

Modelling Paediatric HIV and the need for ART

Report and recommendations from a meeting of the UNAIDS Reference
Group on Estimates, Modelling, and Projections
9th October 2020

REPORT & RECOMMENDATIONS



Abbreviations

ANC	Antenatal clinic
ANC-RT	Routine HIV testing data from antenatal clinics
ART	Antiretroviral therapy
CDC	US Centers for Disease Control and Prevention
CLHIV	Children living with HIV
FRR	Fertility Rate Ratio
IeDEA	International Epidemiology Databases to Evaluate AIDS
PEPFAR	US President's Emergency Plan for AIDS Relief
PHIA	Population-based HIV Impact Assessment
PLHIV	People living with HIV
(P)MTCT	(Prevention of) Mother to Child Transmission
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

The meeting of the UNAIDS Reference Group on Estimates, Modelling, and Projections was organised for UNAIDS by the Secretariat of the Reference Group (www.epidem.org), managed at Imperial College London and the University of Cape Town. Participants of the meeting are listed at the end of this document.

Oli Stevens, October 2020

Background

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 Imperial College London and the University of Cape Town.

Work of UNAIDS Reference Group has been organised broadly into tracks:

- 'Technical update' work streams: These work streams are oriented to conducting research and providing technical feedback and guidance on specific updates for the suite of tools used for annual UNAIDS estimates, i.e. Spectrum, which includes the AIDS Impact Module (AIM), the Estimation and Projection Package (EPP), and the Case Surveillance and Vital Registration tool (CSAVR).
- 'Thematic' meetings: These meetings are focused on convening new research to catalyse innovation on specific aspects of HIV estimates that require substantial conceptual or methodological development

Meeting Objectives

The purpose of this meeting was to provide technical recommendations for updates for Spectrum and accompanying estimation tools, used by countries to furnish annual HIV estimates.

Objectives of this meeting were to:

- Improve the ability for countries to estimate and project the number of children and adolescents living with HIV

Outline

The UNAIDS Reference Group held its virtual thematic meeting on *Modelling Paediatric HIV and the need for ART* on 9th October 2020. The meeting featured presentations and group discussion to generate consensus recommendations. The programme was divided into the following sessions:

1. Paediatric natural history model and ART
2. Births to HIV+ women and breastfeeding

This report presents a summary of the meeting presentations and discussions. The presentations are available to meeting participants at www.epidem.org (others, please contact the Secretariat). The final recommendations can be found at the end of this report. The recommendations drafted at these meetings provide UNAIDS with guidance on generating HIV estimates, provide an opportunity to review current approaches, and help to identify the data needed to further improve the estimates. Previous meeting reports are available at www.epidem.org. This transparent process aims to allow the statistics and reports published by UNAIDS and partners to be informed by impartial, scientific peer-review.

The list of participants and meeting agenda are included in Appendix I and Appendix II, respectively.

The 2020 paediatric estimates

Mary Mahy presented changes to the Spectrum paediatric model implemented for the completed 2020 estimates round, the impact of those changes, and remaining challenges. The number of new child infections and CLHIV increased slightly in 2020 estimates compared to 2019 estimates due to adjustments to default assumptions about ART retention during breastfeeding and breastfeeding duration. PEPFAR programmatic data suggest that the age distribution of children on treatment used in Spectrum provided by leDEA underestimate the proportion at older age groups and overestimates at younger age groups. Countries are encouraged to enter programmatic data by five-year age groups to assist in this validation. [Child Health and Mortality Prevention Surveillance \(CHAMPS\) study](#) mortality data from 1147 individuals find 5.3% of total child deaths are attributable to HIV in three surveillance sites in Kenya, South Africa, and Mozambique, with Spectrum estimating 3.5% for these three countries at the national level. There is increasing focus on the vertical transmission stacked bar chart in Spectrum by country estimates teams, which requires good estimates of incidence, treatment and treatment retention, and breastfeeding in HIV+ women.

