Paediatric HIV estimates

Report and recommendations from a meeting of the UNAIDS Reference Group on Estimates, Modelling, and Projections

18 October 2024

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Abbreviations

AIM	AIDS Impact Model
ANC (-RT)	Antenatal Clinic (Routine Testing)
ART	Antiretroviral Therapy
CDC	US Centres for Disease Control and Prevention
CLHIV	Children Living with HIV
DTG	Dolutegravir
IeDEA	International Epidemiology Databases to Evaluate AIDS
LTFU	Loss to Follow-up
PEPFAR	President's Emergency Plan for AIDS Relief
PHIA	Population-based HIV Impact Assessment
PLHIV	People Living with HIV
SSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
VLS	Viral Load Suppression
WHO	World Health Organization

Background

UNAIDS Reference Group on Estimates, Modelling, and Projections

The Joint United Nations Programme on HIV/AIDS (UNAIDS) relies on impartial scientific advice from international experts in relevant subject areas to provide guidance on how to best calculate estimates and projections of the prevalence, incidence, and impact of HIV/AIDS globally. The UNAIDS Reference Group on Estimates, Modelling, and Projections acts as an 'open cohort' of epidemiologists, demographers, statisticians, and public health experts to provide scientific guidance to UNAIDS and partner organisations on the development and use of the tools used by countries to generate annual HIV estimates, which are the source for UNAIDS Global HIV epidemic estimates. The Group is coordinated by a Secretariat hosted at SACEMA, Harvard School of Public Health, and the University of Cape Town.

Meeting overview

This report contains a comprehensive summary of presentations and discussions from the meeting, forming the foundation for the Reference Group's recommendations. Meeting participants (see Appendix B) can access these presentations on www.epidem.org. For those not in attendance, please reach out to the Secretariat at epidem@sun.ac.za for access requests. Appendix A presents the final recommendations. These recommendations guide UNAIDS in reviewing HIV estimates, assessing current methodologies, and identifying data for refining HIV estimates. The meeting agenda and objectives are in Appendix C. For records of previous meetings, visit www.epidem.org.

Meeting information

Mary Mahy outlined the objectives of the 2024 paediatric meeting and reaffirmed the role of Spectrum and related models in estimating HIV-related outcomes among children. She emphasized that paediatric HIV estimation remains a technical priority, requiring updates informed by emerging data, evolving scientific understanding, and country-level feedback.

Meeting focus

- Incorporating new data into models.
- Understanding how countries use models to estimate HIV outcomes in children.
- Identifying persistent challenges in measuring treatment interruption, prevalence, and mortality.
- Revisiting key assumptions that drive estimates of new paediatric infections and child HIV-related deaths.

She encouraged participants to review **Anna Yakusik's presentation from the 2024 Paediatrics workshop in Munich**, for a summary of the most recent paediatric HIV estimates.

Key topics from the 2023 meeting

Mahy reflected on several limitations in the model, identified during the 2023 paediatric meeting:

- **Treatment interruption**: The previous model did not adequately account for interruptions in ART among pregnant women and children, affecting vertical transmission and ART coverage estimates.
- **Antenatal care (ANC) prevalence**: Challenges in measuring HIV prevalence among ANC attendees were particularly noted in Western and Central Africa, but similar concerns exist in other regions. Since ANC prevalence is a key input in paediatric models for modelling maternal prevalence and new child infections, thus inaccuracies affect overall estimates.
- **Paediatric mortality assumptions**: There was a recognized need to refine child mortality assumptions based on stronger data sources, particularly vital registration and case surveillance systems.

2024 updates and their impact

The 2024 round primarily focused on how countries interact with and apply the models rather than making changes to core model assumptions, with minimal impact on global paediatric HIV estimates:

- **Treatment interruption adjustment**: A default 5% treatment interruption value was introduced to account for interruptions in paediatric antiretroviral therapy (ART) coverage. A validation screen was added in Spectrum to help countries assess when children are on treatment and number experiencing interruptions in treatment per year.
- **Breastfeeding assumptions**: Revised calculations to better reflect breastfeeding duration and associated HIV transmission probabilities among women living with HIV in Eastern and Southern Africa, led to small downward adjustments in new paediatric HIV estimates.
- **Knowledge of HIV status calculations**: Previous models assumed that treatment status directly corresponded to knowledge of HIV status, which likely overestimated linkage to care. The 2024 update distinguished between children currently on ART and those with prior treatment but current interruption. Aging out of paediatric categories was also incorporated. The updates resulted ~2 percentage point increase in knowledge-of-status estimates and it clarified gaps in linkage-to-care.

Mahy stressed that while these updates clarified logical inconsistencies and improved model transparency, overall trends in paediatric HIV estimates remained consistent with previous years.

Validating Spectrum estimates against empirical data

Mahy presented HIV prevalence among children 0-14 years, comparing Spectrum estimates against Population-based HIV Impact Assessment (PHIA) survey data. Despite wide confidence intervals, general alignment was observed in most countries. However, for South Africa, inconsistencies persisted between Spectrum estimates, Thembisa model outputs, and 2016 survey data. The 2022 South Africa survey was not included in the comparison due to unresolved prevalence calculation issues.

Ongoing challenges & areas for improvement

1. **Treatment interruption data for pregnant women and children**

Most countries rely on default values due to poor availability of programmatic data on treatment interruption, impacting understanding where new paediatric infections occur and identifying programmatic gaps. Improved accuracy of country-level treatment interruption data is essential, as this information is increasingly used in HIV incidence analysis.

2. **Fertility assumptions in concentrated epidemics**

Fertility among women living with HIV in concentrated epidemic settings, especially those partnered with men who have sex with men, people who inject drugs, or sex workers, remains poorly understood. Current assumptions may overestimate birth rates in these settings.

