Modelling Paediatric HIV and the need for ART

Report and recommendations from a meeting of the UNAIDS Reference Group on Estimates, Modelling, and Projections
Montreux, Switzerland - 11th October 2019

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 2019

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 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 thematic meeting on *Modelling Paediatric HIV and the need for ART* in Montreux, Switzerland from 11th October 2019. The meeting featured presentations and group discussion to generate consensus recommendations. The programme was divided into the following sessions:

1. Estimating births to HIV+ women
2. Transmission rates and breastfeeding
3. Estimation of the paediatric treatment cascade

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, resp ectively.

The Spectrum paediatric model and 2018/19 paediatric estimates

Mary Mahy presented an overview of the changes to the Spectrum paediatric model implemented for the 2018-19 estimates round, the impact of those changes, and outstanding issues. The stacked bar chart presenting sources of mother-to-child transmission (MTCT) and antenatal care (ANC) HIV testing graphs prompted estimates teams to scrutinise data inputs, and will continue to encourage programmatic data collection to inform parameters currently derived from surveys or regional assumptions (e.g. treatment dropout rates and breastfeeding duration). The fertility rate ratio local adjustment factor fit to ANC-RT data varies widely, which may indicate data quality issues within routine testing data. Untreated survival of children infected with HIV remains an area of uncertainty. Cause of death data from the Child Health and Mortality Prevention Surveillance (CHAMPS) study may offer novel source of validation.

The Spectrum paediatric model estimates new infections and children living with HIV based on estimates of HIV-positive pregnant women and systematic reviews of MTCT rates, and is not calibrated to setting-specific paediatric data during model fitting. Direct estimates of paediatric prevalence from PHIA surveys are similar to those estimated from Spectrum, and could be used as calibration rather than validation data. In several countries, however, in order to make the Spectrum and PHIA point estimates match, substantial changes to key parameter inputs about prevalence among pregnant women, mother-to-child transmission rate, or paediatric survival with HIV would be required. As differences between Spectrum and PHIA are small, it is not recommended that changes be made to paediatric model calibration. Remaining differences may be due to nosocomial transmission. Survey data with serodiscordant mothers and children within DHS data may indicate the scale of such transmission, though evidence of the 'adoption effect' makes investigation of this difficult. MTCT rate is stratified by on and off ART and by treatment duration. Maternal viral load is not currently taken into account, and uncaptured treatment adherence will influence transmission rates. PEPFAR have recently started disaggregated VL data by pregnancy status, and data will be available through 2020. The fertility rate ratio (FRR) local adjustment factor, currently fit to ANC routine testing (ANC-RT) data, could be calibrated to both ANC-RT and paediatric prevalence data which may improve paediatric estimates.

Session 1: Estimating births to HIV$^+$ women

Spectrum uses the number of HIV$^+$ women giving birth to calculate PMTCT need. In several countries, the number of reported ANC visits exceeds the number of projected births. Failing to account for late term miscarriage (i.e. after first ANC visit, median 16 weeks term) could account for some of the discrepancy. Studies indicate that around 20% of pregnancies miscarry, but only around 20% of these occur after 16 weeks, and so Spectrum may be underestimating the number of pregnancies among HIV positive women by 2-3%. The discrepancy between births and ANC programme data, however, is often much larger (10-20%). A global miscarriage adjustment without country-specific data was not recommended.

Unrecorded retesting in antenatal settings introduces bias into ANC-RT prevalence data and, through recording of ART status at ANC, impacts on MTCT transmission rates. Katie Battey presented PEPFAR's ongoing efforts to improve monitoring of pregnant and

breastfeeding women being retested. A new testing indicator, HTS_TST_PMTCT, has been introduced this year, which provides a modality for recording re-testing after 1st ANC or during breastfeeding. Younger pregnant women, who are likely to be more recently infected, were more likely to be diagnosed with HIV at the first ANC visit or at retesting after the first ANC visit. Spectrum will include inputs for ANC retesting in the programme entry screen, and will be visualised as part of the ANC cascade graphs.

In concentrated epidemic settings, HIV prevalence among pregnant women is calculated in Spectrum through the sex ratio of infection, age pattern of HIV prevalence, and fertility rate ratios. The sex ratio of infection cannot be calculated as in generalised epidemics due to the lack of household surveys, and is derived from EPP or case reports. CSAVR will fit to sex disaggregated diagnosis data for the upcoming estimates round, and a tool will be developed to fit age disaggregated programme and mortality data to derive IRRs in concentrated epidemics. Twenty-six of 116 concentrated epidemic countries used the ANC-RT fitting tool to produce a FRR local adjustment factor in 2018-19 estimates. In the 2020 estimates round, concentrated epidemic countries will be encouraged to bring ANC data to workshops to improve estimates of HIV prevalence among pregnant women. Concern remains around the coverage and representativeness of ANC-RT data in concentrated settings. Where available, paediatric vital registration data should be analysed to validate maternal prevalence and vertical transmission rates.

