Paediatric HIV estimates

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

15 May 2023

Stellenbosch, South Africa

REPORT & RECOMMENDATIONS

Index

Abbreviations

ANC	Antenatal Clinic
AP	Asia Pacific
ART	Antiretroviral Therapy
CDC	US Centers for Disease Control and Prevention
CLHIV	Children living with HIV
CSAVR	Case Surveillance and Vital Registration
EPP	Estimation and Projection Package
ESA	East and Southern Africa
FRR	Fertility rate ratio
IeDEA	International Epidemiology Databases to Evaluate AIDS
LTFU	Loss to Follow Up
MENA	Middle East/North Africa
PEPFAR	President's Emergency Plan for AIDS Relief
PHIA	Population-based HIV Impact Assessment
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
SACEMA	South African Centre for Epidemiological Modelling and Analysis
SSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
WCA	West and Central Africa
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 SACEMA, Imperial College London and the University of Cape Town. Participants of the meeting are listed at the end of this document (**Appendix B**).
Cari van Schalkwyk, May 2023

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, Imperial College London, and the University of Cape Town.

Meeting Overview

The UNAIDS Paediatric Reference Group meeting was a hybrid meeting held on 15th of May 2023. The meeting featured presentations and group discussions to generate consensus recommendations, divided into the following 3 sessions:

Session 1 – Estimating births to women living with HIV
Session 2 – Estimates of children living with HIV and ART coverage
Session 3 – Mortality assumptions.

This report presents a summary of the meeting presentations and discussions that underpin recommendations by the Reference Group. The presentations are available to meeting participants (**Appendix B**) at www.epidem.org (others, please contact the Secretariat via epidem@sun.ac.za). The final recommendations can be found at the end of this report. The recommendations (**Appendix A**) drafted at these meetings provide UNAIDS with guidance on generating HIV estimates, review current approaches, and identify required data to further improve HIV estimates. The meeting agenda and objectives are in Appendix C. 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.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.

Introduction

Mary Mahy welcomed meeting participants and led introductions of all meeting participants. She emphasised the persistent challenges associated with estimating HIV indicators among children. ART coverage remains considerably lower in children compared to adults and the number of children living with HIV is declining each year, making it difficult to measure. Mahy highlighted that HIV programming for children keeps evolving as children age out, requiring continual review of methodologies and estimates.

Mahy briefly reviewed 2023 global estimates of births to women living with HIV, new vertical HIV infections, numbers of children living with HIV (CLHIV) and AIDS related deaths among children aged 0 to 14 years, and compared them to the 2022 estimates showing no substantial changes. Spectrum estimates of prevalence among children are consistent with data from national PHIA surveys across 12 SSA countries conducted between 2015–2019.

Mahy then highlighted some of the current and future challenges in paediatric HIV estimation, focusing on SSA countries with generalized epidemics:

- Calibrating to child prevalence from household surveys is not feasible because with falling MTCT rates, a huge sample size would be needed to measure prevalence precisely.
- There is a lack of programme and empirical data on retention on treatment of mothers at delivery and during breastfeeding.
- Reported number of pregnant women receiving ART do not capture variations in viral suppression over course of pregnancy.
- Data are limited to validate assumptions about mortality of children with HIV.
- Interpreting prevalence measured in routine testing of pregnant women from ANC is challenging, given an increasing share of mothers already known as HIV infected and in care and therefore not retested.

The meeting objectives were:

Session 1: Estimates of births to women living with HIV. This session aimed to review assumptions on retention versus drop-out of mothers from ART during pregnancy and consider possible biases in HIV prevalence from ANC.

Session 2: Estimates of children living with HIV and Treatment coverage. This session aimed to review data and Spectrum assumptions on treatment interruption rates among children, age at ART initiation and breastfeeding patterns from PHIA studies.

Session 3: Mortality assumptions. This session reviewed the impact of mortality assumptions on CLHIV numbers and review mortality assumptions in the first year of life.

John Stover presented an **overview of Spectrum child model and LTFU assumptions**. Perinatal and post-natal infections are estimated by the inputs and processes shown in Figure 2. Data on the numbers of women of reproductive age, fertility rates, HIV prevalence and incidence among pregnant women, and the fertility rate reduction due to HIV are combined to estimate births to women with HIV. Combined with PMTCT coverage by regimen, retention at delivery, and perinatal transmission probabilities by regimen, number of perinatal infections are estimated. Data on breastfeeding duration among women with HIV, maternal monthly drop-off from ART option, and postnatal transmission probabilities by ***regimen*** are combined with births to women with HIV to estimate post-natal infections.