3. **Viral suppression during pregnancy and breastfeeding**

There is limited empirical data on viral suppression status across the pregnancy-postpartum continuum. Assumptions about suppression influence vertical transmission probabilities and need updating. New analyses are consolidating available data on HIV transmission probabilities based on ART status before, during, and after pregnancy.

4. **Mortality estimates for children living with HIV**

Paediatric mortality remains difficult to quantify. Existing assumptions may not reflect survival improvements or persistent gaps in treatment coverage.

5. **Challenges in household survey data for children**

As paediatric HIV prevalence declines, household surveys capture fewer cases, limiting their utility. Alternative empirical sources are needed for validating model outputs.

To address these technical challenges, the agenda was structured into four thematic sessions, each focusing on different stages of the paediatric HIV estimation process:

1. **Births to HIV-positive women:** Fertility adjustments and maternal viral suppression.
2. **Estimates of vertical transmission:** Probabilities based on ART status, timing, and regimen.
3. **Treatment coverage & retention:** Impact of interruption and ART initiation patterns.
4. **Child mortality:** Revising assumptions using vital registration and surveillance data.

John Stover reviewed the Spectrum paediatric model, data inputs and model outputs

generated, aimed at providing a basic understanding of methods related to the objectives of the meeting.

Session 1: Estimating births to women living with HIV

Objectives

- Consider updates to Spectrum's default ART retention rates among pregnant women
- Review availability of routine antenatal care (ANC) HIV testing data in concentrated epidemic settings and recommend on suitability of using routine ANC testing prevalence for estimating prevalence among pregnant women
- Review fertility adjustments in concentrated epidemics

Fertility and breastfeeding by women living with HIV on ART in Cambodia – comparison of fertility survey with 2024 Spectrum estimates

Ye Yu Shwe (UNAIDS, Cambodia) presented findings from the 2024 Cambodia Fertility Survey, which was conducted to investigate discrepancies in national paediatric HIV estimates. Despite high reported coverage of prevention of vertical transmission services (>97%) and ART coverage among women living with HIV (WLHIV) (88%), Spectrum estimated a vertical transmission rate of 8% and ART coverage among children living with HIV (CLHIV) at only 56%.

The survey collected data from 1,409 WLHIV aged 15–49 years receiving ART, using a two-stage sampling design aligned with Demographic and Health Survey (DHS) methodology. The survey focused on fertility history and breastfeeding practices.

Model inputs in Spectrum (2024)

- Cambodia used the Asia-Pacific regional default fertility reduction factors and a local adjustment factor (LAF) of 1.0, implying no deviation from default assumptions.
- Breastfeeding inputs were based on small, outdated datasets collected for programmatic purposes. This reflected intention to breastfeed rather than actual practice and were not nationally representative.

Key findings

1. Fertility rates in WLHIV vs. general population:

- Fertility rates among WLHIV on ART were significantly lower than those of the general population, as reported in the 2022 Cambodia DHS and the 2019 Census.
- The Total Fertility Rate (TFR) for WLHIV was substantially below the Spectrum default assumptions.
- These findings suggest that Spectrum may be overestimating the number of births to WLHIV, which could lead to inflated estimates of children living with HIV (CLHIV) and subsequently underestimation of paediatric ART coverage rates.

2. Breastfeeding practices:

- The survey found that WLHIV breastfed for a much shorter duration than the general population.
- Most WLHIV reported breastfeeding durations of less than 6 months, with many opting for exclusive formula feeding or early weaning.
- This diverges from the assumptions in Spectrum, which apply general population breastfeeding patterns to WLHIV, potentially overestimating postnatal HIV transmission in the Cambodian context.

Implications for Spectrum modelling:

- The current default Spectrum assumptions for Cambodia include a fertility rate adjustment (LAF 1.0) that may not reflect the true fertility behaviour of WLHIV.

- Shorter breastfeeding durations among WLHIV could mean lower-than-assumed postnatal HIV transmission rates, especially in concentrated epidemic settings.
- Overestimated births and breastfeeding durations among WLHIV can result in inflated vertical transmission estimates and CLHIV, which in turn may distort metrics such as paediatric ART coverage.

ANC testing data entered, and Fertility Local Adjustment Factors fitted or set, in concentrated epidemics' Spectrum 2024 files

Eline Korenromp presented an analysis of Spectrum files from 134 countries with concentrated epidemics, focusing on the use of ANC HIV testing data and the application of LAFs.

ART retention assumptions in pregnant women

Country files show wide variation in assumptions about ART retention among pregnant women, reflecting differences in data availability and interpretation. In Spectrum, ART retention during pregnancy is currently assumed to be 80% by default, but programmatic evidence from some countries suggests higher retention. However, inconsistencies in how retention is tracked, particularly distinguishing retention among pregnant vs. non-pregnant women, limit the reliability of this assumption.

Use of routine ANC HIV testing data

Routine ANC HIV testing data are entered in many concentrated epidemic country files, but their use for calibrating HIV prevalence among pregnant women varies. In several settings, observed ANC prevalence is lower than expected, which may be driven by pre-pregnancy HIV diagnosis and treatment, particularly in settings with strong pre-conception testing programmes. Concerns remain about the representativeness of ANC data: women who do not attend ANC may have different HIV risks, and ANC-based HIV prevalence may not fully reflect population-level prevalence among pregnant women.