Session 1: Paediatric natural history and ART

John Stover presented an overview of the paediatric model, enumerating proposed changes to the paediatric model for the 2021 estimates process:

Mapping the transition from CD4% to CD4 count

Presently, children aged 0-4 are tracked by CD4 percent, and transitioned to CD4 count for ages 5-14. Data from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) inform the mapping between percent and count categories – each CD4 percent category can be mapped to one or two CD4 count category. A new leDEA mapping analysis suggests a broader mapping distribution where children may be mapped to nearly any CD4 count category (Fig 1). Adopting the new mapping would have negligible effect on CLHIV and a 6% increase on paediatric AIDS deaths in 2019.

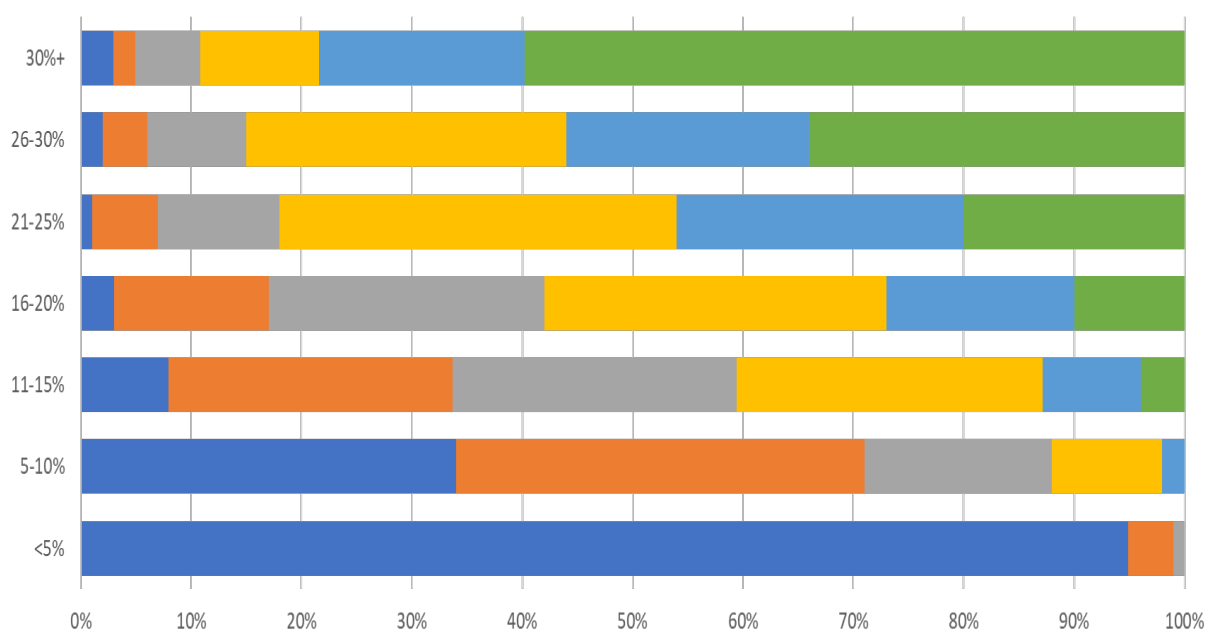


Figure 1: Mapping from CD4 percent to CD4 category from leDEA data

Transition from the paediatric to adult model

AIDS mortality rates by age display discontinuities at the transition between the paediatric and adult models at ages 14-15 and it has previously been suggested to the Reference Group that this transition be smoothed. Discontinuities are common within both the paediatric and adult models in the natural history models and on-ART mortality parameters. Smoothing across all parameter sets by single year of age would lead to deviation from the data provided by five-year age groups. The size of the discontinuity at age 15 will also depend on the composition of the 14-year-old cohort, broken down by timing of infection, CD4 count by treatment status, and treatment coverage. The revised adult natural history model has additionally smoothed the paediatric mortality transition, removing it entirely in Malawi, Cameroon, though a discontinuity remains in Botswana.

Trends in on-ART mortality rates

Spectrum assumes that adult on-ART mortality rates decline over time, reflecting improved drug regimens and viral load monitoring. Thembisa estimates significantly fewer paediatric deaths than Spectrum. A similar decreasing trend over time could be introduced to the paediatric model to align model results in South Africa, which would decrease on-ART mortality in 2020 to around a third of the mortality in 2000, and would increase global CLHIV by 5.2% and decreasing AIDS deaths by 7.4% in 2019.

