks were approached so as to increase the sample size, and involved the forwarding of an introductory email (with the link to the survey) to contacts within these organisations, who then forwarded these emails on to clinics in their organisations. Overall, 130 (60%) health facilities were from the PATA network, with the remaining 88 (40%) sourced through other networks. This meant that 130 of the 258 clinics in the PATA network participated (50% of the PATA network (Table 1). Because network membership was not assessed in the survey, we are unable to identify to which network the remaining 88 facilities belonged or provide response rates for the other networks.

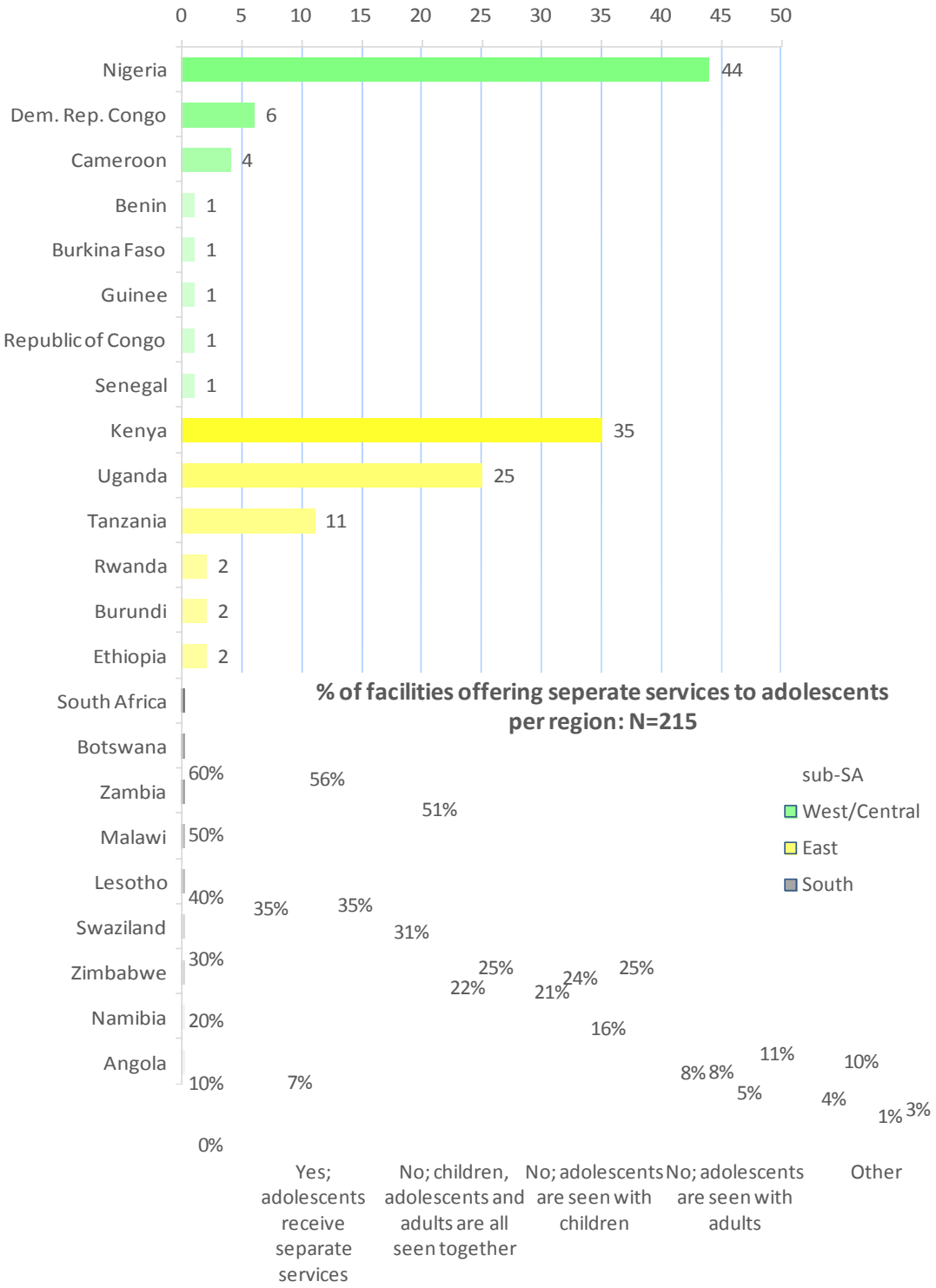
	Total	**West/ Central**	**East**	**South**
Health facilities sampled	218	59	77	82
PATA network (total size: 258 facilities)	130	11	55	64
Other networks (unknown total size)	88	48	22	18
Actual number of adolescents in care	57 299	3 210	26 162	27 927
Actual number of adolescents on ART	43 400	2 536	16 800	24 064
Average number of adolescents in care	367			
Average number of adolescents on ART	289			
Estimated number of adolescents in care	80 072			
Estimated number of adolescents on ART	63 075			

Table 1. Description of sample (n=218)

In terms of health facility location, 50% of the health facility sample was based in an urban setting, 17% in peri-urban and 33% in rural areas. Most surveys were completed by doctors/clinicians (34%), followed by nurses (21%) and administrators/managers (19%). The remainder of the respondent sample was derived from site co-ordinators, counsellors/social workers and pharmacists. The mean number of adolescents[2] in care at each clinic was 367, with a

[2] 'Adolescence' as conceptualised by the health facility definitions.

mean of 289 (79%) of these adolescent patients on ART. The estimated[3] number of HIV-infected adolescent patients in care at the facilities sampled totals 80,072.



[3] Estimations were calculated by multiplying the average number of adolescents at each clinic by the clinics which did not provide this data (62 of 218), and adding that to the actual number as reported in the surveys.

Tool development

The data collection surveys utilized in this study were developed through a review of the literature, as well as consultation with experts and stakeholders. Consultation took the form of inviting written commentary on the most pressing aspects of each theme within the scope of the study. This commentary formed the basis of the conception and development of response items in the survey tools. Commentary was provided by representatives from the WHO, United States Agency for International Development (USAID), Centers for Disease Control and Prevention (CDC), Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), Education Development Center (EDC), the International HIV/AIDS Alliance, Global Network of People Living with HIV (GNP+)/ the Y+ Programme, Partners In Health (PIH), University of Oxford, University of Nairobi and Makerere University.

This process led to the formation of two versions of the survey. A shorter, High Level (HL) version which contained 31 items was sent to a wider network of health facilities (returned surveys n=160), while a longer, Deep Dive (DD) version which contained 61 items was sent to a smaller group of health facilities (returned surveys n=58; total surveys received n=218) (see Appendix 3 & 4 for both survey versions). The selection of health facilities for the DD survey was based on current PATA programming relationships, i.e. where there is currently a PATA programme running, as opposed to the HL surveys which were sent to historic partners. The rationale behind this selection was that clinics with current PATA programmes would be more willing to complete the DD survey. All of the questions in the HL survey appeared in the DD version, with the DD allowing for more contextualisation of responses. Both survey versions were translated into French and Portuguese to facilitate participation of Franco- and Lusophone countries.

		PATA	Other
HL	Sent	200	n/a
	Received	85	75
	Response rate	43%	n/a
DD	Sent	58	n/a
	Received	45	13
	Response rate	78%	n/a

Table 2. Overall responses per PATA and other networks (n=218)

Data collection process

Data collection took place via email, fax, telephonic interview or a web-based survey platform. Personalised emails were sent to each of the health facilities, detailing the purpose of the study, as well as obtaining ethical clearance

considerations. Emails were sent in either English, French or Portuguese, with a link to the corresponding HL or DD version of the survey. Once the initial email had been sent, a research assistant made telephone calls to each facility to ensure receipt. Once confirmation had been given, participants were provided with alternative choices of completing the survey over the telephone or using an MS Word version. Due to the nature of some survey items which required gathering of information from health facility records, most participants chose to complete it online. No client-linked data were collected. A small number of facilities requested an MS Word version, which was returned as an email attachment or by fax. Facilities that had not responded by a certain date were then telephoned as a reminder, which helped to increase the response rate. A maximum of four telephonic reminders/ follow-ups were enacted with each facility before the data collection phase of the study was completed. French and Portuguese surveys were back-translated into English using inbuilt web-based survey platform functionality.

Data analysis

All data were analysed using MS Excel. Based on the descriptive nature of the research aims and design, descriptive statistics (means and percentages) were used to describe central tendencies. Due to fluctuating sample sizes, response rates were calculated (Appendix 1). Fourteen of the HL's 31 items and 49 of the DD's 61 items were open-ended and elicited qualitative data. These data were analysed using a thematic analysis. Themes were generated through familiarisation of the themes emerging. Once saturation had been reached, the data was split into three subsets, each scored by one of three coders. Coders were briefly trained and provided with a few illustrative examples including a brief discussion about scoring logic per item. Once scoring had been completed, codes were summed, producing frequency data, reported as percentages. Denominators used when calculating percentages vary by question, based on coding rules and the open/closed nature of questions (see Appendix 1). In cases where the sample provided sufficient depth ($n \geq 200$), results were displayed in regional groups.

Limitations

There are several limitations to our assessment. First, in an effort to provide a comprehensive situational analysis while remaining conscious of the length of the surveys administered and its potential impact on response rate, the surveys did not enable us to gather a large amount of detail on every thematic area studied. For a few questions, in particular those related to the content of transition and adherence counselling, responses lacked sufficient detail and limited our ability to assess the quality and comprehensiveness of counselling being offered. Second, not all survey respondents provided responses to all of the questions and because of the large sample size we were not able to follow up with them individually to address gaps. To caution against this later in the text, boxes which describe survey type, sample size, and response rates, per item are given where appropriate, for example (HL, n=125, rr=85%).

Third, the results for this study are not representative of the situation in all of the countries included in this research. This is because the analysis was limited to facilities that are part of the PATA and other networks, rather than a random sample of facilities. It may be noteworthy that non-PATA additional health facilities were sourced principally from the West/Central sub-regions. This could introduce a potential bias; however, the direction of this bias is unclear

due to broad heterogeneity of health facilities. For instance, the average number of adolescents in care at clinics is 367, with a standard deviation of 827, and the fact that we report on a reasonable spread between urban (50%), peri-urban (17%) and rural (33%) settings could suggest a fair heterogeneity.

Fourth, while prior to coding the three coders underwent training on coding rules, no inter-rater reliability was calculated. Fifth, due to time constraints, survey responses in Portuguese and French were back-translated to English using automated web-based translate functionality. This automation may have compromised the finer nuance of responses, but previous translation comparisons have proven sufficiently accurate to justify the process. Lastly, our data is based on self-reporting from healthcare staff. Further validation of the results obtained on site or with other stakeholders (including adolescents themselves) was not possible given the scope of research and sample size.

Ethics

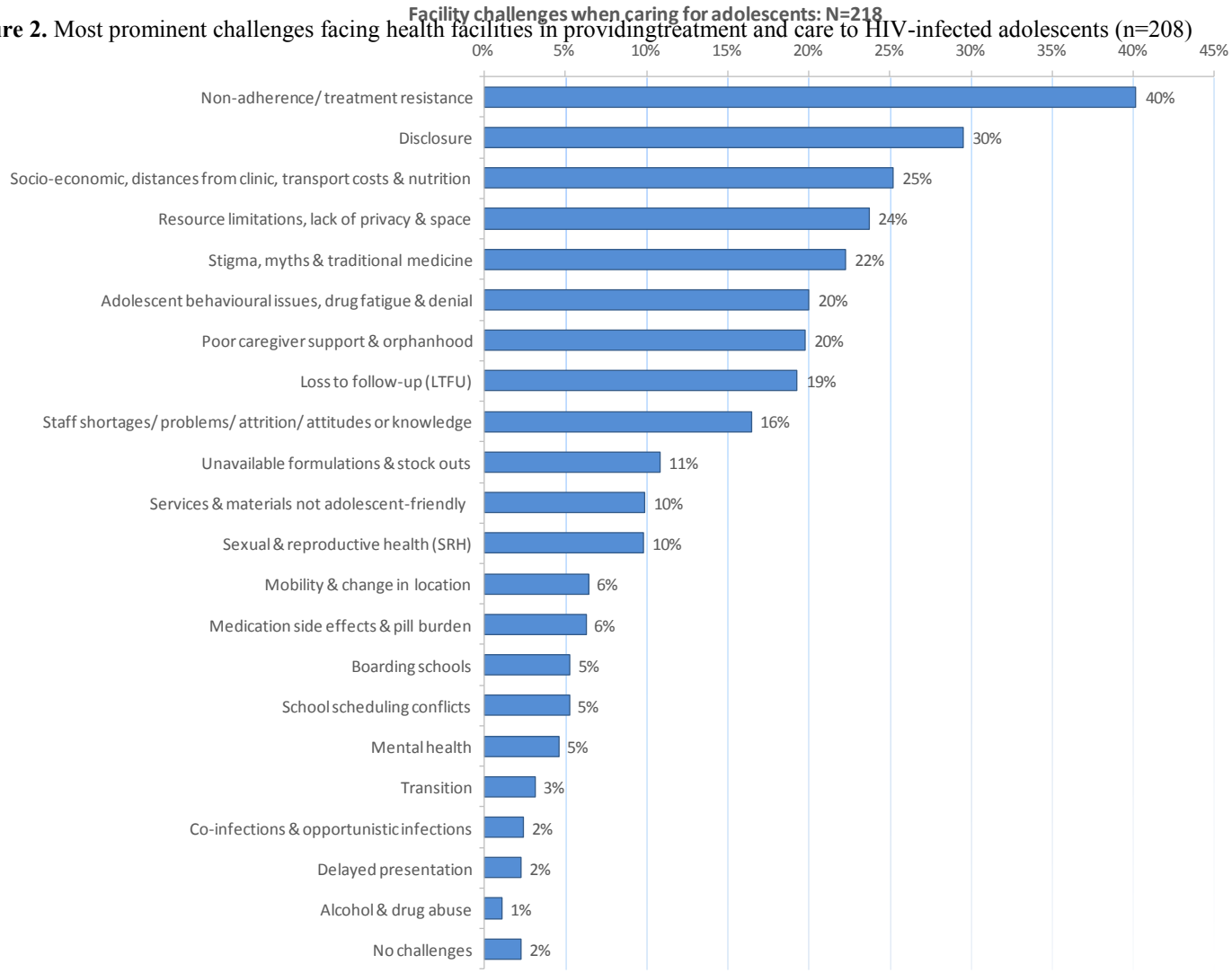
Participants were informed prior to consenting, as well as in the consent form provided, that they were free to withdraw from the study at any time and without any penalty or loss of benefits to which they would otherwise have been entitled. In the web-based survey platform, ethical consent was received before respondents were directed to the survey items. For email and fax collection, respondents were asked to send the consent form attached to their response. As this study examines facility-level data only, participants were informed that results would be presented as aggregated data and would not mention specific facility names, so as to preserve anonymity.

Results

Barriers to treatment and care for HIV-infected adolescents

In the 218 facilities sampled across 23 countries, there was large variation in the areas reported by healthcare providers as comprising the three most prominent challenges to the treatment and care of HIV-infected adolescents (Figure 2). These data were derived through open-ended questions in each survey (HL and DD) which asked about challenges in initiating, caring for, or sustaining adolescents in care. However, respondents provided similar answers to each question. The three response sets were therefore averaged to provide a score per theme related to broad challenges to providing HIV treatment and care to adolescents. A few of the questions did elicit some difference, but these were mostly expected (Table 3).

Figure 2. Most prominent challenges facing health facilities in providingtreatment and care to HIV-infected adolescents (n=208)



	Non-adherence/ treatment resistance	Disclosure	Socio-economic	Stigma, myths & traditional medicine	Poor caregiver support & orphanhood	Loss to follow-up (LTFU)	Sexual & reproductive health (SRH)
Initiating	34%	37%	18%	20%	27%	13%	2%
Caring for	48%	38%	28%	30%	17%	22%	16%
Sustaining	38%	14%	30%	17%	16%	23%	11%

Average	40%	30%	25%	22%	20%	19%	10%
Std. Deviation	7%	14%	6%	7%	6%	6%	7%

Table 3. Themes which were different when comparing questions on initiating, caring for, or sustaining treatment and care to adolescents in HIV care (n=208). Highlighted cells indicate the outlier in all themes which presented with a standard deviation greater than 5%.

The most commonly cited challenge (HL, n=208, rr=95%) noted by 40% of survey respondents, related to non-adherence and treatment resistance in this population group. The second most commonly cited challenge (30%) was that of non-disclosure of HIV status, which included non-disclosure of status to the adolescent (43% of those who cited this challenge) and non-disclosure of status by the adolescent to others (21%), with the remainder of respondents (36%) not specifying to which of these two categories of disclosure they were referring. Socio-economic barriers such as poverty, transportation costs associated with long distances to facilities and food security, were the next most commonly cited challenge (25%), followed by inadequate resources and space limitations in facilities (24%).