Key findings

1. Among 64 concentrated epidemic countries reviewed:
   - **22 countries** entered routine ANC HIV testing data (test numbers and positivity), but most did not use it to calibrate HIV prevalence among pregnant women. Prevalence was **derived from perinatal HIV service coverage and Spectrum HIV estimates.**
2. In concentrated epidemic settings, the **LAF is used to align births to women living with HIV (WLHIV)** with observed HIV prevalence among pregnant women and/or perinatal HIV service coverage.
   - Most countries applied LAFs >1.0, implying higher fertility among WLHIV than the general population, contradicting empirical data from Cambodia and India. High LAF values inflate estimates of births to WLHIV and CLHIV, which in turn lowers calculated paediatric ART coverage.
   - No correlation was found between LAF and perinatal HIV service coverage, but a negative association was observed between LAF and paediatric ART coverage - countries with higher LAF values tended to show **lower ART coverage among children**, suggesting a modelling artefact.

Discussion

- Cambodia was highlighted as a case study demonstrating inconsistencies between reported perinatal service coverage, HIV prevalence in pregnancy, Spectrum's modelled births to WLHIV, and estimated CLHIV and paediatric ART coverage.
- Participants agreed that the Cambodia findings challenge existing assumptions in Spectrum, particularly the use of upward fertility adjustments (LAF >1.0) to reconcile perinatal HIV service data with modelled estimates.

- Similar patterns were observed in India, where WLHIV also exhibited lower fertility rates than HIV-negative women, reinforcing the need for caution in applying upward fertility adjustments.
- The Cambodia survey findings added weight to concerns that routine perinatal HIV programme data may include duplicated counts, especially in settings with fragmented or non-integrated data systems.
- There was consensus on the need for triangulation across multiple data sources — including fertility surveys, ANC HIV testing prevalence, general population HIV prevalence, perinatal HIV service data coverage, and child ART coverage — to validate model assumptions.
- Participants supported further analysis of routine ANC testing data but noted concerns about representativeness and potential bias due to selective testing or incomplete ANC attendance.

Session 2: Estimates of children newly infected with HIV

Objectives

- Consider updates to default Spectrum vertical transmission rate from:
    - Updated systematic review
    - Proposed meta-regression model approach to data synthesis
- Assess impacts of ART regimen class on vertical transmission rate for women on ART during pregnancy

Vertical transmission of HIV: updated systematic review and meta-analysis

Michelle Bulterys and Maggie Walters presented findings from an updated systematic review and meta-analysis of 111 studies, building on previous reviews from 2012, 2015, and 2018.
The review focused on estimating vertical transmission stratified by:

- Maternal immunologic status (CD4)
- Timing of exposure (perinatal vs breastfeeding)
- ART regimen and timing of initiation

The meta-regression models estimated transmission probabilities across three main categories:

1. Women not receiving perinatal HIV service
2. Women receiving short-course perinatal HIV service or seroconverting during pregnancy
3. Women on ART before or during pregnancy

A secondary aim was to assess the effect of ART regimen class on transmission, particularly dolutegravir vs efavirenz.

Key findings

1. Women not receiving perinatal HIV service

- Estimated perinatal transmission probability was approximately 14% for women with CD4 500, decreasing slightly at higher CD4 counts.
- Monthly breastfeeding transmission was ~0.7%. This represents a **9.8% decrease** in perinatal transmission and a **6.4% increase** in breastfeeding transmission relative to current Spectrum defaults.
- CD4 trends in breastfeeding were modelled based on perinatal data due to limited direct evidence - this assumption may require future review.

2. Short-course perinatal HIV service and seroconversion

- Perinatal transmission probabilities for maternal seroconversion during pregnancy were consistent with existing Spectrum values (~30%).
- Transmission rates for older perinatal HIV service regimens (e.g., single-dose nevirapine, dual ARVs) were similar to prior assumptions.
- The model corrected an inconsistency where single-dose nevirapine previously had higher transmission rates than untreated women with low CD4.

3. Women on ART before or during pregnancy

- Each additional week on ART before delivery was associated with a 6% reduction in odds of vertical transmission.
- New estimates for timing-based ART initiation categories:
    - ART initiated <4 weeks before delivery: 2.7% transmission (vs 8.2% default in Spectrum)
    - ART initiated ≥4 weeks before delivery: 1.4%
    - ART before conception: 0.7% (similar to Spectrum default)
- Only ~1% of women in Spectrum files started ART <4 weeks before delivery, limiting the impact of this category.

4. ART regimen class effects

- Women on dolutegravir-based regimens had 80% lower odds of perinatal transmission compared to those on efavirenz.
- However, most dolutegravir data came from high-income countries with high viral suppression and early ART initiation, introducing confounding.
- Presenters advised caution in using regimen-based effects globally at this stage.

Limitations

- Many studies did not disaggregate ART regimens, limiting precision.
- ART regimen exposure often inferred from national guidelines or assumed first-line regimen.
- Only 5 studies included dolutegravir-specific data.
- Viral suppression data were sparsely reported, only 11 of 23 new studies included viral load results.
- ART switches during pregnancy were not captured.
- Breastfeeding and perinatal transmission may not be directly comparable across timing categories due to data gaps.

Discussion

- The updated meta-regression approach was welcomed for its shift from categorical to continuous modelling of ART duration and CD4 count. The updated model structure will not require countries to change their Spectrum data inputs; default settings will remain aligned with previous formats.
- The approach allows more data inclusion and enforces biologically plausible trends but also introduces assumptions that may obscure nuances (e.g., low CD4 or late ART start).
- Participants agreed that the revised estimates for women not receiving perinatal HIV service and those on ART before or during pregnancy are more consistent with current programmatic realities.
- CD4 remains a proxy for viral load in the absence of widespread data. A parallel meta-analysis by Caitlin Dugdale is underway and supports this. However, data remain limited, and viral load–stratified estimates are not yet ready for implementation.
- Currently, Spectrum only stratifies vertical transmission by timing of ART initiation, not by regimen. Concern was raised that midpoint-based classification of ART initiation (e.g., assigning all third-trimester starts a 6-week duration) underestimates transmission risk. Studies reporting broad categories like “third trimester” may dilute the effect of very late ART start (e.g., week 36–38). A proposal was made to limit the model to studies reporting gestational week of ART start, and sensitivity analyses are being investigated.
- The observed 80% lower odds of transmission among women on dolutegravir-based regimens were interpreted cautiously. It was noted that this effect may be confounded by study setting, as most dolutegravir data came from high-income countries with early ART initiation and high viral suppression. A re-analysis is underway to include country income or region as a covariate in the regression model.
- Participants discussed whether to model rapid viral suppression linked to dolutegravir in late pregnancy using proxy adjustments (e.g., impact on viral load suppression). It was noted that very few women (~1%) initiate ART <4 weeks before delivery. A sensitivity analysis is being investigated to improve the model by limiting to studies that report precise gestational age at ART initiation. Walters suggested exploring quadratic terms for ART duration to better reflect nonlinear transmission risk at late initiation.