Session 2: Transmission rates and breastfeeding

Mary Mahy reported the conclusions from the UNAIDS/UNICEF/WHO MTCT Measurement Technical Meeting (September 2019), noting that direct measurement of MTCT fails to capture:

- women outside of programmes;
- seroconversions during breastfeeding; and
    - Missed from facility-based studies
- child death occurring between birth and surveys
    - Missed from community studies

Consequently Spectrum estimates a higher MTCT rate than all studies, and the timing and setting of studies restrict their comparability.

Caitlin Dugdale presented an update to the previously conducted literature review of treatment retention of new treatment initiators during breastfeeding and pregnancy, including Option B+ data inputs and further investigating loss to follow up and clinic transfers. Data indicate that (Fig 1):

- 80% of women are retained on treatment from 1st ANC to delivery.
- Of those, 80% of those are retained at 6 and 12 months
- Of those, 85% are retained at 24 months.

Retention probabilities can be adjusted for transfer rates, and a sensitivity analysis is recommended using transfer rates in the wider on ART population rather than specifically in

pregnant women. Additionally, due to the small number of studies in some regions, global rather than regional retention rates should be used at 1-12 and 13-24 month cut-off intervals.

Region	Delivery	1-6 months	7-12 months	13-24 months	%/mo 12-month	%/mo 24-month
WCENA	N/A	44 (14, 74)	82 (53, 100)	31 (0, 72)	1.7%	4.8%
Eastern Africa	73 (54, 91)	74 (66, 81)	68 (52, 84)	69 (39, 95)	3.1%	1.5%
Southern Africa	79 (67, 90)	82 (77, 87)	81 (71, 91)	69 (51, 84)	1.7%	1.6%
LAC	83 (70, 94)	73 (70, 76)	54 (50, 57)	n/a	5.0%	n/a
WCA	86 (82, 91)	83 (68, 95)	77 (72, 82)	73 (67, 79)	2.1%	1.3%
Overall	**80 (72, 87)**	**80 (70, 90)**	**80 (71, 89)**	**68 (48, 86)**	**1.8%**	**1.6%**
2018 estimate	*80*	*77*	*74*	*68*	*n/a*	*1.6%*

Figure 1: ART retention rates during pregnancy and breastfeeding. The denominator for the retention rate at delivery is women initiated on ART at 1st ANC, and the denominators for retention rates at 6, 12, and 24 months are women initiated on ART at 1st ANC who remain on treatment at delivery.

Breastfeeding duration inputs into Spectrum are not stratified by maternal HIV status. Rob Glaubius presented an analysis of household survey data (DHS, AIS, PHIA) to determine whether breastfeeding duration differs by HIV status. HIV-positive women were found to breastfeed for shorter durations (Fig. 2), resulting in a 10% reduction in the estimated number of new child infections across 10 countries in sub-Saharan Africa. It is noted that DHS and AIS surveys do not include data about ART usage. Therefore the HIV-positive group is an average of treated and untreated populations. Model-based estimates that use multiple surveys are preferred to those based on the last survey alone.