Other common challenges cited by facilities included stigma, myths and traditional medicine; adolescent behavioural issues, drug fatigue and denial; poor caregiver support or orphanhood; loss to follow-up and staff shortages, attrition, attitudes or knowledge. Challenges cited with less frequency by facilities included unavailable formulations and stock outs; lack of adolescent-friendly services or materials and the difficulty of catering to the sexual and reproductive health (SRH) needs of this specific population; patient mobility and change of location, side effects and pill burden, treatment in boarding school environments as well as school scheduling conflicts in general, mental health, transition-related challenges, opportunistic and co-infections, delayed presentation and alcohol or drug abuse. Box 1 provides further insights into these diverse challenges as reported by survey respondents.

Box 1. Feedback from respondents regarding prominent barriers to treatment and care of HIV-infected adolescents

"*Most of the adolescents do not comply with treatment because they are in their self-discovery stage where they start questioning and some feel there is no point for them to take their medication after all they will die like their parents*." Nurse, Swaziland

"*Disclosure, many guardians try as much as possible to delay disclosure because they do not want to hurt/ offend the child, this affects adherence and rapport with the health workers."* Doctor, Malawi

"*[O]ver 50% of our adolescents are orphans lacking in all basic needs and many of them end up looking up to us the health workers, stories like I have not had any meals for 2 days, I have been sent out of school, I do not have clothing are really heart-breaking."* Doctor, Malawi

"Insufficiency of equipment and supplies." Counsellor, Tanzania

"*Stigma and Discrimination; This is one of the biggest challenge in sustaining HIV treatments and care to adolescents, this involves self stigma, stigma perpetrated by others and stigma by association*." Doctor, Kenya

"*Some of the Caregivers do not want to be associated with the infected adolescent. The children are then let to come to the clinic on their own and yet some of them are too young /sick to comprehend or understand the adherence health messages*." Nurse, Kenya

Definition of adolescence

Over a quarter (26%) of the respondents surveyed (HL, n=217, rr=100%) noted that their facility does not have an official working definition of adolescence in place. In West and Central Africa, 49% of facilities do not have a working definition of adolescence.

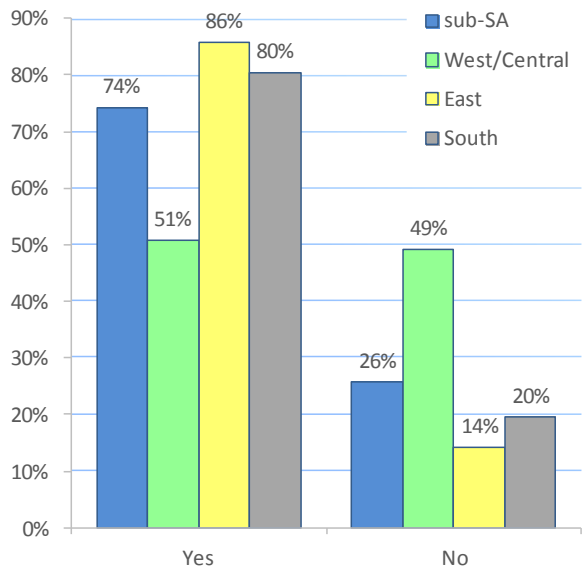


Figure 3. Working definition of adolescence (n=217)

Facility definitions of childhood, adolescence and adulthood vary greatly (Figure 4; HL, n=162, rr=100%), with a reported range of the start of the adolescent period spanning from eight to 21 years. Although just over half (57%) of facilities defined the start of adolescence at 10 years of age and 13% defined the start of adulthood at 20 years –

reflecting some degree of consistency with the WHO definitions thereof – 12 years and 15 years were also noted as entry points into adolescent care.

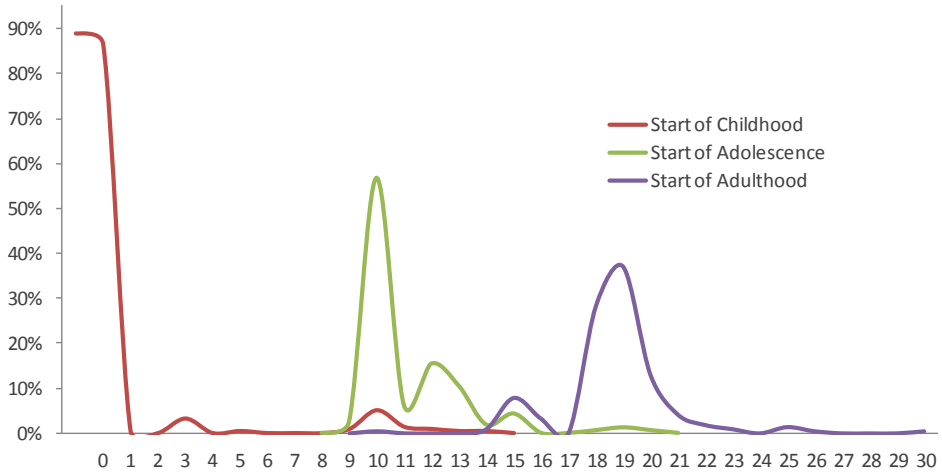


Figure 4. Facility definitions of adolescence (n=162)

Data monitoring and clinical issues

Data monitoring

Sixty six percent of facilities reported that they maintain records which permit discernment of adolescents from the overall patient population (HL, n=215, rr=99%). In 18% of facilities no distinction is made between the categroies of children, adolescents and adults; in 11% adolescents are recorded as children; and in 4% of facilities they are recorded as adults. Figure 5 shows a breakdown of the identification of adolescents in facility records by region, with West and Central African countries reporting the lowest identification rate at 53%.

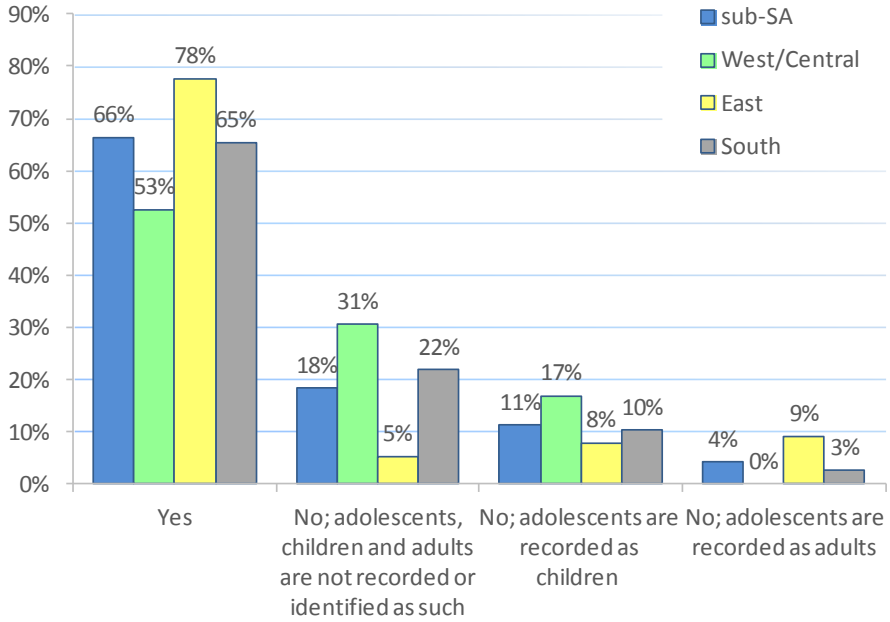


Figure 5. Identification of adolescents in facility records (n=215)

Figure 6 presents the descriptors being recorded in facility records about HIV-infected adolescents (HL, n=214, rr=98%). The most common descriptor is pregnancy status (69%), followed by whether the adolescent was infected

perinatally (37%). Young key population status (young people who sell sex, young people who inject drugs, young men who have sex with men) is recorded in adolescent records at 14% - 18% of facilities. Facilities in West Africa are the least likely to capture each of these descriptors in their records. Twenty-five percent of facilities across all regions are not recording any of these descriptors.

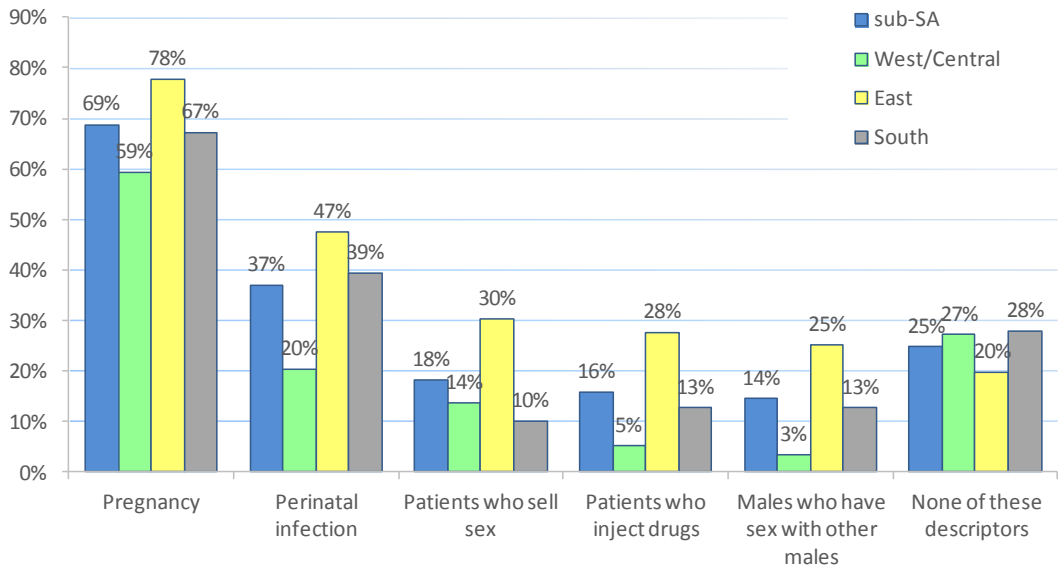


Figure 6. Descriptors recorded about adolescent patients (n=214)

Treatment outcomes data collection

While only 20% of facilities disaggregate treatment outcomes by age, 75% percent of facilities reported tracking first-line treatment regimens, 72% second-line and 17% third-line for their patient populations (Figure 7; HL, n=214, rr=98%). Loss to follow-up rates are being recorded at 77% of facilities. Treatment failure, mortality and virological suppression rates are being monitored at 69%, 63% and 43% of facilities respectively. Thirteen percent of facilities reported not monitoring any of these treatment outcomes. East African facilities report better treatment outcomes monitoring than their West/Central and Southern African counterparts, with the exception of third-line treatment outcomes, which were best monitored by Southern African facilities. This may be a function of third-line regimen availability. Forty-two percent of West and Central African facilities reported not monitoring any of these treatment outcomes.

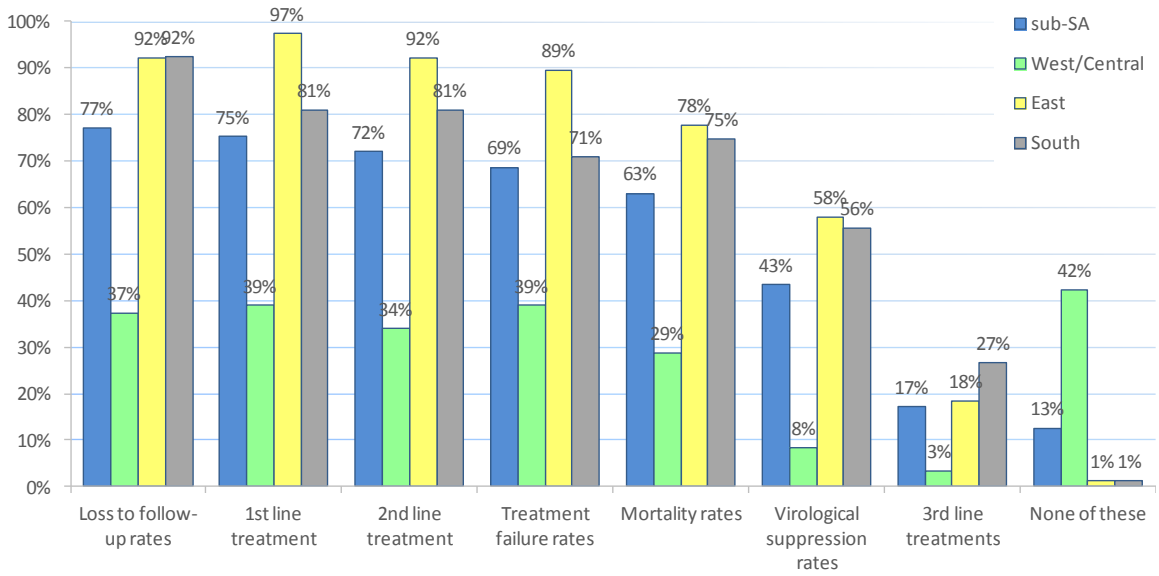


Figure 7. Treatment outcomes data monitored by facilities (n=214)

Figure 8 summarises whether and how this treatment outcomes data is utilized. Where monitored, treatment outcomes data (HL, n=215, rr=99%) are used to prepare reports (79%), track (72%) and manage patients (68%). At 60% of facilities, outcomes data are entered into an electronic database. Only West and Central African facilities, at a level of 27%, reported not utilizing the data at all.

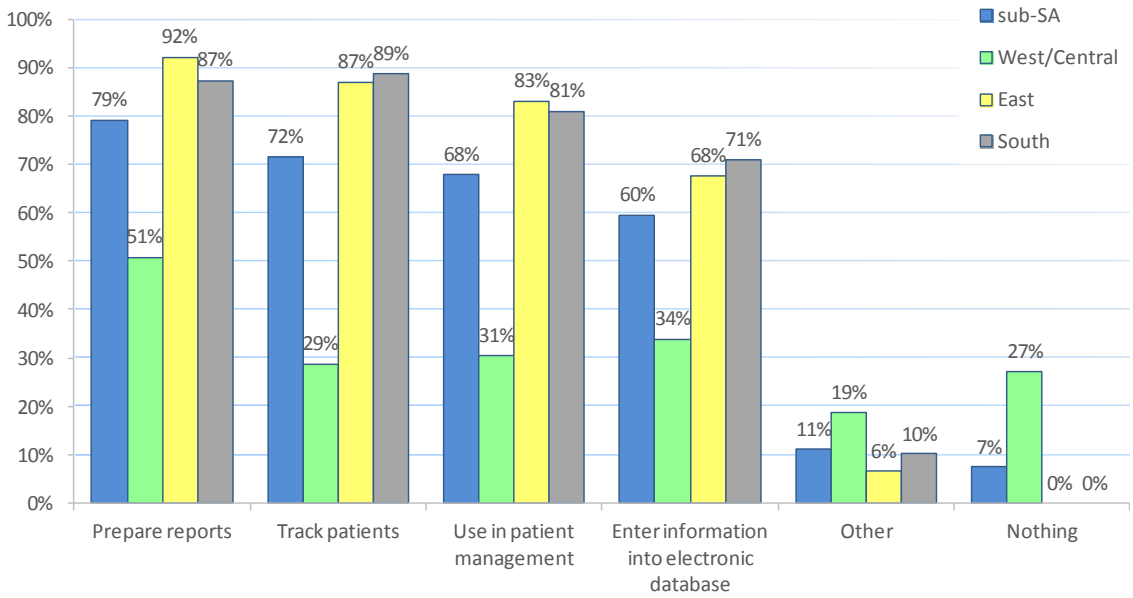


Figure 8. Utilization of treatment outcomes data for all patient age groups (n=215)

Clinical presentation and issues

Findings regarding the most frequent clinical presentations in HIV-infected adolescents are displayed in Figure 9 (DD, n=56, rr=97%). These include delayed growth and puberty (89%), skin conditions (84%) and opportunistic infections

(82%). They also include chronic lung disease (48%), mental health issues (41%), neurocognitive impairment (21%), lipatrophy (9%) and malnutrition (7%).