Session 3: Estimates of children living with HIV including those on treatment

Objectives

- Review impact of default treatment interruption on age distribution at ART initiation

Treatment interruption among children: Impact of 5% default

Maggie Walters presented an analysis evaluating how the 5% default treatment interruption rate, adopted in the 2024 Spectrum files, influenced the age distribution of ART initiation among children. This adjustment was introduced to better reflect patterns observed in PEPFAR program data, which show a greater proportion of ART initiations in older children than previously represented in Spectrum outputs.

Key findings

- In the 2024 Spectrum files, 70% of countries used the 5% default treatment interruption rate for children; 22% used a lower rate, and 8% used a higher rate.
- Spectrum continued to show a higher proportion of ART initiations among children under 1 year (31%) compared to PEPFAR data (16%), which showed the highest share among children aged 1–4 years.
- Increasing the interruption rate from 0% to 5% improved alignment with PEPFAR data in about 75% of countries. A further increase to 10% produced negligible additional effect, suggesting interruption is not a strong lever for changing age distribution.
- Spectrum's age distribution of ART initiation is more heterogeneous across countries than PEPFAR data, which show a more consistent pattern.
- Recognize that treatment interruption is only one factor. Future work should assess how multiple model components jointly affect age-at-initiation estimates.
    - ART initiation patterns are impacted by:
        - Age-specific probabilities of ART initiation (from CIPHER data)
        - Paediatric ART coverage inputs
        - Mortality assumptions (on-ART and off-ART)
        - Age distribution of children living with HIV

Discussion

- The level of age disaggregation in ART coverage inputs may influence the model's ability to align with observed programmatic trends.
- Challenges in reporting ART initiations among children under one year were highlighted. Perinatal HIV service indicators are often tracked separately and may under-report initiations, which can lead to underestimation in program data or misclassification into older age bands once children transition out of perinatal HIV service.
- Spectrum does not distinguish between new initiations and re-engagements; all are treated as new initiations.
- Concerns were raised about overestimation in ART cohorts due to lack of biometric verification, with some countries seeing 10–20% reductions in reported numbers after electronic medical records (EMR) system upgrades. This has implications for interpreting retention, treatment interruption, and ART initiation timing, especially among infants. However, treatment interruption is not a strong lever for shifting the age distribution of ART initiation in Spectrum. Clearer guidance to countries on ART data entry may be warranted, depending on their data quality and modelling objectives.

Session 4: Mortality of children living with HIV, with and without ART

Objectives

- Assess whether varying Spectrum MTCT or off-ART mortality rates improves consistency with observed AIDS deaths by age among children from vital registration
- Review impact of adjusting off-ART mortality for child ART coverage in countries with vital registration data
- Review Spectrum on-ART mortality compared to estimates from systematic review

Systematic review and meta-regression analysis of ART-related mortality in children and adolescents under 15

Jiawei He (IHME) presented findings from a systematic review and meta-regression analysis to estimate the mortality rates of children and young adolescents under 15 years old who have taken antiretroviral therapy (ART). The study aimed to estimate mortality by age, sex, treatment duration, year, and across different regions.

Modelling approach

The modelling approach used meta-regression with Bayesian priors, regularization, and trimming. The model accounted for non-linearity between CD4 count and mortality, and included variables such as sex, treatment duration, age, and healthcare access and quality (HAQ) index. The HAQ index measures the performance of health systems in providing access to quality healthcare. The model used a two-stage framework: the first stage captured the long-term relationship between mortality and CD4 count, and the second stage included additional variables to refine the estimates.

Key findings

The study found substantial reductions in mortality across time, with significant variations by age group and region. For example, mortality rates for children aged 1-2 years in Western sub-Saharan Africa showed a significant decline over the years, with lower mortality for those on ART for more than six months compared to those on ART for less than six months. Similar trends were observed for other age groups and regions, with disparities in mortality rates between Western and Southern sub-Saharan Africa.

Sensitivity analyses were conducted to compare results including all studies versus only high-quality studies. The results were consistent, indicating the robustness of the findings. Additionally, comparisons with UNAIDS estimates showed similar temporal trends and patterns across CD4 counts and treatment durations, although some differences in estimates were noted.

Mortality estimates were compared with UNAIDS estimates for 2005 and 2020. In 2005, the estimates were similar, but in 2020, the study's estimates were slightly lower than UNAIDS estimates. Differences may be attributed to HAQ index adjustments, which has been decreasing over time, and recent studies indicating changes in mortality trends.