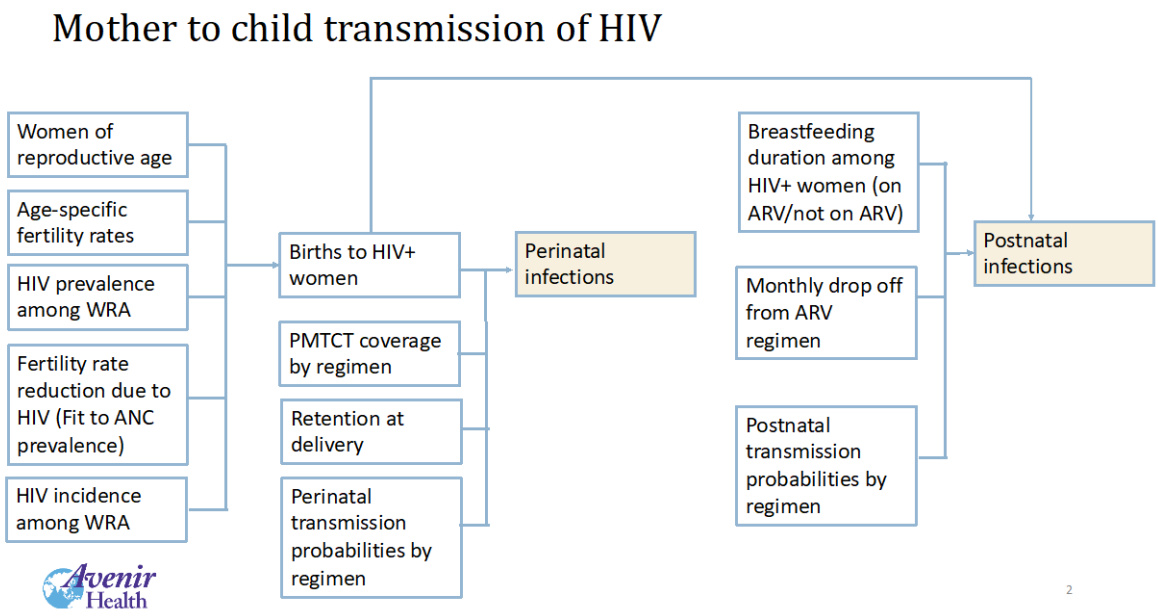

Figure 1: The Spectrum child model

Overall MTCT and CLHIV estimates are determined by Spectrum outputs for HIV prevalence and incidence among adult women, which are estimated from national surveillance data using EPP, CSAVR or AEM. To estimate the number of births among women with HIV, time-varying fertility rate ratios are applied to the estimated number of women of childbearing age living with HIV. After adjusting for age, sex and relative fertility, countries can choose to fit and apply a country-specific local adjustment factor, to improve the model fit for prevalence in pregnant women from national ANC data, considering country specific differences in fertility. After calculating the number of pregnant women with HIV, user entered PMTCT programme data are used to estimate PMTCT coverage, and alongside breastfeeding rates, the MTCT is estimated by applying a (global default) transmission probabilities for different phases of pregnancy and infancy (with/without early or late PMTCT, breastfeeding and postnatal prophylaxis).

For paediatric ART, Stover noted that Spectrum calculates new ART initiations to match the total program-reported number of children on ART, by five-year child age groups, where age stratified data are available. New initiations are drawn proportionally from all categories of CD4 and of timing of infection. Those who drop off ART are returned to the off-ART CD4 category from which they initiated ART. They are allocated to timing of infection categories according to the distribution of all CLHIV not on ART. Since the number of children on ART is fixed by the programme data, this number is not affected by the rate of LTFU. However, LTFU affects mortality, the percentage of ART patients in the first year of treatment, and the age distribution of children on ART.

Session 1 – Estimating births to women living with HIV

The objective of the session was to review default assumptions on ART retention versus drop-out during pregnancy and consider possible biases in HIV prevalence from ANC. This session was chaired by Leigh Johnson.