Mortality among untreated children with HIV

In the adult population, Spectrum assumes that the mortality rate for adults off-ART decreases proportional to ART coverage. This is because as ART coverage reaches high levels individuals at the greatest risk of mortality will be initiated on treatment, leaving only relatively healthier individuals off-ART. A similar phased reduction in off-ART mortality could be introduced in the paediatric model

An updated analysis of paediatric on-ART mortality from leDEA was presented by Reshma Kassanjee, consolidating observational data from children while in care with tracing study data that estimate mortality rates after loss to follow up. Model updates since the 2019 Reference Group paediatric meeting [1] include:

- A monotonic relationship between mortality and CD4
- Revised CD4 mapping
- A simplified model structure
- Refined definitions of last seen alive and last reported complete data from programmes

In children under 5, mortality is five-fold lower for those on treatment for 12 months or more compared to less than 6 months, adjusting for age, sex, and CD4 count at initiation. Mortality experienced by children on-ART in 2017 compared to that in 2005 is between 30-80% lower, varying by time on ART and geographic region. Including the revised CD4 mapping outlined by Stover above leads to flatter patterns over time in on-ART mortality, with more pronounced decreases at longer on-ART durations.

Tracing study data from 221 children lost to follow up were included to determine outcome in children out of care. A Weibull distribution survival was used to estimate mortality, using covariates as at time of LTFU. Probability of death within 6 months after LTFU ranges from 4-34% with higher probabilities amongst younger CLHIV who have been on ART for shorter

periods. As missing data levels were high and sample size was small, CD4 data were not included in the multivariate model.

Outcomes for individuals identified as LTFU in the observational cohort are simulated based on matched baseline characteristics in the tracing study model. These imputed LTFU outcomes are added to the original observational cohort and the observational analysis is conducted again. Including the imputed LTFU outcomes leads to a two-fold increase in on-ART mortality in 2017 compared to the unadjusted observational cohort, with no explicit time trend since 2005. Unpacking these findings, those LTFU are a high-risk population, with short treatment durations compared to those in the observational dataset.

Key points from discussion & recommendations

CD4 Mapping

Recommendation: Accept the new leDEA mapping

Smoothing mortality transition at age 15

Recommendation: Do not smooth the transition. This discontinuity is largely resolved by the revised adult natural history model

Trends in on-ART mortality

Recommendation: Do not implement a time trend in on-ART mortality, pending revision to leDEA on-ART mortality rates

Trends in off-ART mortality

Recommendation: Do not implement a phased reduction in off-ART mortality, and seek additional to validate assumptions

On-ART mortality rates

- Due to data sparsity, it is assumed that those LTFU have the same CD4 distribution over time. If CD4 distribution of those LTFU has changed over time, it may account for the lack of clear time trend when including LTFU outcomes in the consolidated study, as the analysis is likely underestimating mortality from LTFU in the early years (Leigh Johnson, Mary-Ann Davies)

Recommendation: A sensitivity analysis should be conducted for CD4 distribution in those LTFU, targeting the inclusion of the new parameters in the 2021 estimates, pending leDEA partner sign-off.

Session 2: Births to HIV+ women and breastfeeding

Rob Glaubius presented updated estimates of breastfeeding duration for HIV+ women in sub-Saharan Africa. The estimates were derived from a pooled analysis of nationally representative household surveys, excluding all but the first three PHIA surveys due to changes in the questionnaire implemented after the first three PHIA surveys. It is believed that some mothers who were still breastfeeding were incorrectly coded as “formerly” rather than “currently” breastfeeding. This caused underestimation of breastfeeding patterns at young child ages (Fig 2). Using the modified breastfeeding duration patterns would leave to a 1.7% increase in child infections in SSA with <1% increases in CLHIV and paediatric AIDS deaths. The largest changes are seen in ESA, particularly in those countries that had PHIA surveys excluded from the analysis.