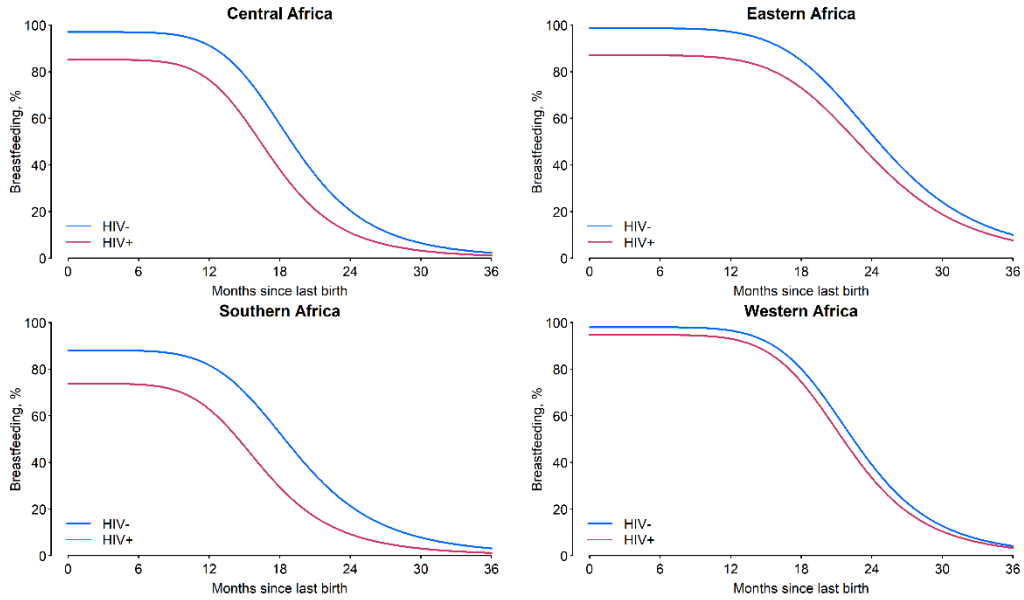

Figure 2: Breastfeeding duration regional averages by HIV status in 2015

Spectrum currently assumes uniform transmission risk over the breastfeeding period. Leigh Johnson presented a literature review which found evidence for both increasing and decreasing risk over the period. It was noted that much of the evidence dates from the pre-ART era, and maternal ART/PMTCT programmes may influence the relationship between risk and breastfeeding duration. It was not recommended for Spectrum to implement differential risk during breastfeeding.

Session 3: Estimation of the paediatric treatment cascade

Katie Battey presented a comparison of paediatric treatment numbers in Spectrum and PEPFAR programme data. In several countries, Spectrum estimates more 0-4 year olds and fewer 10-14 year olds on ART compared to PEPFAR data. This may suggest that paediatric survival is too low; leading to too few older children on treatment. Updating ART initiation rates, currently a single rate for sub-Saharan Africa, to regional rates may also better align Spectrum estimates to PEPFAR data.

Existing parameter estimates for mortality of children on ART utilised IeDEA Collaboration data up to 2014. Reshma Kassanjee presented an updated mixed effects model using data to 2017. Pending results of a comparison between existing and updated mortality rates, the new rates were recommended to be incorporated into Spectrum for the 2019/20 estimates round. A time varying rate by 5-year periods was recommended for implementation, with a smooth age pattern to be implemented alongside other natural history model changes planned for 2020. IeDEA tracing studies enabling adjustment for CLHIV on ART who are LTFU will be available in 2020 for the subsequent estimates round.

Estimates of paediatric knowledge of status (KOS) is frequently requested from UNAIDS, particularly following the use of the shiny90 model to estimate adult KOS. The default estimate of paediatric KOS is equal to treatment coverage, from which 26 countries deviated, suggesting additional data are available. The Thembisa model in South Africa estimates paediatric KOS, but relies heavily on routine testing data which are less consistently available in other settings. In the short term, consideration of the gap between early infant diagnosis and paediatric treatment data as a proxy indicator for knowledge of status is recommended.

Meeting recommendations

Recommendation/Action Item	Lead Person(s)	Proposed timeline
Direct calibration of paediatric estimates to paediatric data		
• Mortality at age 14 should match mortality at age 15 in adult natural history model. Review smoothing of Weibull distributions	Avenir Health	May 2020
• Ascertain whether CHAMPS mortality data can be used for validation	Mary Mahy	December 2019
• Consider the role of iatrogenic transmission ○ DHS and PHIA treatment of HIV+ child, HIV- mother		2020
• Follow CEPAC and PEPFAR progress on evaluating MTCT rate by viral load and disaggregation of viral load by pregnancy status	UNAIDS Reference Group Secretariat	Ongoing
• Consider fitting FRR local adjustment factor to ANC-RT and paediatric prevalences jointly	Avenir Health	May 2020
Session 1: Estimating births to HIV+ women		
ANC retesting		
• Include ANC retesting in ANC testing cascade data inputs and ANC stacked bar	Avenir Health	1st November 2019
• PEPFAR to conduct chart reviews to ascertain high quality data about HIV status at first ANC visit	Katie Battey	2020
Prevalence in pregnant women in concentrated epidemics		
• Encourage countries to enter ANC-RT data so that FRR fitting can be used	UNAIDS	2019/20 estimates round
• Validate estimated paediatric deaths with vital registration data ○ Contact Neff Walker for data availability		May 2020
Miscarriage after 1st ANC		
• No adjustment to births estimate recommended		
Session 2: Transmission rates during pregnancy and breastfeeding		
Retention during pregnancy and breastfeeding		
• Conduct sensitivity analysis of transfer rates in the wider "on ART" population	Caitlin Dugdale	October 2019
• Use global retention probabilities rather than regional		
• Spectrum to implement transmission probabilities by 1st and 2nd year post-partum	Avenir Health	1st November 2019
• Decision on transfer adjustment to transmission probabilities and adoption of new probabilities to be taken after sensitivity analysis	UNAIDS Reference Group	1st November 2019