Mary Mahy presented a **brief review of retention on ART among women in 2023 estimates**. She noted that in SSA, 6% of pregnant women who started ART during current pregnancy were assumed to have stopped treatment during the period of risk and this led to about 30,000 vertical transmissions (23% of all new child infections). ESA has strong empirical data on ART retention during pregnancy that informed default values for all regions in Spectrum (80%, throughout time and regardless of whether ART was started during or before the current pregnancy – literature review summarized below). However, ESA countries in 2023 entered their own estimates of much higher retention. WCA countries mostly retained the default value and may need some encouragement to triangulate this with their programme data. It is critical to know why some countries assume 100% retention and some countries assume less than 80% retention, and to re-review the literature and update or stratify the default to reflect any real variations.
Very few countries have changed the default estimates of treatment interruption during breastfeeding, which is more difficult to measure from programme data.

Caitlin Dugdale summarized and updated the global literature **review of LTFU** (as opposed to 'continued engagement in care') during breastfeeding and pregnancy. The review focused on studies published worldwide between 2012 and 2019, excluding studies from before the adoption of Option B+ and/or Universal Test and Treat, and studies limited to a particular patient sub-population. 54 studies were included in the 2019 review, most from ESA. Importantly, the definition of LTFU varied considerably across eligible studies. Data indicate that (Fig 2):

- 78% of women were retained on treatment from 1st ANC to delivery.
- Of those, 80% were retained at 6 and 12 months after birth.
- Of those, 85% were retained at 24 months after birth.

These probabilities were not yet adjusted for silent transfer of women across clinics (known transfers between clinics were included in these probabilities), so true retention may be higher. A sensitivity analysis on transfer assumptions could use transfer rates observed in the wider on-ART population, when lacking such data for pregnant women. Due to the small number of studies in non-SSA regions, Dugdale recommended to use the same retention rates globally (not regional) retention rates, stratified only between 1-12- and 13–24-month follow-up after birth intervals.

Region	Delivery	1-6 months	7-12 months	13-24 months	%/mo Months 1-12	%/mo Month 13+
WCENA	N/A	44 (14, 74)	82 (53, 100)	31 (0, 72)	1.7	5.7
Eastern Africa	73 (54, 91)	74 (66, 81)	68 (52, 84)	71 (39, 98)	3.1	0
Southern Africa	79 (67, 90)	82 (77, 87)	81 (71, 91)	68 (54, 82)	1.7	1.1
LAC	75 (73, 76)	73 (70, 76)	66 (46, 85)	n/a	3.4	n/a
WCA	86 (82, 91)	83 (68, 95)	77 (72, 82)	73 (67, 79)	2.1	0.4
Overall	**78 (70, 86)**	**80 (70, 90)**	**80 (71, 88)**	**68 (48, 86)**	**1.9**	**1.1**

Figure 2: 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.

In 2023, Dugdale performed a similar literature search to the review in 2019 and found 92 new references (76 from ESA) with data on maternal engagement in care. These new data do not overcome the limitation of the previous review of heterogeneity in LTFU definitions and disproportionately conducted in SSA but may provide more information on silent transfers and enable separation of rates between ART initiation during or before pregnancy (separate parameters in Spectrum but currently still with the same single 80% assumption).

The key points during discussion:

- The majority of data in Dugdale's review that informed the defaults were from ESA, yet nearly all the countries in ESA changed retention to higher values. This necessitates in-depth discussion with countries about the data that informed their decisions.
- Andreas Jahn mentioned that although there is good indication in Malawi that retention has increased post dolutegravir roll-out (at delivery and during breastfeeding), it is hard to translate this to monthly drop-out rate and therefore Malawi (within ESA, a country with relatively better program outcomes and data, across HIV and TB) has used the defaults.
- It was recommended that when the 2019 is updated, focus should be on extracting data on silent transfer/tracing; distinguishing retention rates of women on ART before pregnancy from women initiating ART during pregnancy; and assessing evidence for changes in retention over time.

Jeff Eaton presented on the **association between HIV prevalence and access to ANC attendance and testing in WCA.** In Spectrum, HIV prevalence among pregnant women is calibrated to observed prevalence at antenatal clinics, assuming that HIV prevalence at ANC testing represents prevalence among all pregnant women. In WCA, ANC attendance and testing coverage is lower than in ESA. There are 3 possible reasons why lower ANC

attendance and testing coverage may lead to overestimation of HIV prevalence among all pregnant women:

1) Ecological confounding: higher ANC access and ANC HIV testing in locations that also have higher HIV prevalence (e.g., in most countries in WCA, ANC attendance is much higher in urban areas).
2) HIV testing prioritised in locations with higher HIV burden, and women suspected as being higher risk.
3) Incomplete ANC testing (not testing all HIV negative women), resulting in disproportionately capturing HIV positive women already on ART (who are not tested for HIV and appear in both numerator and denominator of ANC HIV prevalence calculation).