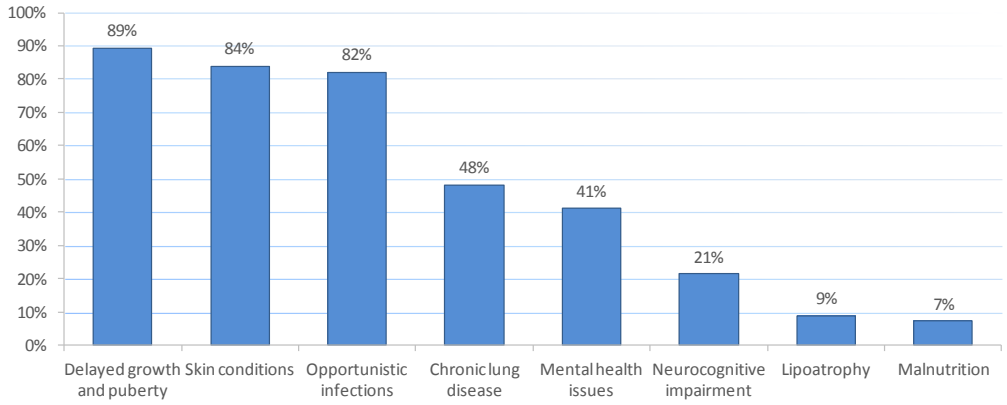


Figure 9. Most frequent clinical presentations in HIV-infected adolescents (n=56)

Figure 10 provides a breakdown of the most commonly cited challenges when switching adolescent patients to second-line ART (DD, n=56, rr=97%). Facilities report ongoing adherence challenges (84%) as their primary difficulty, followed by challenges in defining treatment failure in the absence of viral load monitoring (48%), lack of second-line treatment options (27%) and lack of appropriate formulations (20%). Less common challenges include side effects (9%), pill burden (7%), poor caregiver support and orphanhood (5%), staff knowledge and skills (2%) and laboratory issues (2%).

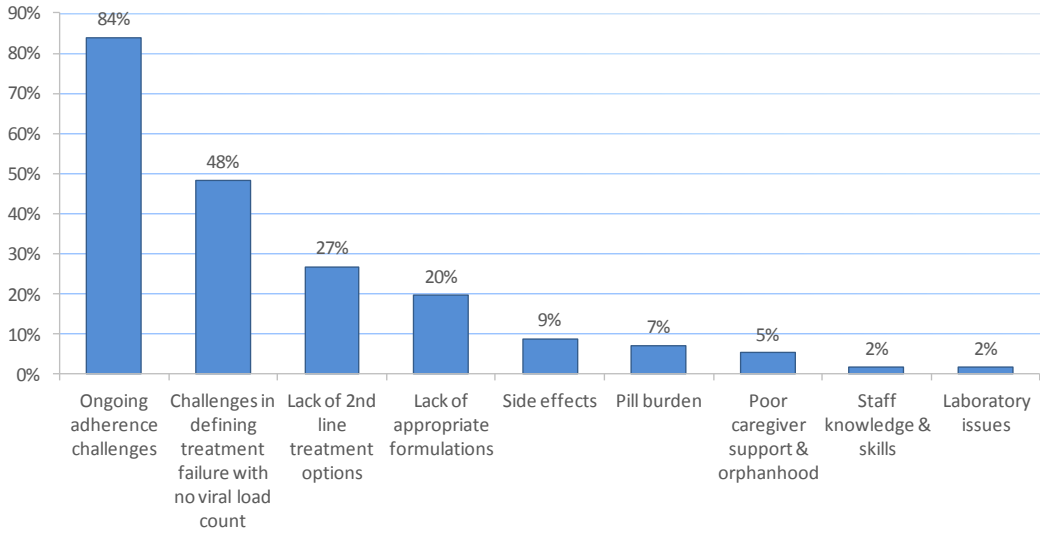


Figure 10. Challenges when switching adolescent patients to second-line ART (n=56)

Adherence and retention

Treatment adherence

It seems many clinics have specific services to improve treatment adherence in adolescents (rather than guidelines or protocols)(Figure 11; HL, n=216, rr=99%). 67% of respondents reported offering such services. Looking across regions, facilities in East Africa are most likely to offer services (84%), followed by Southern Africa (68%), and West and Central Africa (44%).

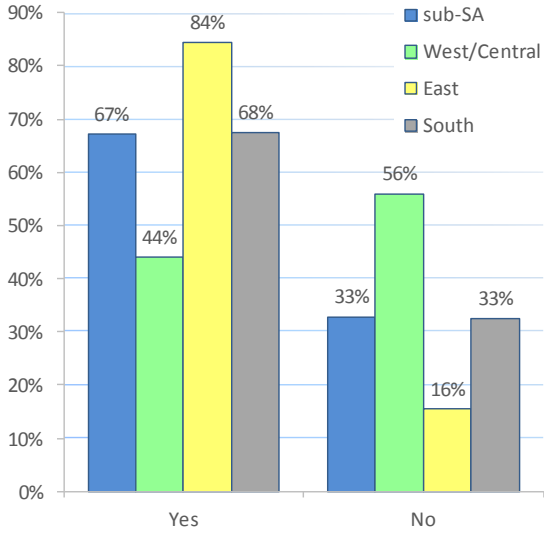


Figure 11. Availability of services to improve adolescent adherence (n=216)

Where respondents answered 'Yes', descriptions of special adherence support activities and services being offered to adolescents (Figure 12; HL, n=145, rr=100%), involved providing peer support, activities and clubs (49%). Other common approaches provided by facilities included home visits, adherence counselling and general counselling. Various other approaches are being utilised, including nutritional support and caregiver engagement and treatment support, by facilities. Overall, most respondents believe that the most effective of these adherence support activities and services (DD, n=43, rr=74%) is peer support, activities and clubs. Other approaches highlighted respondents were adherence counselling, community health workers and CBO engagement and home visits. The effectiveness of these adherence interventions were predominantly based on anecdotal evidence, with only a few respondents having conducted targeted research into this question.

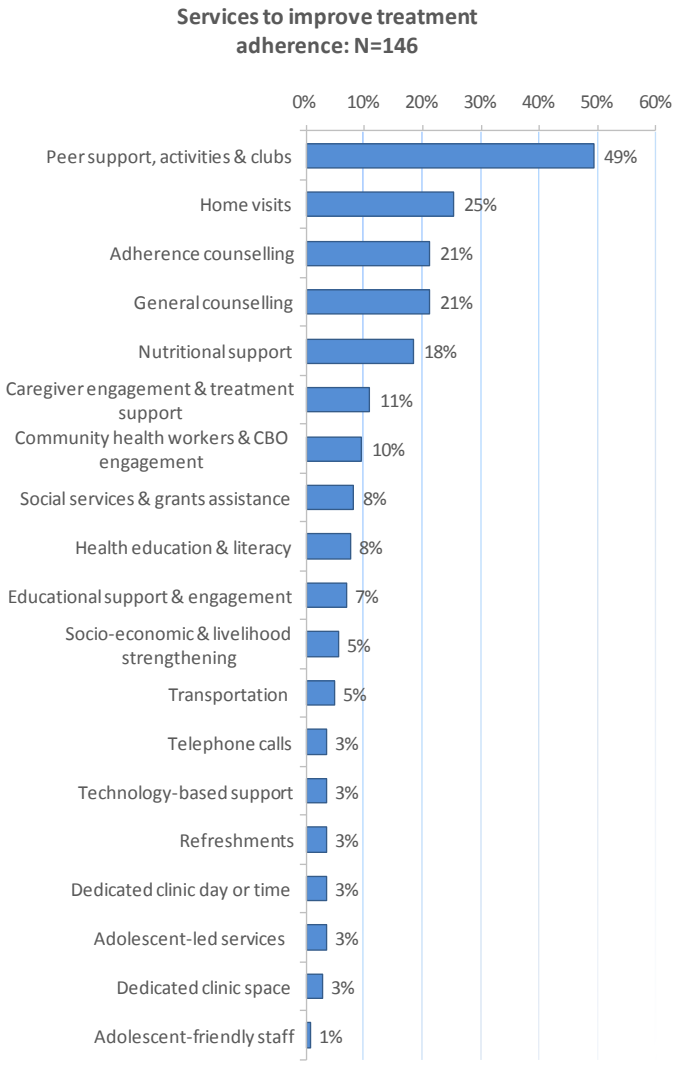


Figure 12. Activities and services offered to improve treatment adherence in adolescents among facilities indicating that adherence support to adolescents was available (n=145)

Adherence counselling was reported (Figure 13; HL, n=216, rr=99%) as being offered at 87% of facilities. Regionally, this counselling is being conducted in 97% of facilities in East Africa, 90% of facilities in Southern Africa and 69% of facilities in West and Central Africa.

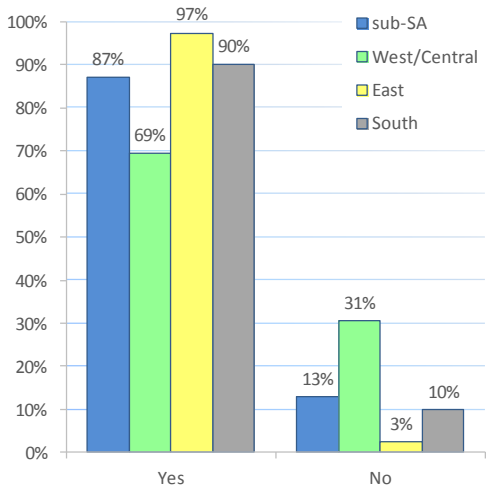


Figure 13. Availability of adherence counselling for adolescents (n=216)

Figure 14 shows that the content of adherence counselling (HL, n=175, rr=93%) predominantly takes the form of general descriptions of adherence and/ or ART and the implications of non-adherence, including resistance. This can sometimes take the form of scaremongering, as is demonstrated by the response "*We counsel on the danger of resistance and the scare of opportunistic infections as well as death.*" Nurse, Namibia. Less frequently, adherence counselling focuses on HIV, health and positive living, SRH, emotional wellbeing and resilience, disclosure support, accessing social support and adherence strategies. Life and psychosocial skills, tools and resources available are mentioned rarely.

Box 2. Feedback from respondents regarding adherence support activities and services

"Peer to peer youth group are highly effective since a common bond forms and adolescents share their own personal issues and find solutions for common problems through open discussion without fear of discrimination." Doctor, Ethiopia

''The Counsellor take more time with the client but each person has a role to play in the client's well being.'' Doctor, Uganda

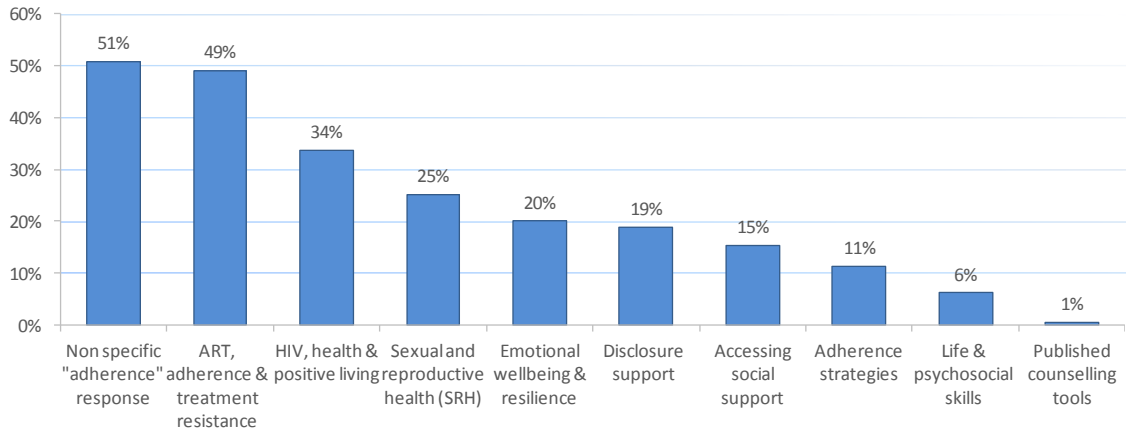


Figure 14. Content of adherence counselling for adolescents (n=175)

Adherence counselling sessions with adolescents usually involve a counsellor, doctor/ clinician, nurse, and caregiver. Less frequently sessions include a community health worker, pharmacist/ pharmacy technician, psychologist, social worker and/or peer supporter (Figure 15; DD, n=53, rr=98%).

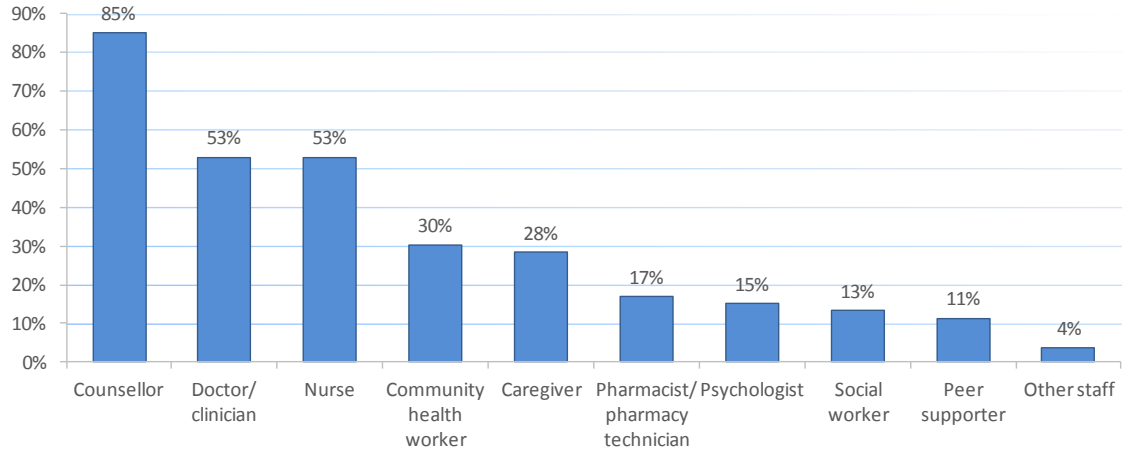


Figure 15. Stakeholders involved in adolescent adherence counselling sessions (n=53)

Many facilities reported that no guidelines and protocols were in place for managing adolescents who experience adherence challenges (DD, n=56, rr=97%). Where such guidelines and protocols are in place, the procedures recommended therein included adherence counselling, caregiver engagement and treatment support, general counselling, peer support, activities and clubs, and home visits. Other interventions mentioned by facilities included disclosure support, community health worker and/or community-based organisation (CBO) engagement, increase in frequency of clinic visits, pill counts and adopting a multi-disciplinary approach to supporting the adolescent.

Treatment failure

When defining treatment failure in an open-ended qualitative question, many clinics produced answers which were the determination points for treatment failure as they are used in their clinics. Of these, 45% provided no clear determination of adherence at their facility (Figure 16; Box 4; DD, n=55, rr=95%). Pill counting was used to

determine adherence by 42% of facilities. Other methods included tracking of pharmacy refills (11%), patient self-report (9%) and viral suppression (4%), or a combination of these.

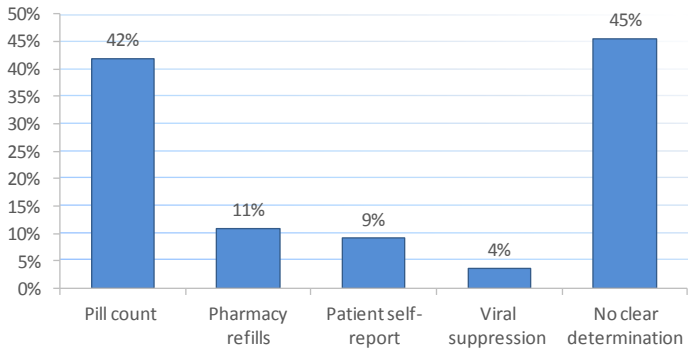


Figure 16. Determinations of treatment adherence (n=55)

An example of the challenges around defining adherence is presented in Box 3 below.

Box 3. Responses to question of how adherence is defined

''Taking drugs (ARV's) regular.'' Counsellor, Tanzania

''We have no strict definition, but check pharmacy refills, monitor whether patients are late for appointments, ask for patients' own estimate of doses missed per week, and occasionally do pill counts.'' Doctor, South Africa

Sixty percent of respondents have access to and utilise viral load monitoring (DD, n=55, rr=95%). Of those that do (DD, n=33, rr=100%), viral load testing is routinely conducted every six months or more frequently, and on an annual basis sometimes, while biennial monitoring is seldom done (Figure 17). Some facilities do not offer viral load testing routinely, but do monitor on suspicion of treatment failure (Box 4).