Discussion

- It was clarified that IeDEA data likely contributed more than 40% of the total data points, especially where systematic patterns were observed, but not the majority. The extracted studies often contributed more granular data points due to age and sex disaggregation.
- HAQ is a key covariate in the second stage of their model. Since fewer studies are available for 2020, the model relies more heavily on HAQ, which has generally improved over time, leading to lower IHME mortality estimates than UNAIDS estimates for East Africa in 2020.
- A participant raised the possibility that IeDEA's more complete mortality ascertainment in East Africa might bias regional comparisons. IeDEA's efforts to trace and confirm deaths

might make East Africa appear to have higher mortality than other regions where deaths are underreported.
- Participants noted that many published studies do not adjust for unascertained mortality (e.g., deaths among those lost to follow-up), however, it was confirmed that the model includes an adjustment based on empirical relationships between loss to follow-up and mortality. Another participant cautioned that these relationships may be changing over time due to earlier diagnosis and treatment, and suggested re-evaluating the adjustment methods.
- The findings suggest a need to revise Spectrum's current assumptions about ART mortality, which are based solely on IeDEA data, especially given that the IHME analysis includes a broader evidence base. It was also noted that IeDEA is working on updated analyses with more recent data and tracing studies, which could inform future revisions.

Mortality data and HIV-related outcomes in children

Anna Yakusik (UNAIDS) presented an analysis comparing Spectrum estimates of child AIDS deaths and ART initiations with WHO vital registration and case surveillance data across nine countries. The objective was to assess the consistency of Spectrum's estimates with observed data and to identify potential areas for improvement in data systems and modelling accuracy.

Methods

The analysis involved comparing Spectrum results for child AIDS deaths and child HIV diagnoses/ART initiations by age against vital registration data and case surveillance data. Data from nine countries across various regions were included in the analysis. Fixed effect regression models were used to assess the influence of vital registration data on modelled AIDS deaths in children aged 0-14 years.

Regional findings

The analysis revealed significant disparities between estimated child AIDS deaths and those reported by WHO across all regions. In Latin America, the Caribbean, Eastern Europe and Central Asia, Asia and Pacific, Middle East and North Africa, and Sub-Saharan Africa, Spectrum consistently suggested higher estimated numbers of deaths in children due to HIV/AIDS than reported through WHO mortality databases.

- For example, in the Caribbean, six countries' data showed that Spectrum estimates were on average higher than the deaths reported through the mortality database, with a few exceptions. In Eastern Europe and Central Asia, six countries also showed similar patterns, with some outliers such as Georgia suggesting higher numbers of AIDS deaths in children than Spectrum estimates.
- In Asia and Pacific, four countries were analyzed, with Malaysia showing significant discrepancies between Spectrum estimates and reported deaths. In the Middle East and North Africa, only Egypt reported data, showing substantial differences between Spectrum estimates and WHO mortality data.
- In sub-Saharan Africa, only two countries reported data through WHO mortality databases, and Spectrum estimates consistently showed higher numbers of deaths.

Regression analysis

- Fixed effect regression models were used to analyze the influence of vital registration data on AIDS deaths in children aged 0-14 years as modelled by Spectrum. The analysis revealed a statistically significant impact of WHO vital registration data on modelled AIDS deaths in children, indicating a correlation between the two data sources.
- Additionally, regression analysis was conducted to assess the influence of child ART initiations on new infections and AIDS deaths in children. The results showed no statistically significant correlation between child ART initiations and new HIV infections or AIDS deaths, suggesting that child ART initiations had no effect on these outcome measures.

Sensitivity testing
Sensitivity testing was conducted to assess the robustness of the findings. The analysis revealed a positive association between vital registration data and AIDS-related mortality as estimated by Spectrum. This correlation underscores the importance of vital registration systems in improving the accuracy of HIV-related mortality estimates.

The analysis revealed significant disparities between estimated child AIDS deaths and those reported by WHO across all regions. The findings highlight the need for improved data systems and modelling accuracy to better align Spectrum estimates with observed data.

Discussion

- The mortality database has lost traction, limiting the availability of new data. No significant additional information has been recovered since the last analysis conducted two years ago. The lack of updated data constrains the ability to refine mortality estimates.
- Analysis confirmed a positive association between AIDS-related mortality reported in VR systems and Spectrum model estimates.
- **Case study selection**:
    - Cambodia was suggested as a potential case study for further analysis.
    - Brazil and Cuba were identified as possible case study options in Latin America and the Caribbean.
    - Belarus and other Eastern European and Central Asian countries were noted for having significant discrepancies in maternal-to-child transmission (MTCT) estimates and outcomes.
- Concerns were raised about the accuracy of mortality data from some countries, particularly those with weak perinatal HIV service reporting systems. It was noted that Argentina's data was unreliable and not suitable for inclusion.
- A question was raised regarding whether the final outcomes data for HIV-exposed infants (HEI) could provide insights into child mortality. It was clarified that the dataset includes mortality as a final outcome but does not disaggregate deaths by cause.
- Participants noted that total mortality could still be informative, particularly in the first year of life, though much of that mortality may be unrelated to HIV.
- There was consensus that underreporting of deaths, particularly in high-quality vital registration (VR) settings, could pose significant challenges in interpreting the data. South Africa was cited as an example where VR data on cause of death is known to be poor, and where higher Spectrum estimates are expected. VR systems, especially in low- and middle-income countries and sub-Saharan Africa, often underreport deaths, particularly HIV-related deaths in children. WHO and partners are working on improving assumptions and data collection, including through initiatives like CHAMPS and the WHO CA-CODE project.
- While a suggestion was made to explore whether discrepancies vary by the quality or completeness of VR data, as classified by WHO, it was noted that WHO no longer publicly classifies VR data by quality, and only high-quality data are published on the WHO mortality database, which were used in the analysis.
- A proposal was made to compare the proportion of AIDS deaths among all child deaths, rather than absolute numbers, to account for underreporting in VR systems. However, it was confirmed that while absolute numbers differ, the age distribution and composition of deaths (e.g., under-5 mortality) are similar between Spectrum and VR data.
- In high-income countries (e.g., Western and Central Europe), VR data are complete and more consistent with Spectrum estimates. However, the focus of the analysis was on low- and middle-income countries, where the largest discrepancies and data gaps remain.
- Sensitivity analyses results were inconclusive or not meaningful based on the available data.