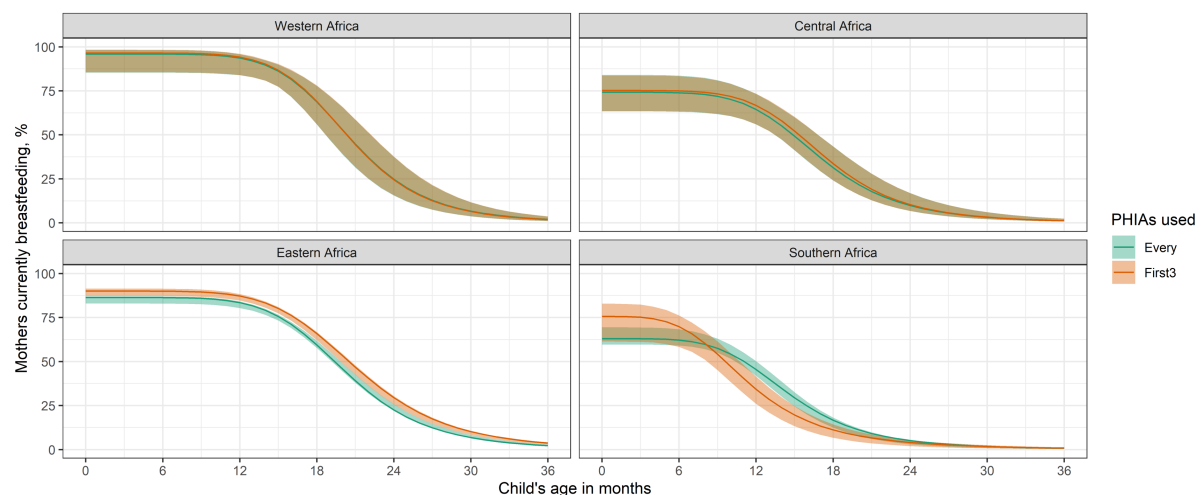


Figure 2: Proportion of mothers currently breastfeeding by infant age using all DHS surveys and all PHIA surveys (blue) or all DHS surveys and the first three PHIA surveys (red)

Caitlin Dugdale presented a meta-analysis of 126 studies vertical transmission rates stratified by viral load (117 on perinatal transmission, 9 on postnatal transmission). Relative to women with viral load <50 (transmission risk = 0.22%), perinatal transmission was 6 times more likely in women with 50<VL<1000, and 20 times more likely in women with unsuppressed viral loads. In sub-analyses by timing of treatment initiation, no cases were found in mothers with VL<50 when ART was started pre-conception, compared to ART started after conception with risk = 0.53%. As only 9 studies were available for postnatal transmission, stratifying by different viral load thresholds was not possible. Pooling studies using the study-defined thresholds of viral suppression, risk of postnatal transmission was ~5 times higher in mothers with detectable viral load, though data were scarce.

Estimates of viral load stratified transmission risks should be used to refine estimates of vertical transmission for women on ART, and do not apply them to untreated women with high viral loads. Further, data are sparse for women on-ART with high viral loads (>1000) and estimates are imprecise.

Sasi Jonnalagadda and Paul Stupp presented an analysis estimating post-partum HIV seroconversion using ANC testing histories in PHIA surveys and HIV testing at the point of survey. Women who reported a negative test at ANC and a positive test at point of survey had dates of seroconversion randomly imputed in the period between ANC and the survey.

Women with positive recency assay results had seroconversion dates randomly imputed in the last 130 days, corresponding to the recent infection assay window. Seroconversion rates ranged from 0.69 to 5.59 per 100 person-years in Kenya and eSwatini respectively.

Milly Marston presented an analysis of HIV acquisition in pregnancy. Studies have showed increased HIV incidence during pregnancy [2], and as Spectrum assumes constant incidence throughout pregnancy and post-partum, estimates of MTCT may be too low. The analysis used DHS data on sexual behaviour and serodiscordant partnership to estimate the monthly relative risk of HIV acquisition stratified by pregnant/in post-partum period and not pregnant women. Condomless sexual activity is higher in pregnant women during the first trimester, decreasing through second and third trimesters, followed by a large decrease at birth, recovering through the six months post-partum. There exists significant regional variation in this pattern. These estimates can be multiplied by survey-derived estimates of relative risk of having an HIV+ partner to produce relative risks of HIV acquisition between pregnant/postpartum and not pregnant women (Fig 3). Using the transmission risk in this analysis would lead to the majority of countries in SSA experiencing a 50-150% increase in new infections in pregnant/post-partum women compared to not pregnant women. These relative risks should not be used directly at population level, due to differences between pregnant/postpartum women and not pregnant postpartum women in the general population.