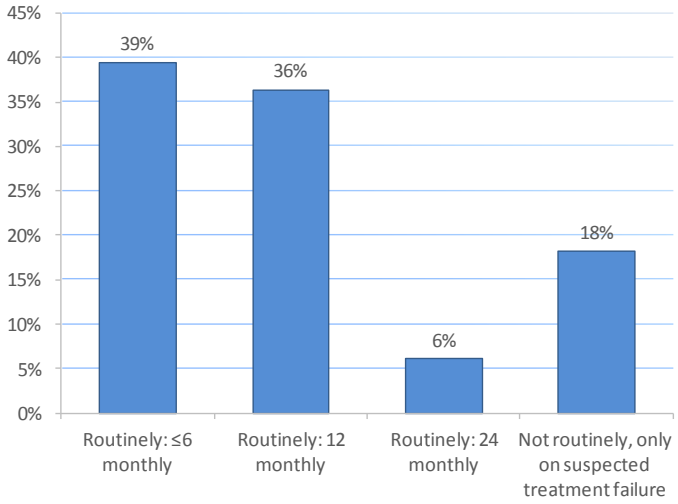


Figure 17. Frequency of viral load monitoring of respondents who do offer monitoring (n=33)

Box 4. Example of non-routine viral load monitoring

''Currently we are doing targeted viral load testing, which means we do when we suspect failure not routine. We don't have a viral load machine and hence we have to send the specimen to a central lab.'' Clinic Manager, Malawi

Seventy three percent of facilities have a definition in place for virological failure (DD, n=55%, rr=95%). The most commonly used threshold for failure (DD, n=39, 98%), was >1,000 copies/ml (68%), followed by >500 copies/ml (16%), >5,000 copies/ml (13%) and >3,000 copies/ml (3%). It is possible that facilities reporting thresholds of >3,000 copies/ml and/or >5,000 copies/ml are relying on dried blood spot technology for viral load assessment. Figure 18 below provides a breakdown of facility procedures following confirmation of viral load failure (DD, n=40, rr=100%). The most common interventions include adherence counselling and switching ART regimens (both 65%), staff consultation (35%) and repetition of viral load test (33%).

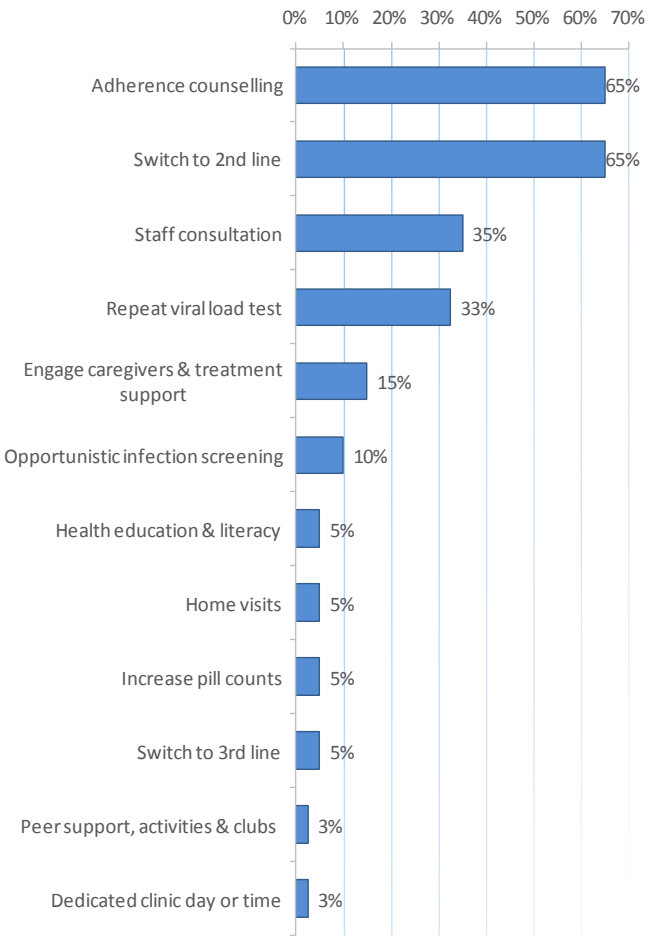


Figure 18. Facility procedures following confirmation of viral load failure (n=40)

Retention in care and loss to follow-up

In contrast with the previous section which reported that nearly half of facilities had no clear definition of adherence, just 4% of facilities reported no clear definition of loss to follow-up (LTFU)(DD, n=53, rr=91%). The most common definition used by facilities for loss to follow-up was when three or more months had passed since an adolescent had last attended a clinic visit (66%). The second most common definition was an adolescent having missed two or more consecutive visits (15%). Box 5 provides an example of the specificity around defining loss to follow-up evidenced in the sample, as well as cautions against expectations and assumptions in the interpretation of the rate of guidelines and protocols in place at facilities.

Box 5. Feedback from respondents regarding retention definitions and guidelines

"[Loss to follow-up] is when clinic staff have lost total contact to that client, cannot be reached on phone, or be found in the village he/she is expected to be and has not been reporting on appointment days for 6 months when not on ART drugs, 3 months when on ART drugs." Doctor, Uganda

"It is not necessarily a guideline, what we are using is a phone, to phone them for appointments." Clinic Manager, South Africa

Forty one percent of respondents reported that no guidelines or protocols were in place for managing adolescents who experience retention challenges (DD, n=56, rr=97%). Where such guidelines or protocols are in place, prescribed interventions principally included home visits (52%) and telephone calls (44%), with other listed procedures including general counselling, caregiver engagement and treatment support (both 12%), peer support, activities or clubs, and disclosure support (both 8%).

Less than two-thirds of facilities (61%) are offering service to support retention in care of adolescents (HL, n=216, rr=99%). This rate is just lower than that of adolescent adherence support rates, which were reported in the last section to be 67%. Figure 19 shows a breakdown across regions. Following the same pattern as that of availability of adolescent adherence support, facilities in East Africa are most likely to offer services (82%), followed by Southern Africa (64%), and West and Central Africa (31%).

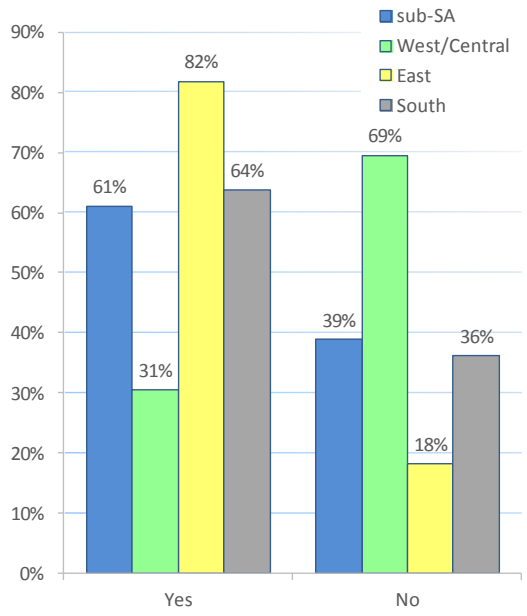


Figure 19. Availability of services to support adolescent retention in care (n=216)

Where retention support services are being offered to adolescents (Figure 20; HL, n=132, rr=100%), as with adherence, the two most common approaches were peer support, activities and clubs (34%) and home visits (31%). Other approaches in use for providing retention support are varied and reported by <20% of facilities. Overall most respondents indicated (DD, n=37, rr=97%) that the most effective of these retention support activities and services are peer support, activities and clubs, and home visits. Other approaches highlighted by respondents were the provision of transportation support and community health worker and CBO engagement. Views on service effectiveness were predominantly based on anecdotal evidence, with few having conducted targeted research into this question.

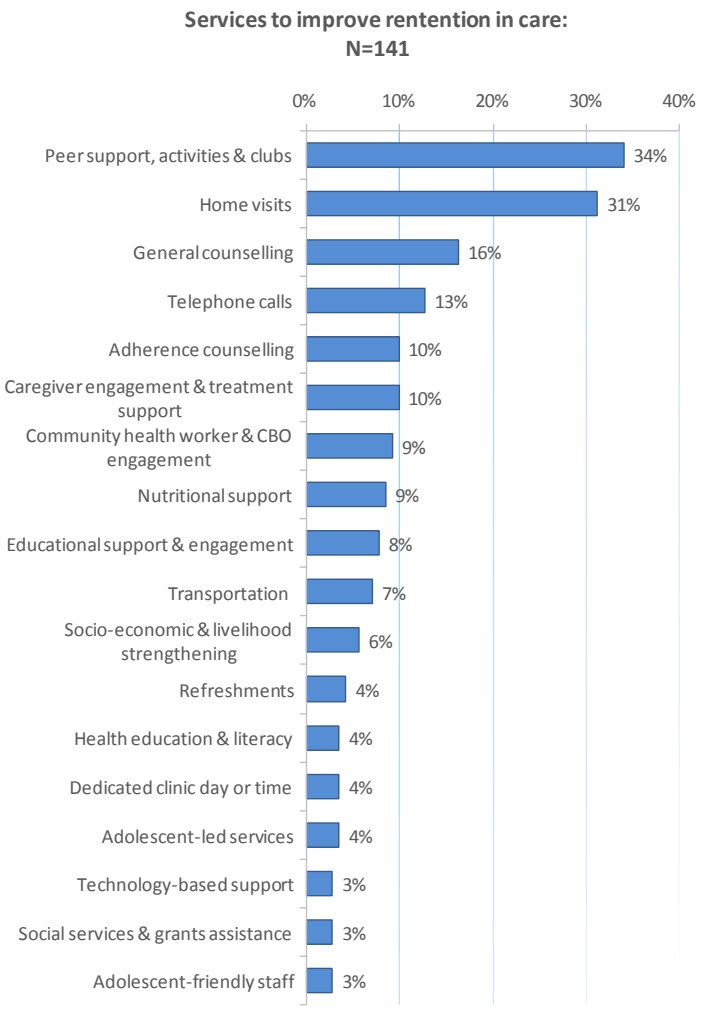


Figure 20. Activities and services offered to improve retention in adolescents (n=132)

When an adolescent has been identified as lost to follow-up (DD, n=54, rr=93%), 76% of facilities report conducting a home visit for follow-up. Telephone calls are made in 50% of facilities, and 30% reporting involving community health workers or CBO's in interventions to return adolescents back to care (Figure 21). Short message service (SMS), email and school visits were mentioned by <5% of facilities.

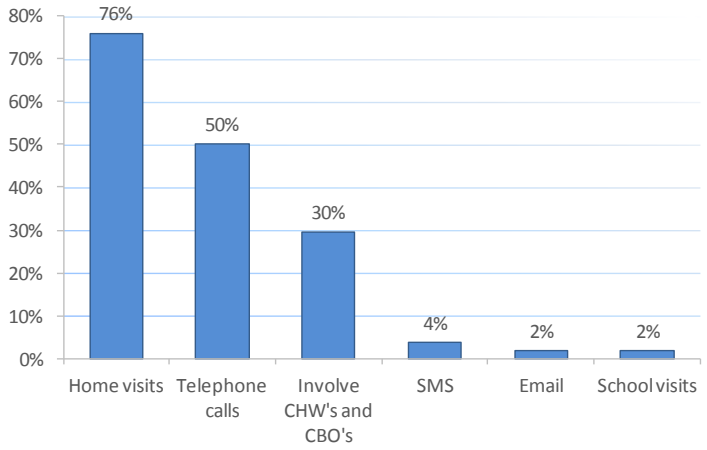


Figure 21. Facility interventions for adolescents lost to follow-up (n=54)

Service delivery and transitioning issues

Adolescent friendliness

Thirty-five percent of facilities report attending to adolescent patients separately from adult and/or paediatric patients (Figure 22; HL, n=215, rr=99%). This is in contrast to 31% of facilities where children, adolescents and adults are attended to together (on the same day/ time, at the same place, by the same staff), 21% of facilities where adolescents are seen with children, and 8% of facilities where adolescents are seen with adults. In the remaining 4% of facilities, respondents noted that adolescents were being attended to using some combination of these approaches. While West/ Central African and Southern African facilities tended not to provide separate services (at 7% and 35% respectively), favouring combined services across all three population groups or accommodation of adolescents with either children or adults, more than half of East African facilities (56%) had adopted an adolescent-specific services model.

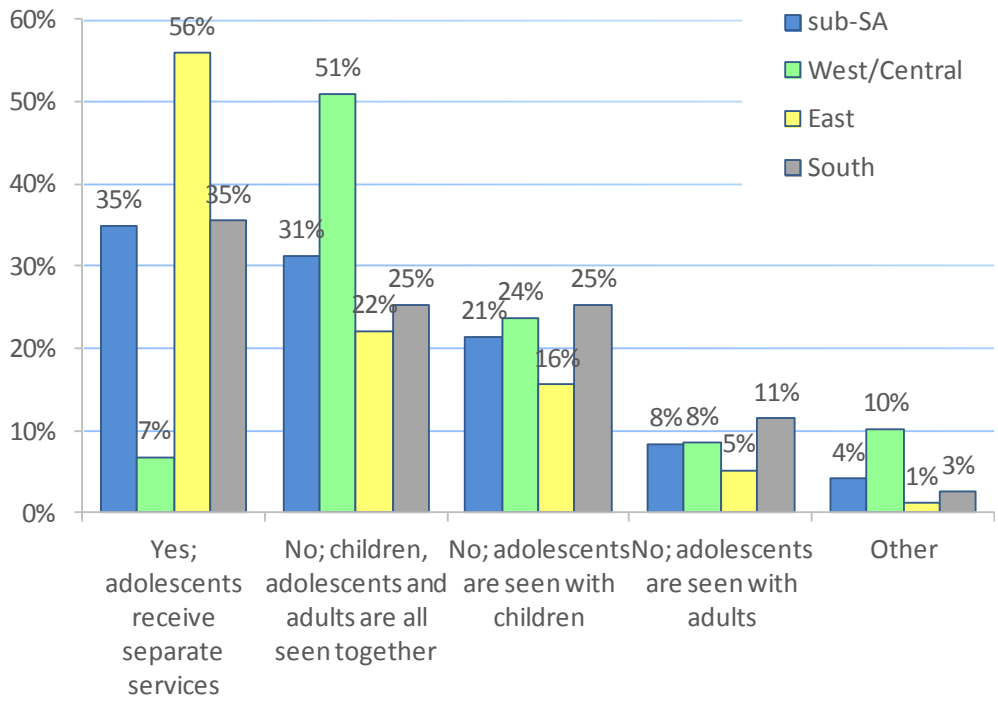


Figure 22. Facilities offering separate services to adolescents (n=215)

Where separate services are offered to adolescents (Figure 8; HL, n=72, rr=96%), the most common feature is the allocation of specific clinic day or time of day to attend to adolescents only. This is the approach being taken in 88% of these facilities. Of the remaining facilities, 10% are serving adolescents by having dedicated clinic staff available to attend to them, and the remaining 8% of facilities have a dedicated clinic space for adolescents.

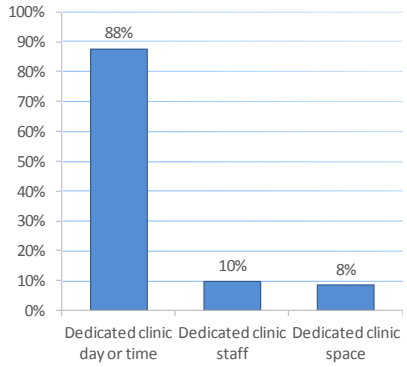


Figure 23. Variations in models for adolescent-specific service delivery (n=72)

Illustrative examples of common service delivery models utilised to provide separate services to adolescents is presented in Box 6 below.

Box 6. Service delivery models used to provide dedicated services to HIV-infected adolescents

''They are seen on Thursdays, twice a month, where they are offered services friendly to them.'' Doctor, Uganda

''Adults, adolescents and children are all seen in the same building but we have 3 nurses dedicated to the care of adolescents. The adolescents have a youth centre… where they can wait for their appointments and interact with peer counsellors and their peers. IEC material is provided at the youth centre. '' Doctor, Zimbabwe

''Adolescents attend once a month clinic on a Saturday. This is clinic is only for those that have been disclosed, so we have some adolescents that are still [following] the general adults and children clinic. '' Doctor, Malawi

''We do have a specific day (Wednesday) for adolescents, even though sometimes other patients missed appointments on Tuesday do come on this day. '' Administrator, South Africa

Transitioning

Where respondents reported that there is a standard process for transitioning clients out of paediatric services, the findings show that the age at which this transition occurs varies greatly (Figure 24; DD, n=43, rr=74%). The most common age for transition from paediatric services is at 18 years of age (23%), followed by 10 years (14%), 12 years (12%), 15 years (12%) and 20 or 21 years of age (each 7%). Of the 39 facilities that on whether they had guidelines or protocols to guide the transition process, just over half (51%) reported that these were in place.