Impact of adjusting off-ART mortality for child ART coverage in countries with good VR data

John Stover presented findings on a potential adjustment to paediatric off-ART mortality within Spectrum, motivated by earlier modifications introduced for adults in high-income countries. The adult adjustment was based on the hypothesis that as ART coverage increases, individuals remaining off treatment are healthier, thus reducing mortality among this group. A linear adjustment was applied such that mortality is unadjusted at 0% ART coverage and fully reduced at 100% coverage. This method improved alignment with mortality data in European countries.

The feasibility of applying a similar adjustment for children in countries with high-quality vital registration (VR) systems, primarily in Europe was explored, ART coverage in these settings is generally high.

The proposed adjustment led to a 25% reduction in estimated AIDS-related deaths among children not on ART. However, previous analyses showed that applying this adjustment globally resulted in elevated paediatric HIV prevalence, worsening alignment with independent estimates (e.g., from PHIA surveys). Therefore, it was previously decided not to implement the adjustment globally.

It was concluded that:

- The adjustment is feasible and results in reduced mortality estimates in high-quality VR countries.
- It may help align estimates with VR data in those specific settings.
- However, applying it globally remains problematic due to inflation of prevalence estimates.
- Further comparison with Yakusik's presentation data could help assess whether regional application is justified.

Discussion

- The need to disaggregate HIV-related mortality from overall child mortality was emphasized.
    - The PEPFAR final outcomes for HEI (HIV-exposed infants) dataset was suggested as a potential data source, though it does not explicitly separate causes of death.
    - Concern was raised about under-ascertainment of child mortality in current datasets, making interpretation challenging.
- Participants agreed that non-HIV-related mortality accounts for a significant portion of child deaths in the first year of life, which complicates the direct application of the adult ART-adjustment model to children. Modelling approaches need to consider changes in baseline child mortality, ART uptake, and broader healthcare improvements.
- It was clarified that the rise in paediatric HIV prevalence under the adjustment stems from reduced mortality alone.
- In generalized epidemics, older children initiating ART when symptomatic may still show selection effects similar to adults, but this may not hold in all settings.
- Participants suggested considering the adjustment selectively for high-income or low-burden settings where off-ART mortality assumptions may be less accurate. Members of the Reference Group agreed that the effect might be more limited in high early-infant-diagnosis coverage settings.
- Changes to perinatal and breastfeeding transmission rates could affect mortality estimates differently in concentrated settings, particularly given shorter breastfeeding durations.
- Multiple analyses suggest underestimated child deaths (leading to higher prevalence), despite stakeholder feedback that Spectrum may already overestimate the number of children living with HIV, even outside PEPFAR countries.

Appendix A – Recommendations

Recommendation	Lead person(s)	Timeline
Session 1: Estimating births to women living with HIV (chair: Jeff Imai-Eaton) **Objectives:** • Consider updates to Spectrum's default ART retention rates among pregnant women • Review availability of routine ANC testing data in concentrated epidemic settings and recommend on suitability of using routine ANC testing prevalence for estimating prevalence among pregnant women • Review fertility adjustments in concentrated epidemics		
ART retention among pregnant women Summary: Regarding default Spectrum assumptions about retention on ART among pregnant women: • Current Spectrum defaults assume 80% of women already on ART before pregnancy and 80% of women initiating ART before pregnancy will be retained on ART at delivery, based on systematic review by Dugdale and colleagues reporting data published 2012-2018. • There was general consensus that systematic upward adjustments to ART retention in Spectrum files that changed defaults along with other recent evidence likely indicates **Spectrum default assumptions of 80% ART retention are inaccurately too low.** o The assumption that only 80% of women who were already on ART before the current pregnancy are retained at delivery was perceived as particularly inconsistent with recent data implying very high overall ART coverage in many countries. • However, there was concern about using country-entered data to define new regional defaults, given potential for selection biases or non-systematic adjustments. **Recommendations:** • Intend to revise default assumptions about ART retention during pregnancy and breastfeeding to increase percentage of women retained for UNAIDS 2025 HIV estimates process • Proposed approach: o Review more recent literature review data on ART retention during pregnancy assembled by Caitlin Dugdale o Convene a working group to determine final assumptions by mid-November based on further evidence review, including options: ▪ Adopt updated assumptions from more recent Dugdale review ▪ Assume women who initiated ART before pregnancy have same treatment interruption rate as entered for all adults on ART	Working group	Nov 2024
HIV fertility rate ratios in concentrated epidemic settings Summary: • Most countries adjust the HIV fertility rate ratio 'local adjustment factor' to greater than one, indicating increases to births to HIV positive women in order to reconcile recent perinatal HIV service provision or HIV prevalence among pregnant women. • However, evidence from Cambodian study on fertility among HIV positive women found overall **lower** fertility among HIV positive women compared to		

Recommendation	Lead person(s)	Timeline

Spectrum defaults. Previous analysis of India Demographic and Health Survey found similar results.
• Analysis of 2023 Spectrum file results identified no association between local adjustment factor and perinatal HIV service coverage. However, it found a negative association of higher local adjustment factor being associated with lower paediatric ART coverage.
  o This may suggest that increasing local adjustment factor to be consistent with recent perinatal HIV service data might inadvertently inflate historical HIV positive pregnant women and therefore children with HIV, reducing estimated paediatric ART coverage
  o This may be indicative of duplicated or over-reporting of numbers of unique women accessing perinatal HIV service at ANC in concentrated epidemic settings, similar to that which has been of recent concern in African epidemic settings.
• **Recommendation:** Despite evidence of LAF consistently specified above 1.0, recommend **not to** revise default LAF or relative fertility patter due to lack of corroborating evidence from Cambodia survey, India DHS, or other sources.
• **Recommendation:** During next HIV estimates round, encourage careful review and scrutiny of perinatal HIV service programme data, particularly for concerns about potential double counting
  o During HIV estimates process, highlight the relationship between adjusting FRR to reconcile recent perinatal HIV service data and impacts on historical children born with HIV and child ART coverage.
  o Review consistency of perinatal HIV service need with routine ANC HIV testing prevalence, while carefully considering representativeness and accuracy of measured routine ANC HIV testing
	UNAIDS	2025 estimates