Breastfeeding duration by HIV status		
• Analyse duration differences by self-reported testing and treatment in DHS data	Rob Glaubius	1st November 2019
• Renew analysis of breastfeeding duration by ART status	Jeff Eaton/Rob Glaubius	2020
• Recommend time varying estimates based on multiple surveys		
• Recommend using breastfeeding duration adjustment with single survey as implemented for 2018/19 estimates as fallback option		
Transmission risk by breastfeeding duration		
• Implementing changing risk over time is not recommended		
Session 3: Paediatric treatment cascade estimation		
Age at ART initiation		
• Include comparison with CLHIV and TX_NEW in Spectrum validation with PEPFAR data	Katie Battey	November 2019
• Consider using regional IeDEA ART initiation rates rather than single SSA rate	Leigh Johnson	October 2020
• Consider use of age pattern of ART initiation data to inform prevalence estimates	Avenir Health	
Paediatric mortality in IeDEA		
• Compare CD4 count and CD4 percent with existing distribution in Spectrum. ○ CEPAC to share additional data	Reshma Kassanjee Andrea Ciaranello	October 2019
• Compare updated rates with existing Spectrum defaults	Reshma Kassanjee	October 2019
• Recommend monotonic relationship between mortality and CD4 count		
• Implement changing mortality rates by 5 year periods	Avenir Health	1st November 2019
• Implement smooth age pattern following updated IeDEA analysis	Avenir Health	2020
• Incorporate paediatric tracing study data in mortality estimates	Leigh Johnson/Mary-Ann Davies	2020
Estimation of paediatric knowledge of status		
• Investigate gap between early infant diagnosis and paediatric treatment data as proxy indicator for knowledge of status	Leigh Johnson	2020

Appendix I – Meeting agenda

Time	Duration (mins)	Topic	Presenter(s)/ Lead Discussant
9.00	30	Welcome and introductions Meeting objectives and overview Review of 2019 estimates and outstanding challenges	Leigh Johnson Mary Mahy
9.30	15	Overview of Spectrum paediatric model in 2019	John Stover
10.05	45	Direct calibration of Spectrum estimates to paediatric data: • Survey testing and diagnosis data • Age-specific ART & VLS programmatic and survey data Discussion	John Stover All
10.50	15	Coffee	
Session 1: Estimating births to HIV+ women (chaired by Leigh Johnson)			
11.05	15	Stillbirths after 1st ANC visit	John Stover
11.20	20	ANC retesting in PEPFAR data	Katie Battey
11.40	20	Prevalence estimates amongst pregnant women in concentrated epidemics	John Stover
12.00	20	Discussion	
12.20	60	Lunch	
Session 2: Transmission rates and breastfeeding (chaired by Martina Penazzato)			
1.20	30	Transmission rate meeting results	Mary Mahy
1.50	20	Retention during breastfeeding and pregnancy	Caitlin Dugdale
2.10	20	Differential breastfeeding duration by HIV status	Rob Glaubius
2.30	10	HIV transmission by breastfeeding duration	Leigh Johnson
2.40	20	Discussion	
Session 3: Estimation of the paediatric treatment cascade (chaired by Mary Mahy)			
3.00	20	Age at ART initiation	Katie Battey
3.20	20	Coffee	
3.40	20	Paediatric ART mortality in IeDEA	Reshma Kassanjee
4.00	20	Review of methods and assumptions for paediatric first 90 estimates	Kim Marsh
4.20	20	Discussion	
4.40	20	Meeting summary and recommendations	Mary Mahy
5.00	CLOSE		

Appendix II – Participant list

John Stover	Avenir Health
Rob Glaubius	Avenir Health
Ray Shiraishi	Centres for Disease Control and Prevention
Katie Battey	Centres for Disease Control and Prevention
Tim Brown	East West Center
Jeff Eaton	Imperial College London
Oli Stevens	Imperial College London
Deepa Jahagirdar	Institute for Health Metrics and Evaluation, Seattle, USA
Caitlin Dugdale	Massachusetts General Hospital, USA
Andrea Ciaranello *	Massachusetts General Hospital, USA
Newton Chagoma	Ministry of Health, Malawi
Irum Zaidi	PEPFAR
Ian Wanyeki	UNAIDS, Geneva, Switzerland
Keith Sabin	UNAIDS, Geneva, Switzerland
Kim Marsh	UNAIDS, Geneva, Switzerland
Mary Mahy	UNAIDS, Geneva, Switzerland
Peter Ghys	UNAIDS, Geneva, Switzerland
Aleya Khalifa *	UNICEF, New York, USA
Leigh Johnson	University of Cape Town
Reshma Kassanjee	University of Cape Town
Mary-Ann Davies *	University of Cape Town
Morkor Newman	World Health Organization, Geneva, Switzerland
Martina Penazzato	World Health Organization, Geneva, Switzerland

* Remote participants