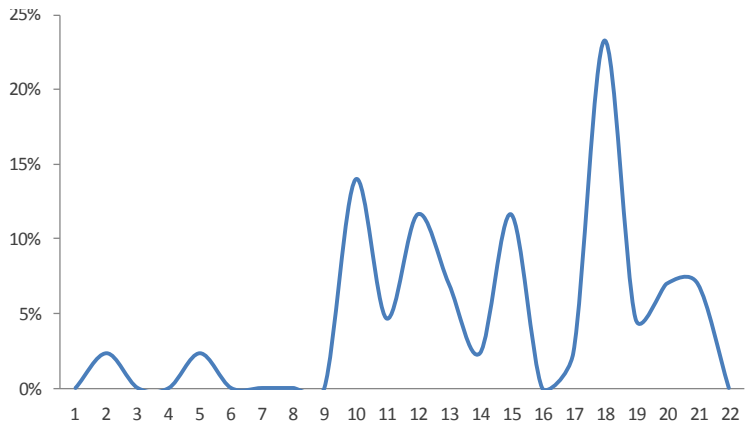


Figure 24. Age of transition from paediatric services (n=43)

Sixty-three percent of facilities provide counselling to aid in the transition process(DD, n=54, rr=93%). This transitioning-specific counselling is most commonly conducted over the course of three sessions, with the next most common frequency being two or four sessions. The majority of counselling sessions last more than 15 minutes (DD, n=34, rr=100%). The counselling tends to focus on the transition process itself, and less frequently SRH, the importance of adherence, HIV disease, health implications, and positive living, emotional wellbeing and resilience, disclosure support, routine counselling, socio-economic and livelihood strengthening, life and psychosocial skills and accessing social support (DD, n=32, rr=94%). These transition counselling sessions are typically conducted with the adolescent in the presence of a counsellor, doctor/ clinician, nurse and/or social worker and caregivers. Less frequently, these sessions include a community health workers, peer supporters, pharmacists/ pharmacy technicians, psychologists and other staff (DD, n=32, rr=94%).

The transition process for female adolescents who become pregnant varies, with some respondents noting that pregnant adolescents are moved into adult HIV/AIDS services earlier than standard procedures due to pregnancy (DD, n=57, rr=98%). Box 7 provides descriptive responses from sites where this earlier transition determined by pregnancy occurs. Where there is this earlier pregnancy-determined transition for pregnant adolescents into adult services, support seems to be offered infrequently.

Approximately half (46%) of respondents reported that their facility caters to the special needs of HIV-infected pregnant adolescents (DD, n=57, rr=98%). Of these, services include prevention of mother-to-child transmission (PMTCT), antenatal care (ANC), management as special cases, support groups for HIV-infected pregnant adolescents, general counselling and social services and grants assistance.

Box 7. Feedback from respondents regarding early transition of HIV-infected pregnant adolescents

"*The reason why we move them is we try to discourage unwanted pregnancies. We counsel them before they are pregnant that there are two ways to graduate to adult group, by age and falling pregnancy so it becomes pretty easy to move them because they already know*." Nurse, Namibia

"…explain due to the pregnancy she cannot fit in her age mates and she will be harassed, better to leave her where she fits at that time, she has to learn how to care for her baby, attend ANC clinics with other mothers. After delivery and after nursing her baby should be left to re-unite with her fellow youth but this time with caution not to mess up again but concentrate on studies." Doctor, Uganda

"…once they become pregnant they automatically fall out [of teen club]. As a result many of them defaulted because there was no process of transition." Doctor, Malawi

Service integration

SRH services are being provided to HIV-infected adolescents at 63% of facilities. East African facilities are more likely to provide these services (84% providing versus 16% not doing so), as are Southern African facilities albeit to a lesser degree (68% versus 32%). Seventy-three percent of West and Central African facilities are not providing SRH services to adolescents (Figure 25; HL, n=217, rr=100%). These services most frequently include (Figure 26; HL, n=137, rr=100%) family planning and contraceptives (72%), general counselling and health education (40%) and sexually transmitted infection (STI) screening and treatment (31%). Cervical cancer screening is offered in 14% of facilities, as well as PMTCT and ANC, and voluntary medical male circumcision (VMMC)(both 10%).

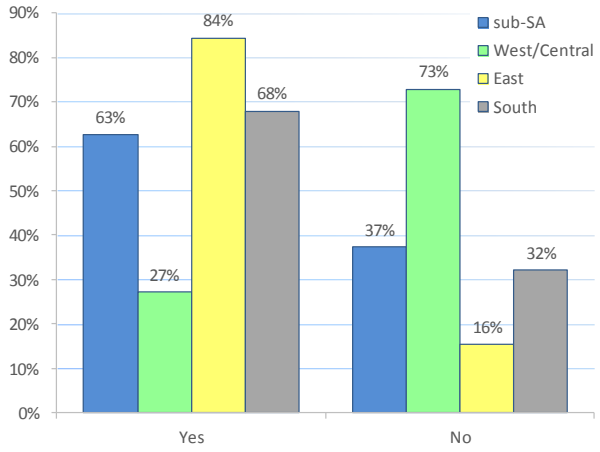


Figure 25. Sexual and reproductive health services offered to adolescents (n=217)

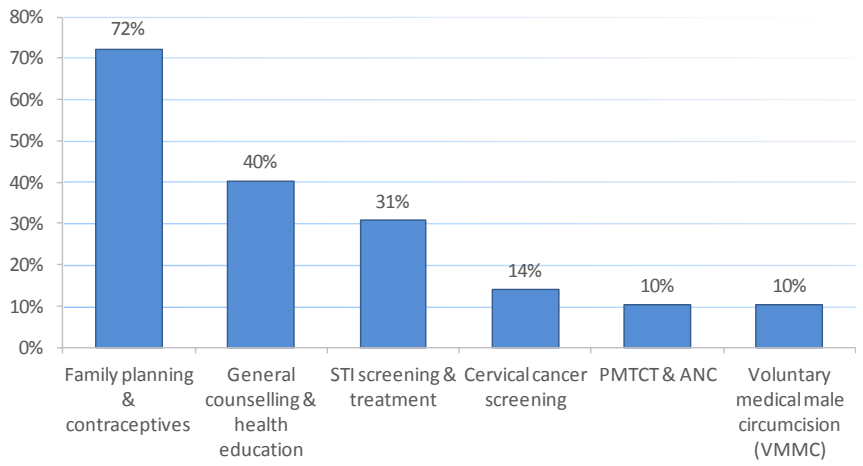


Figure 26. Types of sexual and reproductive health services offered to adolescents (n=137)

With regards to service integration more generally, less than half (46%) of respondents felt that other health services (e.g. nutrition, counselling, skills training etc.) for adolescents were fully integrated with HIV services in their facilities. Of the remainder, 43% stated that HIV services were partially integrated and 11% reported no integration at all (DD, n=56, rr=97%).

Community integration and broader referral networks

In response to the question of whether relationships or referral systems exist between health facilities and other structures in the community that provide additional support or complementary services to HIV-infected adolescents, 57% of respondents reported relationships with non-governmental organisations (NG0s), 52% with community-based organisations (CBOs) and 20% with faith-based organisations (FBOs). 11% reported relationships with other community level support structures, while 16% responded that they have no external relationships (DD, n=56, rr=97%).

Discussion

It is clear that the increasing numbers of HIV-infected children who are surviving into adolescence require a targeted approach which takes into account their particular stage of life and the concomitant challenges that transitioning inevitably brings. It is also evident that many of these challenges are not well understood, and that the degree to which these challenges are being addressed remains unclear. This study seeks to explore the availability of specialized and appropriate HIV treatment and care services for adolescents in health facilities in sub-Saharan Africa. We received survey responses from 218 health facilities across 23 countries, with facilities from across the Southern, East and West and Central African regions, including key countries with large adolescent HIV populations (South Africa, Kenya and Nigeria), as well as good variety of respondents across various health care professions.

These findings confirm that the lack of a standardised definition of adolescence and the identification of adolescents as a sub-population with special needs at the facility level remains a significant challenge. Our assessment confirms that many facilities do not have a standard definition in place, and that most treatment centers continue to attend to adolescent patients with adult and/or paediatric populations (UNICEF, 2013). Over a quarter of facilities surveyed do not have an official working definition of adolescence, and of those that do, only 57% define the start of adolescence at 10 years of age and only 13% define the start of adulthood at 20 years. This challenge should be overcome so that facilities adopt and operationalise the WHO definition of adolescence. It will be difficult for adolescent-specific needs and adolescent-friendly services to be offered until this has taken place. Additionally, this limits the degree to which guidelines or protocols related to transitioning, adherence and retention for adolescents can be specified, implemented and monitored

Furthermore, our assessment confirms that a proportion of facilities still do not collect age-disaggregated data for this group. Only 66% of facilities surveyed identify adolescents in their facility records. Where adolescents are recognised as a sub-population and where data is captured, there is a wide range of variability. The age ranges vary from setting to setting, as described above, and the type of data captured is inconsistent and not comprehensive. Additionally, our findings are in line with previous research which has noted that the collection of data disaggregated by mode of infection is not being done consistently, nor is it being done in a way that enables disaggregation by sub-groups (Sohn & Hazra, 2013). Twenty percent or more of facilities in each of the regions are not capturing any of the descriptors (pregnancy, perinatal infection, young people who sell sex or inject drugs, young males who have sex with males) which are important in terms of addressing the special needs of adolescent sub-groups. Additionally, treatment outcomes data are not being recorded for adolescents specifically in 80% of facilities. The strengthening of data collection systems for monitoring HIV-infected adolescents including mode of infection, other key descriptors, and treatment outcomes is therefore another critical area. Until this is addressed, it will be difficult to conduct research required to inform policy and identify best practice implementation approaches for adolescents living with HIV.

The most common age for transition from paediatric services is at 18 years of age, and just over a third (35%) of facilities reported providing separate services to adolescents. These findings suggest that it is still common for facilities to maintain youth in paediatric services and transition them directly into adult services in late adolescence and early adulthood, without offering any adolescent-specific services. Where transitioning is being done, the ages at

which transition occurs are varied, transition-specific counselling is provided only 63% of the time, the content and participants in counselling sessions vary greatly, and in only half of these facilities are there guidelines or protocols in place to guide the transition process. This is an area where the revised guidelines could provide more guidance on what a more standardized approach should look like for transition and to ensure high quality counselling during this critical period in adolescents' lives.

Our findings suggest that the management of pregnant adolescents may require further attention. Although the numbers of respondents who commented on this are small and the findings should be interpreted with caution, our assessment shows that where transitioning is taking place, pregnant adolescents are perhaps being forced to transition abruptly out of adolescent services without adequate transition counselling or additional support, and may be facing stigma from healthcare providers and peers. This is an emerging issue which may require additional research, and guidance on how pregnant adolescents should be managed to ensure that they receive the special support they require and that this is done in a non-stigmatizing environment may be helpful.

Survey results indicate that in 45% of facilities there is no clear means of determination of adherence, which is troubling as this is a critical precursor to adherence interventions. Over a third of facilities have no guidelines and protocols in place for managing adolescents who experience adherence challenges, and overall only 67% of facilities are providing services to improve treatment adherence. Less than half of facilities have guidelines or protocols in place for managing adolescents who experience retention challenges. Additionally, less than two thirds of facilities are offering any services to support retention in care of adolescents. Counselling content related to adherence and retention was not well described by respondents nor did many mention the use of counselling tools, likely indicating a need to improve the quality of counselling being offered. Clear recommendations related to definitions, protocols and counselling content as it specifically relates to adherence and retention should be incorporated into the revised WHO guidelines.

An interesting finding is that the most common approach being implemented for adolescents having difficulty with adherence or retention is the engagement of peer support, activities and clubs. Additionally, a large percentage of respondents felt that these peer-based activities are the most effective for addressing both adherence and retention issues. Not all facilities, however, report having peer-based services, suggesting that the expansion of these services should be assessed as a best practice and emerge as a possible recommendation in the revised guidelines. It is important to note that these beliefs about the effectiveness of peer activities are predominantly based on anecdotal evidence and there is a need for further research to ascertain whether this is in fact the case or whether peer structures are being overly relied upon to address systemic barriers that themselves also need to be rectified. Although some research exists that suggests that peer support groups can have a beneficial effect on adolescents' acceptance and perceptions of their HIV infection, this research is very limited (Funck-Brentano et al., 2005).

Our findings also raise the question of whether adolescent patients are being switched to second-line treatment too readily. Best practice would dictate that switches would only be done following staff consultations, however our data suggests that this is currently not being implemented as standard practice. This is an area where more in depth

research is warranted to further examine to what extent this is in fact the case.

The limited amount of service integration indicated by our findings is an area of concern. Only the integration of SRH services appears to be more widespread, and even this is limited to 63%. Additionally, SRH services are not being offered comprehensively at these facilities and in many instances this is limited to the provision of family planning and contraceptives. This requires further attention in the revised guidelines given the large amount of existing evidence around the importance of these services in lowering transmission rates, the missed opportunity to provide health education, and the global campaign for elimination of mother to child transmission of HIV. A basic package of SRH for HIV-infected adolescents should include information, counselling and services when needed to support safer sex, safer pregnancy, prevention of unintended pregnancy and disclosure.

Our findings show that the barriers to adolescent treatment and care are many and varied, ranging from service delivery barriers (e.g. resource limitations, lack of privacy or dedicated space), to access challenges (e.g. stigma keeping patients away from facilities) and client-related barriers (e.g. behavioural issues). The most commonly cited challenge was non-adherence and treatment resistance. Socio-economic barriers – including costs of transport and services – were also highlighted by respondents, and this is aligned with a large body of existing research on barriers to healthcare access more broadly. The need for the provision of assistance to youth with disclosure, both self-disclosure and selective disclosure to others, also came out as a prominent theme requiring further attention. Our findings indicate that non-disclosure is posing significant challenges to adherence and retention of HIV-infected adolescents, and this is in line with existing research that shows that disclosure to a supportive person can have a beneficial effect on both adherence and retention (Arrivé et al., 2012). An interesting finding was the specific mention of the challenges of adolescent treatment in boarding school environments by 5% of respondents, in addition to the mention of school scheduling conflicts in general by an additional 5% of survey respondents. This may be the result of a high-visibility peer environment or lack of contact with a supportive adult to supervise and/or reinforce adherence. Other challenges that may have been anticipated to arise more prominently – transition the most notable example – were not raised with great frequency.

Looking at a regional breakdown of study results, a common finding across the various themes assessed is that the region furthest behind with regards to having guidelines, processes, services and systems in place for the provision of treatment and care for adolescents is West and Central Africa. Only 7% of facilities in this region are providing separate services for adolescents, and the absence of tracking of any treatment outcomes in 42% of facilities in this region is of particular concern. The region furthest along is East Africa, which consistently surpassed Southern Africa as well as West and Central Africa in terms of having guidelines, processes, services and systems in place for adolescent treatment and care. For example, facilities in East Africa are almost twice as likely to offer services to improve treatment adherence when compared to West and Central Africa.

Overall, this multi-country study of adolescent HIV treatment and care across PATA network facilities in sub-Saharan Africa provides important insights into the status of HIV treatment and care services for adolescents in the region. Furthermore, it highlights an urgent need for increased attention in the global HIV response to the HIV epidemic,

specifically amongst the increasing adolescent population.

Conclusion

These findings provide a comprehensive situational analysis of adolescent HIV treatment and care in sub-Saharan Africa, which may inform the consolidated guidelines currently being updated by the World Health Organisation. Standardized definitions of adolescence and sufficient disaggregation of data (age, mode of infection, and by key sub-groups) are two critical missing pieces in most settings, and remain a key barrier to the development of youth-friendly HIV services and systems. Having these in place is imperative to enable transitioning protocols to be developed as individuals graduate from paediatrics services to adolescent services, and subsequently adult services. It also will facilitate the tracking of adherence, retention and treatment outcomes in this key population group which at present is taking place very inconsistently, if at all. In the updated consolidated guidelines, there is therefore a need for clear guidance to be provided on data recording systems (both paper-based registers and electronic systems) that need to be in place to address these challenges. Other key considerations include the need for clear definitions, guidelines or protocols and recommendations around counselling content to help standardize approaches around supporting transition, adherence and retention in adolescents. Further guidance around service integration, and SRH service integration in particular, is also required in addition to recommendations around how facilities can best address disclosure-related challenges.

These findings also highlight a few key questions that should be considered in shaping the research agenda for adolescent HIV treatment and care going forward. For example, the question of how pregnant adolescents are currently being managed emerged as an area that merits further investigation in order to better understand current practice, challenges and identify effective models for delivering services to this key sub-population. Additionally, findings suggest that peer support structures could be an effective approach to improve adherence and retention of HIV-infected adolescents in treatment and care programs in resource-poor settings, however further research is needed. In general, this assessment highlighted that there are a wide variety of approaches being taken to deliver adolescent services in the region and research is needed to identify which service delivery models are most effective in different contexts to improve retention, adherence and treatment outcomes. However, data recording systems will need to be strengthened across all sub-Saharan Africa in order to better monitor HIV-infected adolescents, otherwise it will remain a challenge to conduct this research and assess evidence of effective approaches to improve quality, uptake and impact of adolescent HIV services.