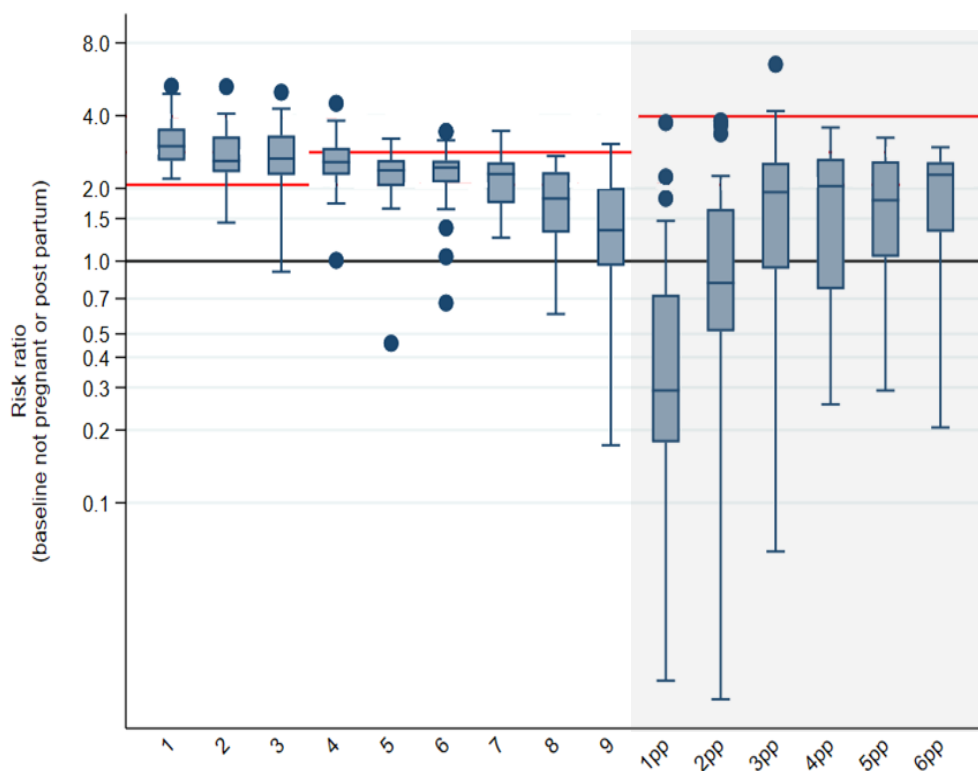


Figure 3: Relative risk of HIV acquisition in pregnant/post-partum women compared to not-pregnant women. Red lines are the relative risk of HIV acquisition per condomless coital act from Thomson et al. (2018) [2]

Leigh Johnson presented an update to a 2016 systematic review [3] on fertility in HIV-positive women by treatment status which underpins estimating births to HIV-positive women and assessing trends in antenatal HIV prevalence. Five studies have been published since a which report both increased and decreased fertility by treatment status, as found in the 2016

review. Though the research does not come to a consensus, four hypotheses are suggested for future research:

1. ART effects depend on parity
2. ART effects depends on marital status
3. ART effects depend on specific drugs
4. Contraceptive use affects ART uptake

Key points in discussion

- Using leDEA data to inform LTFU for pregnant women is difficult because of silent transfers, and the paucity of data outside of ESA.