• **Recommendation:** Cambodia fertility survey implied considerably shorter breastfeeding duration among HIV positive women. Rapidly review evidence on breastfeeding duration among HIV positive women in concentrated epidemic settings and assess accuracy of Spectrum default assumptions	Working Group	Nov 2024
• **Recommendation:** Further develop Cambodia example to demonstrate inconsistency and triangulation of fertility rate, HIV prevalence among pregnant women, perinatal HIV service coverage, and children living with HIV and child ART coverage.	Ye Yu Shwe, Avenir Health, Imperial College London	

Recommendation	Lead person(s)	Timeline
Session 2: Estimates of children newly infected with HIV (chair: Cari van Schalkwyk) **Objectives:** • Consider updates to default Spectrum vertical transmission rate from: - Updated systematic review - Proposed meta-regression model approach to data synthesis • Assess impacts of ART regimen class on vertical transmission rate for women on ART during pregnancy		
Systematic review of mother-to-child transmission rates and comparison of results with Spectrum Provisional recommendation to implement updated estimates of vertical transmission (VT) for 2025 UNAIDS HIV estimates, pending further review of data and model structure about VT among women initiating ART during third trimester of pregnancy. Specifically recommended further investigation and review of the following prior to adopting new estimates: • Alternative meta-regression model structure and assumptions: o <u>VT among untreated women (Model 1)</u>: Check sensitivity of results to different specifications of CD4 category bounds and choice of mid-point CD4 to determine category transmission rate o <u>VT among women initiating ART during pregnancy (Model 3):</u> Review inclusion of studies and meta-regression model assumptions for estimating VT rates among women initiating ART within four weeks before delivery Regard reflecting the impact of changing ART regimens over time in Spectrum VT rate assumptions, the group recommended **no immediate change to model assumptions** but to continue reviewing evidence: • It was perceived that estimated substantially lower transmission rate for dolutegravir (DTG) versus efavirenz (EFV) may reflect confounding by study location / region, and other trial data have not found evidence that DTG reduces VT or viral load at delivery compared to other regimens when started before or early in pregnancy. o <u>Recommendation:</u> further review study characteristics, balance of evidence, and adjust meta-regression for region. Ensure that results of meta-regression are presented and interpreted in context of totality of evidence about regimen effects on DTG. • Trial and observational evidence indicate that when ART is started very late in pregnancy, more rapid VLS with DTG may reduce VT compared to other regimens. o <u>Recommendation:</u> Review results of Dugdale *et al.* systematic review of VLS and VT. o <u>Recommendation:</u> Consider potential magnitude of effect of implementing effects of regimen changes over time on VT from late ART initiation in Spectrum, noting relatively small overall proportion of mothers in the late ART initiation group.	Imperial College London, Working Group	Nov 2024

Recommendation	Lead person(s)	Timeline
Session 3: Estimates of children living with HIV including those on treatment (chair: Mary Mahy) **Objective:** Review impact of default treatment interruption on age distribution at ART initiation		
Based on its influence on the age distribution of new ART initiations, there is not compelling evidence to change the default treatment interruptions in children away from default assumption 5% per year.		

Age distribution at ART initiation
 	
• To assess the influence of data on ART initiation by age derived from CIPHER (approx. 2016) on child ART coverage estimates:
  o Review the number of countries that enter ART programme data for all children <15 vs. by 5-year age bands.
  o Assess whether age distribution of children initiating ART and child ART coverage by age are systematically different according to whether data are entered by <15 years vs. 5-year age bands
  o Compare CIPHER data age distribution to contemporaneous HIV programme data reported to national electronic medical records, PEPFAR, and IeDEA
 	
• Conduct detailed triangulation of modelled CLHIV and new diagnoses by age with paediatric HIV testing data and electronic medica record data on ART initiation and continuation. Recommend analysis reconstructing child infections, treatment initiations, and interruptions by *birth cohort.*
  o Kenya recommended as case study based on strong EMR system
  o Include HIV testing by modality programme data reported to PEPFAR
	To be identified	May 2025

Session 4: Mortality of children living with HIV, with and without ART (chair: Leigh Johnson) **Objectives:** • Assess whether varying Spectrum MTCT or off-ART mortality rates improves consistency with observed AIDS deaths by age among children from vital registration • Review impact of adjusting *off-ART* mortality for child ART coverage in countries with vital registration data • Review Spectrum on-ART mortality compared to estimates from systematic review		
Systematic review of child on-ART mortality Assess amount of child ART mortality data identified in the systematic review that are from IeDEA analysis (already included in existing Spectrum ART mortality rates) versus amount of new data. Review approach to adjusting child ART mortality for observed proportion LTFU, including whether recent evidence on changes over time in proportion deceased among LTFU are incorporated in mortality rate adjustments.	IHME	May 2025