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Appendix 1: Survey and response data for all survey items

Related figure	Related survey item	Survey type (High Level: HL; Deep Dive: DD)	Total possible responses	Responses received	Non-responders	Response rate (<90%=red)	Nature of response options	Single or multiple scores/codes per participant
-	Please enter your position in the clinic	HL & DD	218	218	0	100%	Open-ended	Single
-	Please select which of the below applies to the location of your clinic (Urban, Peri-urban, Rural)	HL & DD	218	218	0	100%	Closed-ended	Single
Figure 4	In your clinic, childhood (including adolescence) is defined as?	HL & DD	218	217	1	100%	Open-ended	Single
Figure 4	In your clinic, adulthood is defined as?	HL & DD	218	217	1	100%	Open-ended	Single
Figure 3	Does your clinic have a working definition of adolescence?	HL & DD	218	217	1	100%	Closed-ended	Single
Figure 4	If YES, please define the age range:	HL & DD	162	162	0	100%	Open-ended	Single
Figure 2	What are the THREE biggest challenges your clinic faces when caring for/initiating/sustaining HIV+ adolescents IN TREATMENT?	HL & DD	218	208	10	95%	Open-ended	Multiple
Figure 22	Does your clinic offer SEPARATE HIV treatment and care services for adolescents or are they combined with children or adults?	HL & DD	218	215	3	99%	Closed-ended	Single
Figure 23	If YES, please describe:	HL & DD	75	72	3	96%	Open-ended	Multiple
Figure 23	If OTHER, please describe:	HL & DD	9	5	4	56%	Open-ended	Multiple
Figure 5	Does your clinic register have a way to IDENTIFY or RECORD HIV+ adolescent patients?	HL & DD	218	215	3	99%	Closed-ended	Single

Figure 6	Does your clinic RECORD any of the following information about HIV+ adolescents?	HL & DD	218	214	4	98%	Closed-ended	Multiple
Figure 7	Please select the HIV TREATMENT OUTCOMES data that your clinic currently captures.	HL & DD	218	214	4	98%	Closed-ended	Multiple
-	Of the ABOVE treatment outcomes data that your clinic captures, is this done specifically for adolescents?	HL & DD	218	212	6	97%	Closed-ended	Single
Figure 8	What does your clinic DO with the treatment outcomes data that you capture?	HL & DD	218	215	3	99%	Closed-ended	Multiple
Figure 8	If OTHER, please describe:	HL & DD	24	9	15	38%	Open-ended	Multiple
-	Does your clinic provide VIRAL LOAD MONITORING of HIV+ adolescents?	DD	58	55	3	95%	Closed-ended	Single
Figure 17	If YES, please describe how often:	DD	33	33	0	100%	Open-ended	Single
-	Does your clinic define VIRAL LOAD FAILURE?	DD	58	55	3	95%	Closed-ended	Single
-	If YES, please describe:	DD	40	39	1	98%	Open-ended	Single
Figure 18	If YES, please describe what PROCEDURES YOU FOLLOW once failure has been confirmed:	DD	40	40	0	100%	Open-ended	Multiple
Figure 10	What are the KEY CHALLENGES that you face when switching an HIV+ adolescent patient to 2ND LINE TREATMENT?	DD	58	56	2	97%	Open-ended	Multiple
Figure 9	What are the most common or frequent CLINICAL PRESENTATIONS seen amongst HIV+ adolescents?	DD	58	56	2	97%	Closed-ended	Multiple
-	How many, in TOTAL, adolescents does your clinic currently treat?	HL & DD	218	156	62	72%	Open-ended	Single
-	How many HIV+ adolescents are currently on ANTIRETROVIRAL TREATMENT?	HL & DD	218	150	68	69%	Open-ended	Single

-	What is the rate of LOSS TO FOLLOW UP in adolescent patients?	DD	58	37	21	64%	Open-ended	Single
-	How many HIV+ adolescent patients are on 1ST LINE TREATMENT?	DD	58	45	13	78%	Open-ended	Single
-	How many HIV+ adolescent patients are on 2ND LINE TREATMENT?	DD	58	41	17	71%	Open-ended	Single
-	How many HIV+ adolescent patients are on 3RD LINE TREATMENT?	DD	58	25	33	43%	Open-ended	Single
Figure 16	How does your clinic DEFINE TREATMENT ADHERENCE?	DD	58	55	3	95%	Open-ended	Multiple
-	Does your clinic have GUIDELINES or PROTOCOLS in place for managing adolescents who are facing ADHERENCE CHALLENGES?	DD	58	56	2	97%	Closed-ended	Single
-	If YES, please describe:	DD	34	34	0	100%	Open-ended	Multiple
Figure 13	Does your clinic offer ADHERENCE COUNSELLING to HIV+ adolescents?	HL & DD	218	216	2	99%	Closed-ended	Single
Figure 14	If YES, please describe the CONTENT OF COUNSELLING:	HL & DD	188	175	13	93%	Open-ended	Multiple
Figure 15	If YES, please describe who is INVOLVED in these counselling sessions:	DD	54	53	1	98%	Open-ended	Multiple
Figure 11	Does your clinic offer any OTHER support or services to ensure TREATMENT ADHERENCE for HIV+ adolescents?	HL & DD	218	216	2	99%	Closed-ended	Single
Figure 12	If YES, please describe:	HL & DD	145	145	0	100%	Open-ended	Multiple
-	Which of the above approaches is MOST EFFECTIVE and WHY?	DD	58	43	15	74%	Open-ended	Multiple
-	Have you ever MEASURED the effectiveness of the above? and if so, HOW?	DD	58	46	12	79%	Open-ended	Single
-	How does your clinic define LOSS TO FOLLOW UP?	DD	58	53	5	91%	Open-ended	Multiple

-	Does your clinic have GUIDELINES or PROTOCOLS in place for managing adolescents who are FACING RETENTION CHALLENGES?	DD	58	56	2	97%	Closed-ended	Single
-	If YES, please describe:	DD	23	23	0	100%	Open-ended	Multiple
Figure 19	Does your clinic offer any support or services to ensure RETENTION IN CARE for HIV+ adolescents?	HL & DD	218	216	2	99%	Closed-ended	Single
Figure 20	If YES, please describe:	HL & DD	132	132	0	100%	Open-ended	Multiple
-	Which of the above services are MOST EFFECTIVE and WHY?	DD	38	37	1	97%	Open-ended	Multiple
-	Have you ever MEASURED the effectiveness of the above? and if so, HOW?	DD	38	36	2	95%	Open-ended	Single
Figure 21	What does your clinic do to TRACK HIV+ adolescents who have been lost to follow up and BRING THEM BACK into care?	DD	58	54	4	93%	Open-ended	Multiple
Figure 24	At what age are patients MOVED OUT OF paediatric services?	DD	58	43	15	74%	Open-ended	Single
-	When a child LEAVES PAEDIATRIC SERVICES, are they offered any COUNSELLING about this move to new services?	DD	58	54	4	93%	Closed-ended	Single
-	If YES, please describe the FREQUENCY and DURATION:	DD	34	34	0	100%	Open-ended	Single
-	If YES, please describe the CONTENT of counselling given during TRANSITION, and how does this DIFFER from content of counselling given during NON-TRANSITION times?	DD	34	32	2	94%	Open-ended	Multiple
-	If YES, please describe WHO IS INVOLVED in these TRANSITIOING counselling sessions:	DD	34	32	2	94%	Open-ended	Multiple

-	Does your clinic have GUIDELINES or PROTOCOLS in place that outline the process for transition?	DD	58	55	3	95%	Closed-ended	Single
-	If an adolescent BECOMES PREGNANT, is she moved into adult services SOONER?	DD	58	57	1	98%	Closed-ended	Single
-	If YES, please describe the process of how this is done:	DD	13	13	0	100%	Open-ended	Multiple
-	Does your clinic manage the SPECIAL NEEDS of pregnant adolescents?	DD	58	57	1	98%	Closed-ended	Single
-	If YES, please describe:	DD	26	26	0	100%	Open-ended	Multiple
Figure 25	Does your clinic offer SEXUAL and REPRODUCTIVE health services to HIV+ adolescents?	HL & DD	218	217	1	100%	Closed-ended	Single
Figure 26	If YES, please describe WHICH services are provided and WHERE they are offered:	HL & DD	137	137	0	100%	Open-ended	Multiple
-	To what extent are other health-related services INTEGRATED into HIV treatment and care services?	DD	58	56	2	97%	Closed-ended	Single
-	Does you clinic have RELATIONSHIPS or REFERAL SYSTEMS with any of the below community structures that provide ADDITIONAL SUPPORT or COMPLEMENTARY SERVICES for HIV+ youth	DD	58	56	2	97%	Closed-ended	Multiple

Appendix 2: Cover sheet of both High Level and Deep Dive surveys

Greetings!

The World Health Organisation (WHO) and Paediatric AIDS Treatment for Africa (PATA) are collecting data in preparation for an Adolescent Technical Treatment meeting to be held in September 2014. This meeting will aid in the prioritisation of adolescent content for the 2015 Consolidated ARV Guidelines update and support the development of the adolescent treatment research agenda and strategy. The purpose of this work is to conduct a collection of facility based programmatic data on adolescent HIV services with a focus on adolescent treatment. All 273 PATA linked clinics have been offered the chance to participate. The research's conclusions will be fed back to the PATA network so that you can better understand the context of your own work with adolescents.

We are trying to gain a better understanding of the state of adolescent HIV/AIDS treatment in sub-Saharan Africa. We are doing this research because there is a lack of information about the specific challenges that clinics face when trying to deal with the adolescent population. One of the reasons for this lack of knowledge is that children who are now surviving into adolescence are faced with different types of problems. Some of these problems relate to the long-term nature of their treatment, which makes them different to young people who have not been on antiretroviral therapy (ART) for many years. Other challenges are because adolescence itself is a difficult period in a young person's life, with a shift from being dependant on caregivers to being increasingly independent. This is your opportunity to provide data so that the WHO and PATA may advocate on your behalf to improve HIV treatment and care infrastructure and policies which help you in your aims.

If you have any questions or problems in completing this survey, please contact Ms. Lorrein Muhwava at WHO@teampata.org. Once complete, please email the survey back to WHO@teampata.org or you can fax it to 086 619 1623 (from within South Africa only). Alternatively, if you have followed the link in the email, the survey will be saved once you click on the "Submit" button. This is a once-off survey that will take about 10 minutes and your input would be appreciated. Thank you in advance for your time!

Please ensure that the below research ethics have been read and understood before completing the form.

- All content will be treated with confidentiality and will be stored in a secure state once collected.
- You, the respondent, are under no obligation to complete this survey.
- If at any point in this survey you would like to withdraw from the study, please note that there will be no negative consequence, either to you as an individual or your clinic.
- Anonymity can be assured to the degree that all data will only be presented at a country level, which means that no clinic will be named in the report or future presentations of findings.

If you understand and agree to the above considerations, please sign or write your name in the space provided.

Name or signature	Date

Appendix 3: High Level survey

Clinic information:

Country:	
Clinic name:	
Respondent name & surname:	
Respondent email:	
Position in the clinic:	
Rural/peri-urban/urban	

How does **your clinic** define the age ranges below?

	From:	To:
Childhood (Incl. adolescence)	0	
Adulthood		100

Does **your clinic** have a **working definition of adolescence**?

○ Yes

If yes, please describe the age range:

From:	To:

○ No

If No, please answer the rest of the survey using the **WHO definition of 10–19 years old** when responding.

Adolescent HIV treatment and care information:

1. What are the **three biggest challenges** your clinic faces in **initiating** HIV treatment and care to adolescents?

2. What are the **three biggest challenges** your clinic faces when **dealing with** HIV+ adolescents **in treatment**?

3. What are the **three biggest challenges** your clinic faces in **sustaining** HIV treatment and care to adolescents?

4. In total, how many adolescents receive care from your clinic?

5. How many of these adolescents are on antiretroviral therapy?

6. Does your clinic offer **separate HIV treatment and care services for adolescents** or are they combined with children or adults? For example: Special clinic days, times or venues

- ○ No; adolescents, children and adults are all seen together
- ○ No; adolescents are seen with children
- ○ No; adolescents are seen with adults
- ○ Yes; adolescents receive separate services

If yes, please describe:

- ○ Other

If other, please describe:

7. Does your clinic **register** have a way **to identify or record** HIV+ adolescent patients?

- ○ Yes
- ○ No, adolescents, children and adults are not recorded or identified as such
- ○ No, adolescents are recorded as children
- ○ No, adolescents are recorded as adults

8. Does your clinic **record any of the following information** about HIV+ adolescents? Please select all of those that apply.

- ☐ Perinatal infection
- ☐ Pregnancy
- ☐ Males who have sex with other males
- ☐ Patients who inject drugs
- ☐ Patients who sell sex
- ☐ None of the above

9. Please select the **HIV treatment outcomes data** that your clinic **currently captures**. Please select all of those that apply.

- ☐ Mortality rates
- ☐ Treatment failure rates
- ☐ Virological suppression rates
- ☐ 1st line treatment
- ☐ 2nd line treatment
- ☐ 3rd line treatment
- ☐ Loss to follow-up rates
- ☐ None of the above

10. Of the **above treatment outcomes data** that your clinic does capture, **is this done specifically for adolescents**?

- ○ Yes
- ○ No

11. What does your **clinic do with the treatment outcomes data** that you capture? Please select all of those that apply.

- ☐ Nothing
- ☐ Enter information into electronic database
- ☐ Track patients
- ☐ Prepare reports
- ☐ Use in patient management
- ☐ Other

If other, please describe:

12. Does your clinic offer **adherence counselling** to HIV+ adolescents?

- ○ No
- ○ Yes

If yes to any of these, please describe the content of counselling:

13. Does your clinic offer **any other support or services** to ensure **treatment adherence** for HIV+ adolescents?

- ○ No
- ○ Yes

If yes, please describe:

14. Does your clinic offer any **support or services** to ensure **retention in care** for HIV+ adolescents?

- ○ No
- ○ Yes

If yes, please describe:

15. Does your clinic offer **sexual and reproductive health services** to HIV+ adolescents? If yes, please describe which services are provided and where they are offered.

- ○ No
- ○ Yes

If yes, please describe:

Thank you for your time!

Appendix 4: Deep Dive survey

Clinic information:

Country:	
Name of clinic:	
Respondent name & surname:	
Respondent email:	
Position in the clinic:	
Rural/peri-urban/urban	

How does **your clinic** define the age ranges below?

	From:	To:
Childhood	0	
Adulthood		100

Does **your clinic** have a **working definition of adolescence**?

○ Yes

If yes, please describe the age range:

From:	To:

○ No

If No, please answer the rest of the survey using the **WHO definition of 10–19 years old** when responding.

Adolescent HIV treatment and care information:

1. What are the **three biggest challenges** your clinic faces when **caring for** HIV+ adolescents in treatment?

2. What are the **three biggest challenges** your clinic faces in **initiating** HIV treatment and care to adolescents?

3. What are the **three biggest challenges** your clinic faces in **sustaining** HIV treatment and care to adolescents?

4. Does your clinic offer **separate HIV treatment and care services for adolescents** or are they combined with children or adults? For example: Special clinic days, times or venues

- ○ No; adolescents, children and adults are all seen together
- ○ No; adolescents are seen with children
- ○ No; adolescents are seen with adults
- ○ Yes; adolescents receive separate services

If yes, please describe:

- ○ Other

If other, please describe:

5. Does your clinic **register** have a way **to identify or record** HIV+ adolescent patients?

- ○ Yes
- ○ No, adolescents, children and adults are not recorded or identified as such
- ○ No, adolescents are recorded as children
- ○ No, adolescents are recorded as adults

6. Does your clinic **record any of the following information** about HIV+ adolescents? Please select all of those that apply.

- ☐ Perinatal infection
- ☐ Pregnancy
- ☐ Males who have sex with other males
- ☐ Patients who inject drugs
- ☐ Patients who sell sex
- ☐ None of the above

7. Please select the **HIV treatment outcomes data** that your clinic **currently captures**. Please select all of those that apply.

- ☐ Mortality rates
- ☐ Treatment failure rates
- ☐ Virological suppression rates
- ☐ 1st line treatment
- ☐ 2nd line treatment
- ☐ 3rd line treatment
- ☐ Loss to follow-up rates
- ☐ None of the above

8. Of the **above treatment outcomes data** that your clinic does capture, **is this done specifically for adolescents**?

- ○ Yes
- ○ No

9. What does your **clinic do with the treatment outcomes data** that you capture? Please select all of those that apply.

- ☐ Nothing
- ☐ Enter information into electronic database
- ☐ Track patients
- ☐ Prepare reports
- ☐ Use in patient management
- ☐ Other

If other, please describe:

10. Does your clinic provide **viral load monitoring** of HIV+ **adolescents**?

- ○ No
- ○ Yes

If yes, please describe how often:

11. Does your clinic **define viral load failure**?

- ○ No
- ○ Yes

If yes, please describe:

If yes, please describe what **procedures you follow once failure has been confirmed**:

12. What are the **key challenges** that you face when switching an adolescent HIV+ patient **to 2nd line treatment**? Please select all that apply.

- ☐ Lack of 2nd line treatment options
- ☐ Lack of appropriate formulations
- ☐ Challenges in defining failure where viral load is not provided
- ☐ Ongoing adherence challenges
- ☐ Other

If other, please describe:

13. What are the most **common or frequent clinical presentations** seen amongst HIV+ adolescents? Please select all of those that apply.