References

- [1] UNAIDS Reference Group on Estimates Modelling and Projections, “Modelling Paediatric HIV and the need for ART,” 2019.
- [2] K. A. Thomson *et al.*, “Increased Risk of HIV Acquisition among Women Throughout Pregnancy and during the Postpartum Period: A Prospective Per-Coital-Act Analysis among Women with HIV-Infected Partners,” *J. Infect. Dis.*, vol. 218, no. 1, pp. 16–25, Jun. 2018, doi: 10.1093/infdis/jiy113.
- [3] S. Yeatman, J. W. Eaton, Z. Beckles, L. Benton, S. Gregson, and B. Zaba, “Impact of ART on the fertility of HIV-positive women in sub-Saharan Africa,” *Trop. Med. Int. Heal.*, vol. 21, no. 9, pp. 1071–1085, Sep. 2016, doi: 10.1111/tmi.12747.

**UNAIDS Reference Group on Estimates, Modelling, and Projections
Paediatric recommendations I Autumn meeting 2020**

Recommendation		Timeline
Session 1: Paediatric natural history and ART		
<u>Updates to the Spectrum paediatric model</u>		
<u>2020/21 estimates round</u>		2020/21 estimates
<ul style="list-style-type: none"> • Accept revised CD4% to CD4 count mapping • Do not implement a time trend in on-ART mortality, pending revision to leDEA on-ART mortality rates • Seek additional data before implementing off-ART mortality adjustment as ART scales up • Do not smooth mortality rates at the age 15 transition, pending changes to adult natural history model 	UNAIDS Reference Group	
<u>Longer term recommendations</u>		2021 and beyond
<ul style="list-style-type: none"> • Revisit additional strata for perinatally and non-perinatally infected 15-19 year olds • Paediatric ART initiation rates stratified by CD4 count • Estimate leDEA mortality and initiation rates by single year age 	Sophie Desmond Avenir Health Leigh Johnson	
<u>On-ART mortality rates</u>		November 2020
<ul style="list-style-type: none"> • Accept updated on-ART mortality rates pending: <ul style="list-style-type: none"> ○ Sensitivity analyses around CD4 at baseline in LTFU analyses ○ Review of Spectrum outputs with preliminary mortality estimates ○ Review by leDEA partners 	Reshma Kassanjee Avenir Health leDEA Consortium	
Session 2: Estimating births to HIV+ women and breastfeeding		
<ul style="list-style-type: none"> • Accept revised breastfeeding parameters, omitting PHIA surveys that use the more recent question variant • Review data on maternal viral load as programmatic data become available • Review EID positivity data and consider for incorporation into Spectrum • No systematic scaling of HIV incidence is recommended in pregnant women • No adjustment to fertility of HIV+ women by treatment status is recommended • Revisit fertility rate ratios following revised natural history model 	UNAIDS Reference Group UNAIDS Reference Group Rob Glaubius	2020/21 estimates 2021 and beyond 2021 and beyond

UNAIDS Reference Group on Estimates, Modelling and Projections
Paediatric Reference Group meeting
 9th October 2020

All times are GMT+1 (London)

14.00	20	Welcome and introductions Meeting objectives	Mary Mahy / Martina Penazzato Leigh Johnson
14.20	20	The paediatric model in Spectrum	John Stover
Session 1: Paediatric natural history and ART (chaired by Leigh Johnson)			
14.40	45	Updates to the paediatric natural history model <ul style="list-style-type: none"> - Mapping from CD4% to CD4 count - Updated baseline CD4 and age distributions from leDEA - Smoothing the paediatric-to-adult natural history model - Adjusting mortality in untreated children at high ART coverage - On-ART age distributions 	John Stover
15.25	20	Paediatric on-ART mortality: updated analyses from leDEA	Reshma Kassanje
15.45	40	Discussion	
16.25	10	Break	
Session 2: Estimating births to HIV+ women and breastfeeding (chaired by Jeff Eaton)			
16.35	20	Breastfeeding differences between DHS and PHIA	Rob Glaubius
16.55	15	MTCT and maternal viral load	Caitlin Dugdale
17.10	15	Estimating fertility in HIV+ by treatment status	Leigh Johnson
17.25	15	Estimating post-partum incidence using ANC testing history	Sasi Jonnalagadda Paul Stupp
17.40	15	HIV incidence during pregnancy and the post-partum period	Milly Marston
17.55	35	Discussion & recommendations <ul style="list-style-type: none"> • LTFU in pregnancy and post-partum 	Leigh Johnson
18.30	CLOSE		