Recommendation	Lead person(s)	Timeline
HIV-related deaths in concentrated settings with high quality vital registration data		
• Stratify analysis to focus comparisons on settings with high-quality death registration data to better understand where the discrepancies with VR data likely reflect true differences between Spectrum model results and AIDS-related deaths. o Consider comparing % of deaths due to AIDS (rather than absolute numbers), to account for incompleteness of deaths or cause of death reporting in some settings.	UNAIDS	May 2025
• Although the adjustment to off-ART mortality (based on ART coverage) could resolve some of the discrepancies in Spectrum vs VR AIDS deaths, it is insufficient to explain all of the difference, and also increases paediatric HIV prevalence above the levels measured in the PHIA surveys. Therefore, it was recommended not to implement ART mortality reduction proportional to adult ART coverage.		
• Recommend should more systematically explore the effect of other possible model changes, including reducing MTCT (likely to be too high in many non-SSA settings), updating the MTCT probabilities based on Bulterys and Walters review, and possible interactions between EID coverage and the off-ART mortality adjustment. o Consider case studies of countries with detailed paediatric HIV data across multiple outcomes (perinatal HIV service cascade, diagnoses, number on ART, AIDS-related deaths). Initial suggestions include: Cambodia, Brazil, Cuba, Belarus.	TBD	May 2025
• Revisit the version of Spectrum that was created for South Africa (late 2010s or early 2020s), which implemented the off-ART mortality adjustment in order to match Thembisa to address: o Was the custom version used in recent estimation rounds? o If not, what changes to Spectrum or Thembisa enabled reasonable correspondence to the Thembisa child HIV mortality estimates?		

Appendix B – Participants

Name	Organisation
Ali Judd	UCL
Amanda Novotney	IHME
Andrea Ciaranello	Harvard University
Andreas Jahn	MoH Malawi
Anna Yakusik	UNAIDS
Austin Carter	IHME
Cari van Schalkwyk	SACEMA
Chibwe Lwamba	UNICEF
Constantin Yiannoutsos	Indiana University
Eleanor Gouws	UNAIDS
Eline Korenromp	UNAIDS
Fatima Tsiouris	EGPAF
George Siberry	USAID
Guy Mahiane	Avenir Health
Hmwe Kyu	IHME
Ian Wanyeki	UNAIDS
Italia Rolle	UNAIDS
Ivy Kasirye	WHO
Jeannie Collins	UCL
Jeff Imai-Eaton	Harvard University
Jiawei He	IHME
John Stover	Avenir Health
Kathleen Powis	Harvard University
Keith Sabin	UNAIDS
Kimi Sato	CDC
Leigh Johnson	University of Cape Town
Lynne Mofenson	Independent Consultant
Maggie Walters	Imperial College London
Margo Sabin	Simmons University
Mary Mahy	UNAIDS
Mary-Ann Davies	UCT
Mathieu Maheu-Giroux	McGill University
Michele Montandon	CDC
Michelle Bulterys	UW
Michelle Selim	PEPFAR
Michelle Yang	PEPFAR
Nandita Sugandhi	WHO
Rachel Esra	Avenir Health
Ray Shiraishi	CDC
Reshma Bhattacharjee	USAID
Robert Glaubius	Avenir Health
Sarah Hicks	UW
Tim Brown	East West Centre

Wilford Kirungi	MoH Uganda
Ye Yu Shwe	UNAIDS
Yuri Munsamy	SACEMA

Appendix C - Agenda

18 October 2024

Time	Duration (mins)	Topic	Presenter(s)
14:00	15	Welcome and introductions Review of 2024 estimates and pending challenges Meeting objectives	Mary Mahy
14:15	5	Overview of Spectrum child model	John Stover
Session 1: Estimating births to women living with HIV Objectives: Consider updates to Spectrum's default ART retention rates among pregnant women Review availability of routine ANC testing data in concentrated epidemic settings and recommend on suitability of using routine ANC testing prevalence for estimating prevalence among pregnant women Review fertility adjustments in concentrated epidemics			
14:20	10	ART retention among pregnant women	Eline Korenromp
14:30	20	Discussion	
14:50	10	Availability of routine ANC data, coverage of ANC testing, and local fertility adjustments in concentrated epidemics	Eline Korenromp
15:00	15	Comparing Spectrum fertility rates among women on ART to results from survey in Cambodia	Ye Yu Shwe
15:15	20	Discussion	
Session 2: Estimates of children newly infected with HIV Objectives: Consider updates to default Spectrum vertical transmission rate from: Updated systematic review Proposed meta-regression model approach to data synthesis Assess impacts of ART regimen class on vertical transmission rate for women on ART during pregnancy			
15:35	15	Systematic review of mother-to-child transmission rates and comparison of results with Spectrum	Michelle Bulterys/ Maggie Walters
15:50	30	Discussion	
16:20	10	BREAK	

Time	Duration (mins)	Topic	Presenter(s)
Session 3: Estimates of children living with HIV including those on treatment Objective: Review impact of default treatment interruption on age distribution at ART initiation			
16:30	15	Treatment interruption among children: Overview of adoption of 5% default in 2024 Spectrum files Review impact of new defaults on age distribution at ART initiation	Maggie Walters
16.45	20	Discussion	
Session 4: Mortality of children living with HIV, with and without ART Objectives:			

Assess whether varying Spectrum MTCT or off-ART mortality rates improves consistency with observed AIDS deaths by age among children from vital registration Review impact of adjusting off-ART mortality for child ART coverage in countries with vital registration data Review Spectrum on-ART mortality compared to estimates from systematic review			
17:05	15	Systematic review of child on-ART mortality	Jiawei He
17:20	20	Discussion	
17:40	20	Mortality in settings with good vital registration data: Compare Spectrum results for (1) child AIDS deaths and (2) child HIV diagnoses/ART initiations by age vs. vital registration data and case surveillance Sensitivity of Spectrum results when varying MTCT or off-ART mortality rates Impact of decreasing off-ART mortality as child ART coverage increases in countries with VR data	 Anna Yakusik Anna Yakusik John Stover
18.00	20	Discussion	
18:20		CLOSE	