- ☐ Delayed growth and puberty
- ☐ Skin conditions
- ☐ Chronic lung disease
- ☐ Neurocognitive impairment
- ☐ Mental health issues
- ☐ Lipoatophy
- ☐ Opportunistic infections
- ☐ Other

If other, please describe:

14. Please could you fill in the **number of adolescent patients** that your clinic treats for each outcome below. If not applicable, please write **'not applicable'** in the box provided.

Number of adolescent patients?	Number of adolescent patients on antiretroviral treatment?	Rate of loss to follow up in adolescent patients?
Number of adolescent patients on 1st line treatment?	**Number of adolescent patients on 2nd line treatment?**	**Number of adolescent patients on 3rd line treatment?**

15. How does your clinic **define treatment adherence**? Please describe.

16. Does your clinic have **guidelines or protocols** in place for managing adolescents who are facing **adherence challenges**?

No

Yes

If yes, please describe:

17. Does your clinic offer **adherence counselling** to HIV+ adolescents?

No

Yes

If yes, please describe **the content of counselling**:

If yes, please describe **who is involved** in these **adherence counselling** sessions:

18. Does your clinic offer **any other support or services** to ensure **treatment adherence** for HIV+ adolescents?

- ○ No
- ○ Yes

If yes, please describe:

Which of the **above approaches is most effective** and **why**?

Have you ever **measured** the **effectiveness** of the above? And if so, **how**?

19. How does your clinic **define loss to follow-up**? Please describe.

20. Does your clinic have **guidelines or protocols** in place for managing adolescents who are facing **retention challenges**?

- ○ No
- ○ Yes

If yes, please describe:

21. Does your clinic offer any **support or services** to ensure **retention in care** for HIV+ adolescents?

- ○ No
- ○ Yes

If yes, please describe:

Which of the **above services are most effective** and **why**?

Have you ever **measured** the **effectiveness** of the above? And if so, **how**?

22. What does your clinic do to **track** HIV+ adolescents who have been **lost to follow-up** and **bring them back into care**? Please describe.

23. At what age are patients moved out of paediatric services (if applicable)?

24. When a **child leaves paediatric HIV services** (if applicable), are they offered any **counselling** about this move to **new services**? If yes, please state the number of sessions offered and how long they last. For example, 3 sessions of 15 minutes.

- Not applicable
- No
- Yes

If yes, please describe:

Frequency	Duration

25. What is the **content of counselling given during transition** (if applicable), and how does this differ from the content of counselling given during non-transition times?

If yes, please describe **who is involved** in these **transitioning counselling** sessions:

26. Does your clinic have **guidelines** in place that outline the **process for transition**?

- ○ Not applicable
- ○ No
- ○ Yes

27. If an **adolescent becomes pregnant**, is she moved into adult services **sooner**? How is this done?

- ○ Not applicable
- ○ No
- ○ Yes

If yes, please describe the process:

28. Does your clinic manage the **special needs of pregnant adolescents**, and if so **how**?

- ○ No
- ○ Yes

If yes, please describe:

29. Does your clinic offer **sexual and reproductive health services** to HIV+ adolescents? If yes, please describe which services are provided and where they are offered.

- ○ No
- ○ Yes

If yes, please describe:

30. To **what extent are other health-related services integrated** into HIV treatment and care services? For example these could include nutrition, counselling, skills training.

- ○ Not at all
- ○ Partially
- ○ Fully

31. Does your clinic have **relationships or referral systems** with any of the below **community structures** that provide **additional support or complementary services** for HIV+ youth? Please select all that apply.

☐ No external relationships

☐ Community based organisations (CBO)

If CBO, please describe the nature and/or the structure of this relationship:

☐ Faith based organisations (FBO)

If FBO, please describe the nature and/or the structure of this relationship:

☐ Non-governmental organisations (NGO)

If NGO, please describe the nature and/or the structure of this relationship:

☐ Other

If Other, please describe the nature and/or the structure of this relationship:

Thank you for your time!

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Values and Preferences on the use of Pre-exposure prophylaxis (PrEP) – A systematic review of the literature

Florence Koechlin, June 2015

Background

To date two recommendations on the use of PrEP have been released by the World Health Organization. The first one was released in 2012[1] for serodiscordant couples, men and transgender women who have sex with men, in the context of demonstration projects. A second recommendation for men who have sex with men was released in 2014[2] as part of the WHO ARV guidelines, suggesting the use of PrEP as an additional tool within the realm of combination prevention.

Following a large stakeholders consultation led by the WHO in March 2015, decision was made to consider including a recommendation on the use of PrEP for all populations at significant risk of HIV, as part of the WHO ARV guidance update to be released in 2015. This review of the values and preferences on PrEP of populations at substantial risk of acquiring HIV was mandated by the WHO as part of the process of reviewing the overall evidence on PrEP. It was conducted by Florence Koechlin with the support of Ginny Fonner and Sarah Dalgish in the context of their work in systematic review of the evidence on PrEP.

Method

A systematic review of articles and conference abstracts reporting on PrEP acceptability was embedded into the GRADE review. Data from those articles and abstracts were coded and entered into a spreadsheet. Findings were categorised by population groups - namely women, men, young women and adolescent girls, female sex workers, serodiscordant couples, people who inject drugs, transgender people-; country/region; study size; specific themes (awareness, willingness to use PrEP, barriers/facilitators, dosing/route of administration/dispensing facility, risk compensation, adherence); relevance/type of study (linked to a trial or demonstration project/ participants took PrEP/ theoretical use of PrEP). Other values and preferences reviews and consultation reports were also considered to verify consistency of findings.

Overall themes reflecting common values and preferences across populations were first extracted from those articles. Those findings reflecting the views of a clear majority of respondents or most of the population groups are listed in the section ‘overall themes’. Findings specific to particular groups were then identified through qualitative grouping and analysis. Values and preferences of those groups will then be highlighted later on to reflect on the wide array of findings more specific to those groups.

Men who have sex with men (MSM) were not included in the detailed review: as part of the WHO ARV guidelines released in July 2014, a recommendation already exists on the use of PrEP for MSM. However, a brief scan of the recent literature was conducted to ensure no major differing new trend could be observed from what was initially reviewed. No differing trend was found. The articles and abstracts covering MSM only are included in the list of references, but are not included in the findings highlighted in the rest of the document.

Description of Studies

The number of studies evaluating the acceptability of PrEP has grown exponentially among all populations since the first time PrEP was considered for recommendations by WHO in 2012. A total of 131 peer-reviewed articles and 46 abstracts were included for this review, totalling 177 references.

Theoretical versus actual use

Of the studies included in this review which were not focused only on MSM, 25 were dealing with patients who actually took PrEP or a placebo, or healthcare workers dispensing it, against 79 who evaluated a theoretical use of PrEP.

Populations stratified by sub-groups

	Total	W*	SDC	FSW	AG/ YW	PWI D	TG**	HC	Men	MSM
Articles	**131**	19	19	11	5	5	13/7	20	7	72
Abstracts	**46**	21	6	2		1	4/0	6	3	20

**Not including the studies covered in FSW, AG/YW, SDC*
*** Study included some TG / Stratification available or proportion of TG high*
W: Women, SDC: Serodiscordant Couples, FSW: Female Sex Workers, AG: Adolescent Girls, YW: Young Women, PWID: People Who Inject Drugs, TG: Transgender People, HC: Healthcare Workers, MSM: Men Who Have Sex With Men.
Please note the numbers exceed the totals since some studies covered more than one population. In those cases, those studies are counted in both groups covered.

Geographical coverage

Studies have a very wide geographical coverage across all continents; see detail by country / continent below. Three studies had a global coverage.[28, 97, 264] This list does not include MSM-only articles and abstracts.

- **Africa**: Botswana,[28,264] Ghana,[47] Kenya,[15,20,21,22,28,48,80,81,90,101,118,153,158,164,169] Nigeria,[53] South Africa,[11,20,21,22,28,80,83,85,90,97,100,130,154,164,169] Uganda,[28,97,101,157,159,164] Zimbabwe;[99]
- **Americas**: Argentina,[139] Brazil,[76] Canada,[31,57,75,131,133] Peru,[24,28,37,112,142,164] US;[5,6,7,17,18,26,30,32,33,38, 42,43,44,58,59,62,66,68,70,71,72,77,82,97,102,108,111,121,127,132,135,136,140,141,145,147,148,160,161,166,167,168]
- **Asia**: China,[55,93,113,117,171,177,178] India,[115,128,129] Thailand,[61,143,163,170] Vietnam;109
- **Europe**: France,[120] Italy,[116] Switzerland,[155] UK,[25,40,165,173] Ukraine.[28,164]

Overall Themes

The themes highlighted in this section reflect common values and preferences expressed by the majority of respondents or most of the specific population groups. Findings specific to particular groups are presented in detail in the next section.

Interest and support for PrEP: This literature review has found overwhelming and growing support and interest for PrEP among most populations. The two main caveats to this support for PrEP are as

follows. (i) **PrEP should not undermine current HIV prevention programs**, but rather add to those. Special efforts should be made to integrate PrEP into existing HIV combination prevention program packages. This was particularly emphasized in the context of needle and syringe programs and opioid substitution therapy for people who inject drugs,[189] and in the context of condoms programs for female sex workers.[191] (ii) **PrEP must never undermine individual choice**. It was frequently highlighted that offering more prevention options will allow addressing the needs of people. It was emphasised that extreme care must be taken to ensure this remains a choice made by the individual and not imposed by programs and health providers.

Barriers and facilitators: The most cited barriers and facilitators to using PrEP were **safety considerations, effectiveness, cost and side effects**. Other relevant barriers most commonly mentioned were low risk perception of oneself or of one's partner(s); low education level; stigma surrounding HIV and ARVs in general; and the idea that the 'use of a pill is only for sick people'. Facilitators most often cited were the discreteness of a PrEP pill in comparison for example to condoms, especially in the context of coercive sex and inability to negotiate condom use; partners support in particular in the context of serodiscordant couples; and peers also knowing about PrEP and/or already using it.

Additional work needed to raise knowledge and awareness more broadly: A number of studies warned however that for a PrEP program to be effective, additional interventions would be needed (i) to raise the knowledge of PrEP in order to increase levels of awareness and interest, while decreasing stigma surrounding ARVs for prevention and treatment, (ii) to increase HIV risk awareness, especially among younger populations.

Healthcare workers generally positive about PrEP: Though the vast majority of healthcare workers have not yet prescribed or dispensed PrEP, they do see a potential for PrEP for most if not all populations. They prioritised the provision of PrEP to serodiscordant couples or to population groups which they consider most at risk in their local context. They caution however about three potential risks with providing PrEP: viral resistance, increased risk behaviours and poor adherence to PrEP.

Given the immense variability in settings, needs of different populations, and logistical challenges at the local level, it is difficult to draw conclusions on many other aspects such as the most appropriate dispensing points, the most effective ways to reach specific populations, etc. Further research is needed at a country and at a local level to define what will be the best implementation modalities and which populations would most benefit from PrEP in those settings.

Information about and experience with implementing PrEP is currently limited, and this must be considered when interpreting the findings from the literature review.

Population-Specific Highlights

Women [7,8,11,15,17,18,20,21,22,26,32,33,42,47,53,57,61,62,68,70,71,72,83,85,90,94,97,100,107,111,118,120,136,148,154,161,167,169,173]

Awareness: A low awareness of PrEP was noticeable globally among women outside of a clinical trial context. Awareness levels ranged from 'almost no women'[7] to 7.5% knowing about it.[167] Very few had ever used it. One study in the US even mentioned 'anger' not to have heard about PrEP.[8]

Willingness to use: Based on 18 sources which offered information stratified by gender, women expressed overall a definite interest and willingness to use PrEP. Those studies included close to 15,000 women in total, with a willingness to use ranging from 54.2% to 87.4%, the latter one among 5180 women in Kenya.[94] Only one study found a very low willingness to use PrEP of 20.4% in a small subgroup of Caribbean women living in the US.[71] This theoretical interest has been confirmed in practice when women were given the chance to actually take PrEP, for example in the HPTN 067/ADAPT open-label study, whereby the effectiveness of PrEP had been confirmed by clinical trials, and participants knew they were taking the active drug. In this instance, the majority of women did opt to take it.[11]

Barriers and facilitators: Outside of the sex work context, women tended to be more sensitive to the cost associated with PrEP use, and less aware of their HIV risk, compared to other populations. One abstract on the Partners PrEP study also reported an association between reported recent intimate partner violence (IPV) and a 43% higher likelihood of low PrEP adherence.[118]

Dosing and dispensing: Overall results varied greatly within and across countries in terms of dosing preference between a daily regimen versus a coïtally dependent one. One study in South Africa highlighted the issue that a pre-intercourse regimen could be a problem for women since it is often the men who decide when sex occurs.[130] No broad conclusion can be drawn from this review on which dosing would be most appropriate if deemed effective, and will need further investigation at the local level. However, it should be highlighted again that the HPTN067/ADAPT study found that daily dosing resulted in better coverage of sex acts and adherence, and therefore higher drug levels.[11] No broad theme in dispensing preferences could be drawn either, whether it be dispensed in pharmacies, hospitals, general practitioners, family planning clinics, schools, etc.

Risk compensation: In the majority of studies, participants were confident to see only a limited decrease in condom use and limited increase in number of partners. These findings do fit with the results from the meta-analysis in the GRADING of PrEP evidence which also showed no significant effect of PrEP on behavioural outcomes, including condom use and number of sexual partners, or reproductive health outcomes, including adverse pregnancy events and contraception effectiveness. However, some studies did show an expected decrease in condoms, for example 1543 women in the US who expected a decrease of 26%.[168] Another study found that 6% of women expected that PrEP use may lead to an increase in number of partners.[62]It was suggested that some populations at higher risk, especially sex workers, might be more likely to change their behaviour if using PrEP, for reasons explained later on.

Adherence to PrEP was low in two trials that targeted women only, while adherence was substantial among women enrolled in trials that included both men and women. Factors associated with low uptake and adherence among women in women-only trials included lack of support from sexual partners, stigma related to PrEP use and participation in blinded clinical trials, mixed community support for trial participation, and uncertainty around product effectiveness.[154] However, PrEP adherence was substantial among women in the HPTN 067/ADAPT open label trial of PrEP conducted after safety and efficacy was proven.[11] This suggests that PrEP adherence may be higher in real life implementation where PrEP is a choice and persons are aware they are taking active and effective medication. Research also showed that adherence could be facilitated by personal motivations such as risk reduction, and by adherence strategies consisting of external cues, reminders and support.[20]

Serodiscordant Couples (SDC) [15,28,34,40,48,53,68,77,80,86,93,101,106,107,118,120,130,148,155,157,158,159,161,165,178]

Awareness: Overall, the literature review found little (2.8%)[93] to no knowledge among serodiscordant couples about the fact that PrEP could be used to prevent transmission.[15,130] In comparison, serodiscordant couples had overall good knowledge about the use of antiretrovirals for prevention of mother-to-child transmission of HIV (PMTCT).[130] One study in South Africa found that counsellors themselves also had limited knowledge about conception beyond 'treatment as prevention' (TasP).[130]

Willingness to use: The majority of serodiscordant couples showed a definite willingness to use PrEP, whether to protect one's partner or specifically related to safer conception. One study found 84.9% were willing to use PrEP,[93] though another found mixed feelings when having to choose between PrEP and TasP.[34] In a third study taking place in the context of a clinical trial, 57.9% said they were willing to take TasP while 86.1% were willing to take PrEP, though those tended to prefer the option they would control themselves.[48] So results showed high levels of interest but varying preferences whether to favour TasP or PrEP.

Uptake is also starting to rise, further supporting the evidence. A study showed that since the launch of the Kaiser's PrEP program in San Francisco in April 2012, more than half of the 123 men and women referred by both HIV-specialty providers and non-HIV-specialty providers had initiated PrEP,[77] demonstrating a very high uptake once given the option to take it. Another study in the US showed consistent increase in interest in PrEP for safer conception based on the number of calls from both patients and clinicians to a specialised hotline.[161]

Barriers and facilitators: One study showed that some serodiscordant couples had strong views against the idea of taking an ARV for prevention, with the thinking that 'one should not take a drug when one is not sick,' this being probably related to the context of their HIV-positive partners considering the use, or already taking ARVs as treatment on an ongoing basis and for life. It also showed a level of HIV positive partners' guilt to have their HIV negative partner take and ARV because of their own disease.[34] Some people expected 'less stigma' would be linked to taking PrEP for the HIV negative partner,[34] while others were precisely more concerned about it in this context of PrEP.[93] Some HIV-positive women also expressed concerns about experiencing varying levels of coercion to have condomless sex if their partner was taking PrEP.[34]

Risk compensation: A number of studies found limited levels of expected risk compensation in serodiscordant couples, for example in China where 96.6% expected they would not increase their number of partners and 88% would not decrease their use of condom.[93] On the other hand, others did show 25% of participants indicating a desire to stop using condoms,[34] or mentioned PrEP 'might replace condoms and reanimate couple's sex lives […], with an overwhelming consensus that PrEP could, should or will replace condoms.'[80]

Adherence: The Partners PrEP study showed that stable SDCs were motivate and could support one another to adhere to PrEP to preserve the relations.[159] PrEP adherence was also high in pregnant women (98% pill count, 71% plasma samples).[86]

Female Sex Workers (FSW) [24,28,37,55,80,81,106,113,117,153,171,177,178]

Awareness: Awareness remains low among FSWs, with only 3 studies in China reporting awareness ranging from 11.55% to 16.5%.[113,171,177] One of those studies also showed that only 1.4% had ever used PrEP before.

Willingness to use: Once the concept of PrEP introduced, female sex workers express strong enthusiasm for PrEP with profuse number of studies showing high interest in PrEP: 7 studies showed positive responses to PrEP, 4 of which were conducted in China with large cohorts, ranging from 61% in 2012[28] when fewer clinical trial results were available to 85.9% in 2014.[171]

Barriers and facilitators: In some studies, a higher sense of risk of HIV acquisition among FSW was associated with a stronger likelihood of PrEP use. Regular condom use was also correlated with PrEP acceptance.[117] There was also a strong call for awareness campaigns with the general public to reduce stigma that could become associated specifically with HIV, PrEP and FSWs. However, such an approach has to be planned and managed carefully so that it doesn't inadvertently backfire if specifically targeted at FSWs. It was suggested that the provision of night HIV testing services, 'Moonlight VCTs', that would also distribute PrEP, could help in reaching out and following up with SW helping to address this particular challenge linked to their irregular schedules and lifestyles.[81]

Adherence: It was suggested that unpredictable schedules and irregular lifestyles are also likely to affect FSW's ability to adhere appropriately to PrEP.[153] High levels of alcohol consumption by FSW was also raised repeatedly as a concern for adherence.[80]

Risk compensation: Concerns were raised that PrEP could undermine highly successful and acceptable condom programs that have already helped reduce incidence among FSW,[191] especially where PrEP may be seen as an opportunity for more money to be earned using condoms less frequently,[80] although evidence for such condom migration is lacking. Many FSW have greatest risk of HIV though their non-commercial sexual partnerships, where condom use may be low. It was suggested that PrEP should perhaps be made available for FSW who could benefit from it and wanted to take it according to their sexual exposure rather than their occupational status.

Adolescent Girls and Young Women (AG/YW) [28,81,102,121,135]

Willingness to use: Overall evidence with young women, and even more so with young girls, is still very limited compared to other population groups. However, within the limited amount of evidence, the general response was positive. In one study, 63.5% of 595 young girls aged 20-29 said they would take PrEP.[121] In another study among adolescent girls aged 14-17 and young women aged 18-24, all showed interest in PrEP.[80] A third study showed general acceptance if PrEP was provided for free and was proven to be effective.[135]

Barriers and facilitators: Young women's decision making process is particularly strongly influenced by concerns over stigma and by social influences. One study showed that out of 1453 women, compared to women 30-45, YW 20-29 experienced stronger social influences on PrEP uptake.[121] Another study also confirmed concerns over stigma among young women.[80] Some young women expressed concerns that it may be difficult to negotiate with their partners.[80] Some were amenable to taking a rapid oral test every 3 months.[135]

Dosing, dispensing, adherence: YW in South Africa thought the most important aspect of PrEP is its route of administration.[28] AG and YW appreciated the idea of an oral pill since it is more discrete than using a condom, it is 'just a pill', and doesn't require waiting at a clinic like an injection would.[80]

Adherence: 77% of YW thought they could adhere for 2 months to a daily regimen.[121] Some YW said they liked coïtally dependent gel because they expected it would be easier to remember.[80]

Risk compensation: The idea that 'a pill is more discrete' than other prevention methods may imply that it could lead to less condom use, with PrEP use replacing condoms. In one study, 20.2% of YW did suggest that they expected they would use condoms less.[121] However, in many settings AG and YW already have considerable barriers and difficulties in negotiating condom use.

People Who Inject Drugs (PWID) [28,31,70,140,141,178]

Willingness to use: Among people who inject drugs, there was some support for PrEP as an additional choice for preventing sexual transmission of HIV, though this was generally lower than with other population groups. One study showed 58 % of PWID would be willing to use PrEP if it was 90% effective, and 35% PWID would use it if it was 40% effective.[141] Another study showed 35.4% would be willing to use PrEP, with higher rates among women (42.1%), and with adjusted models indicating that younger age, no regular employment, requiring help injecting, engaging in sex work, and reporting multiple recent sexual partners being positively associated with willingness to use PrEP. This study also showed that PrEP was acceptable to some PWID at heightened risk for HIV infection.[31]

There were concerns however about PrEP undermining community-based harm reduction activities, including the provision of clean needles and syringes.[191] It was considered that all HIV prevention among PWID should occur within a harm reduction context which has wider health benefits including parenteral prevention of HIV and other infections.

Barriers and Facilitators: PWIDs were sensitive to costs, whereby co-payment made it somewhat or very unlikely they would take the medication. Another strong potential barrier was the need to take it daily, and less important were regular blood tests, the need to continue the use of condoms, to see regularly a clinician and to test regularly for HIV.[141]

Healthcare providers: Despite anticipated challenges, providers supported the introduction of PrEP in outpatient drug treatment clinics, though comprehensive training being needed, including PrEP eligibility criteria, strategies to support adherence and medication monitoring guidelines.[140]

Transgender People (TG) [5,24,30,37,38,42,43,44,82,108,111,112,142,143,160,163,170]

Awareness of PrEP: Literature on this remains limited among transgender people. One Thai study, however, showed high awareness at 66% among transgender people.[170]

Willingness to use: Willingness to use PrEP ranged from 37% in that same Thai study that showed 37% of TG were 'very likely' to use PrEP with stated efficacy of 50%, to 'highly acceptable', and 'great interest.'[38] The Thai study that showed 37% of TG were 'very likely to use PrEP, also showed that this rate would rise to 61% with private insurance coverage.[170] PrEP was also considered highly acceptable among Peruvian TG women, particularly among those at the highest HIV infection risk.[112]

Barriers and Facilitators: Costs affected willingness to use of PrEP substantially in two studies, one mentioned just above, and the other where out-of-pocket cost was mentioned as having the greatest impact, followed by efficacy and side effects, other attributes having no significant effects.[24] Concerns were also expressed in a study in Peru about rejection, discrimination and lack of sensitivity from healthcare providers dispensing PrEP.[37] Similar concerns were expressed in a study in the US, where early results reported some fear of rejection by healthcare professionals and discriminatory practices.[108] Other concerns were raised about drug interaction with sex hormones, as well as other

medications (73%[170]) although no such interactions are expected based on the different metabolic pathways for sex hormones and PrEP medications.

Dosing: Daily dosing was deemed impractical or incompatible by some respondents with a lifestyle where people 'live in the moment.'[37] One study in Thailand reported 44% regular medication use among TG,[170] offering an opportunity for daily use of PrEP alongside those medications.

Risk compensation: A risk that condom use may decrease as a result of PrEP was highlighted in one study, although current condom use may be low.[37]

Men [17,18,61,75,85,111,115,128,129,135]

Very little literature is available on men specifically and/or stratified by gender, and outside of the MSM / TG, IDU and SDC focused studies. Two studies looked into the theoretical acceptability of truckers and their helpers/cleaners in India with just under 2000 participants.[115,128,129] Acceptability of PrEP was 87%, as opposed to 9% for male circumcision, showing a great potential in some male populations at high risk of HIV acquisition.

Healthcare Providers (HC) [5,25,53,58,59,66,68,81,99,102,106,116,127,130,131,132,133,136,139,140,142,145,148,161,164,166]

From pharmacists in Zimbabwe to physicians in the US, the consensus is that '*PrEP will empower women.*'[99,148] A very definite increase in awareness globally was evident among healthcare workers, with a US study showing 'low knowledge' in 2010[136] to up to 90% who were familiar with the results of iPrEx in 2013.[145] Despite this substantial increase in knowledge, healthcare workers are still currently often reluctant to actually provide PrEP to potential users. Only 9%[58,59] to 19% clinicians actually prescribed[145] and 22% pharmacists[132] dispensed PrEP in 2014 out of 5 studies which reported numerically. The likelihood of prescribing increased with physicians caring for more HIV-positive patients,[58] higher knowledge of PrEP, older age, and in those who believed HIV would empower women.[148] A majority of studies concurred that healthcare providers felt that insufficient information was provided and that they were not knowledgeable enough to feel comfortable prescribing PrEP at this point.

Most healthcare providers saw PrEP primarily for SDC, although some already consider prescribing to other high risk groups. In Italy, 70% said they would prescribe PrEP, 64% to SDC but also 56% to other people at ongoing, high risk of HIV infection.[116] In Argentina, 39.6% said they would consider prescribing PrEP to SDC and 34.8% would consider offering it to SWs.[139] Most cautioned against primarily resistance, increased risk behavior and poor adherence.

The majority agreed that additional information, community education campaigns,[5] normative guidance in Canada[133] to local implementation guidelines in Peru,[142] and general information to be disseminated among physicians[133] would help increase knowledge and demand.

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Name, institution	Region	Country	Declaration of conflict of interest												Conflicts and management plan
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
			Employment	Consulting	Research support	Non-monetary support	Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for a commercial entity or organization	Office or position to represent interest relating to the subject of the meeting or work			
Andrew Anglemyer California State University Monterey Bay	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
Hana M Azman Firdaus University of California, San Francisco – Global Health Sciences	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
Virginia Fonner Johns Hopkins Bloomberg School of Public Health	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
Hacsi Horvath University of California, San Francisco – Global Health Sciences	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
Aimee Leidich University of California, San Francisco	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
George Rutherford University of California, San Francisco – Global Health Sciences	AMR	USA	0	0	0	0	0	0	0	0	0	0	1 Travel to Geneva to attend Clinical Guideline Development Group meeting concurrent with another project. Travel paid by Itad Ltd under contract with the	0	Financial non-significant

Annex 2.3 Declaration of Interests for contributors to the guideline

													Global Fund to Fight AIDS, TB and Malaria		

Table 2.3.1. Declaration of Interests for external systematic review teams

Name, Institution	Region	Country	Declaration of Conflict of interest												Conflicts and management plan
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
			Employment	Consulting	Research support	Non-monetary support	Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
Ruth Birgin International Network of People who Use Drugs (INPUD)	WPR	Australia	0	0	0	0	0	0	0	0	0	0	0	0	None
Agata Dziuban Institute of Sociology, Jagiellonian University and International Committee on the Rights of Sex Workers in Europe (ICRSE)	EUR	Poland	0	0	0	0	0	0	0	0	0	0	0	0	None
Olga Denisuk International HIV Alliance in Ukraine	EUR	Ukraine	0	0	0	0	0	0	0	0	0	0	0	0	None

Robert Grant University of California, San Francisco	AMR	USA	0	0	1 Research grant from ViiV Healthcare/ GSK to institution US$ 150 000	1 Study medication was dontated by Gilead for PrEP research	0	0	0	0	1 Expert testimony to US FDA related to new drug application (TDF-FTC) Expert testimony to advisory committee of European Medicines Authority Lectures on PrEP coordinated by Clinical Care Options	0	1	0	Financial significant Institutional Non-financial significant Comments interpreted in the context of conflict of interest
Praphan Phanuphak Thai Red Cross AIDS Research Centre	SEAR	Thailand	0	0	1 Unlimited educational grant Gilead to research unit	0	0	0	0	0	0	0	0	0	Financial significant Institutional Comments interpreted in the context of conflict of interest
Jae Sevelius University of California, San Francisco	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
Joseph Tucker University of North Carolina at Chapel Hill	WPR	China	0	0	0	0	0	0	0	0	0	0	0	0	None

Table 2.3.2 Declaration of Interests external reviewers

Annex 2.3 Declaration of Interests for contributors to the guideline

Name, institution	Region	Country	Declaration of conflict of interest												Conflicts and management plan
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
			Employment	Consulting	Research support	Non-monetary support	Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
Elaine Abrams ICAP, Columbia University (Co-Chair, Clinical Guideline Development Group)	AMR	USA	0	1 Participation in advisory board GSK/ViiV Healthcare, US$ 4500	0	1 Principal investigator for implementation science study: Merck donated ARV drugs	0	0	0	0	0	0	0	0	Financial non-significant Non-financial significant Partial exclusion from the decision-making process and voting for relevant PICOs A1.1 and A1.3 Comments interpreted in the context of conflict of interest
Tsitsi Apollo Zimbabwe Ministry of Health and Child Care	AFR	Zimbabwe	0	0	0	0	0	0	0	0	0	0	0	0	None
Janet Tatenda Bhila Y+ AFRICAID Zandiri	AFR	Zimbabwe	0	0	0	0	0	0	0	0	0	0	0	0	None
Serge Eholie University Felix Houphouet-Boigny (Co-Chair)	AFR	Côte d'Ivoire	0	0	0	0	0	0	0	0	0	0	Principal investigator for TEMPRANO study	0	Financial significant Institutional Non-financial significant Partial exclusion from the decision-making process and voting for relevant PICOs; Did not chair discussion on when

															to start A1.1 and A1.3 Comments interpreted in the context of conflict of interest
Waffa El Sadr ICAP, Columbia University	AMR	USA	0	1 Attended pharmaceutical board meeting, ViiV Healthcare, USD 3000	0	0	0	0	0	0	0	0	0	0	Financial non-significant
Paul Garner Liverpool School of Tropical Medicine	EUR	UK	0	0	0	0	0	0	0	0	0	0	Director of DFID-funded research programme – effective health care based on reliable research summaries	0	Non-financial significant
Timothy Hallett Imperial College	EUR	UK	**0**	1 Bill & Melinda Gates Foundation, World Bank and University of Washington and New York, US$ 20 000 over 2 years	1 Bill & Melinda Gates Foundation, UNAIDS, RUSH Research, support to institution, US$ 8 million	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	Financial significant Comments interpreted in the context of conflict of interest
Anthony Harries International Union against TB and Lung Disease	EUR	UK	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None
Salim Abdool Karim CAPRISA	AFR	South Africa	**0**	0	0	**0**	**0**	**0**	**1** **Patent for effect of tenofovir gel on HSV**	**0**	**0**	**0**	**0**	**0**	Non-financial significant
Yogan Pillay National Department of Health of South Africa	AFR	South Africa	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None
Rebecca Matheson ICW	AFR	Kenya	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None
Fabio Mesquita Department of STDs, AIDS and Viral hepatitis	AMR	Brazil	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None

Annex 2.3 Declaration of Interests for contributors to the guideline

Julio Montaner BC-CFE, University of British Columbia	AMR	Canada	**0**	0	1 Supported by grants to institution by British Columbia Ministry of Health Grants from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb and Gilead Sciences, Janssen, Merck and ViiV Healthcare	**1** Financial support from US NIH, IAS, UNAIDS, WHO, ANRS, IAPAC, UNICEF, MAC AIDS Fund and OSF									Financial significant Comments interpreted in the context of conflict of interest
Natalia Nizova Ukraine Centre of Social Disease Control	EUR	Ukraine	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None
Douglas Shaffer Office of The US Global AIDS Coordinator	AMR	USA	**0**	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	None
Nandi Siegfried Independent Clinical Epidemiologist (methodologist Clinical Guideline Development Group)	AFR	South Africa	0	1 Consulting as methodologist for WHO, 2011–2015, remuneration > US$ 40 000	0	0	0	0	0	0	0	0	0	0	Financial non-significant Comments interpreted in the context of conflict of interest
Kenly Sikwese African Community Advisory Board AFROCAB	AFR	Zambia	0	0	1 Grants for community consultation, ViiV Healthcare , Gilead and Janssen to institution, US$ 30 000 , US$ 35 000	0	0	0	0	0	0	0	1 AFROCAB is seeking further support from Janssen, Gilead, ViiV Healthcare and Merck to provide financial support	0	Financial significant Institution Comments interpreted in the context of conflict of interest
David Sinclair	EUR	UK	0	0	0	0	0	0	0	0	0	0	0	0	None

Liverpool School of Tropical Medicine															
Annette Sohn TREAT ASIA/amfAR	SEAR	Thailand	0	0	1 Research and training grants to institution **Medicine donation for research study on hepatitis C to research unit only**	0	0	0	0	0	0	0	0	0	Financial significant Comments interpreted in the context of conflict of interest
Stefano Vella Instituto Superiore di Sanità	EUR	Italy	0	0	0	0	0	0	0	0	0	0	0	0	None

Table 2.3.3 Declaration of Interests Core Group