Spectrum in most SSA calibrations estimates lower ART coverage among pregnant women than among adults aged 15-49. This is expected because pregnant women are younger and likely to be more recently infected. However, this difference is greater in WCA than in ESA, indicating possible overestimation of HIV prevalence among pregnant women in WCA.

To assess the association between subnational (cluster-level) HIV prevalence and ANC testing probability (hypothesis 1 above), the outcome "HIV tested at ANC during the last pregnancy" restricted to HIV negative women was investigated using a logistic mixed effect model. This analysis used data from 25 household surveys (DHS and PHIA) with HIV testing conducted between 2015 and 2019. The main exposure of interest, HIV prevalence by geographical/sampling cluster among females aged 15-49 years, was adjusted for 5-year age-group; survey-level random intercepts and random slopes were included to adjust for country and time differences in ANC attendance/testing and HIV prevalence. The model did not adjust for rural/urban differences.

In WCA countries, analysis show 1%-pt higher cluster HIV prevalence is associated with 3.3% (95% CI 1.6–4.9%) higher odds of ANC testing among HIV negative women. In ESA countries, 1%-pt higher cluster HIV prevalence is associated with 2.5% (95% CI 1.0–4.1%) higher odds of ANC testing. This confirms the hypothesis that ANC testing in ESA and especially WCA is biased toward higher-HIV locations, and so Spectrum's pregnant women prevalence calibrations to routine ANC data probably inflated across WCA; however the potential magnitude of such bias was not quantified.

To improve Spectrum calibrations in WCA, Eaton recommended reviewing programme data on ANC attendance and testing, including the availability of ANC testing at facilities, at subnational level.

Ian Wanyeki presented on **challenges measuring HIV prevalence among pregnant women.** These include:

- Different approaches to data entry: summing district-level numbers inputted to Naomi often differ from national totals entered to AIM > Program, Statistics, and (the sum of urban and rural subpopulations in EPP)
- Incorrect indicators were extracted from DHIS
- Indicators not recorded in national DHIS/HMIS, notably numbers of known positives
- Inability to categorize data by urban versus rural
- Prevalence incorrectly calculated (possibly due to excluding known positives, known negatives, including re-testers, etc)

- Reporting does not reliably identify first test at ANC vs. follow-up (repeat) tests
- Systematic double counting of HIV negative tests
- Inability to de-duplicate women attending (i.e., transferring between) multiple facilities
- Stock outs of test kits disrupting testing services and coverage and sometimes shifting, retargeting testing coverage to higher-risk regions and patients
- Implausible data entries such as: number of ANC1 visits surpassing births, sharp year-on-year changes in prevalence or numbers of clients (reporting issues, stock-outs, etc.)

The challenge of questionable routine ANC prevalence data in some countries remains. For example, in Gaza Province, Mozambique where ANC prevalence decreased by 13% within 6 years or Haiti, where ANC prevalence is increasing in contrast to declines in household survey prevalence.

Possible solutions include having one single disaggregated data source, i.e., all required ART and ANC data is entered as part of the requirements for the Naomi model and this data is automatically aggregated upwards and used in the national Spectrum file. It was also suggested that countries move away from using the urban/rural split in EPP and have only one, national file. Updated guidance on site selection for ANC trend data was recommended.

Johnson mentioned his group had simulated that in South Africa, a significant proportion of pregnant women with HIV were recently infected (in the last year), implying that recent changes in incidence trends might be disproportionately reflected in antenatal prevalence compared to prevalence among all women. Andreas Jahn confirmed that also in Malawi, declines in prevalence mirror age-specific declines in incidence.

Session 2 – Estimates of children living with HIV and ART coverage

The objective of this session, chaired by **Jeff Eaton**, was to review Spectrum model assumptions about ART interruption and re-initiation and impact on paediatric HIV estimates.

Jimmy Carlucci presented on a **literature review to inform default paediatric treatment interruption rate in Spectrum**. He acknowledged the limited information about ART interruption rates in children, but that some inferences can be made from studies of LTFU in children (i.e., the sum of interruption and deaths). LTFU rates among children on ART are high, at around 25% after two years, in Fox & Rosen systematic review in LMIC (2015). Of those not retained, 37% were known to have died. In a similar study by Carlucci et al. in 2019, including attrition from ART and pre-ART HIV care, the authors found that most of the attrition happened in the first six months, reaching 23% by 3 years. Carlucci showed results from several tracing studies where known interruption ranged from 26-55% (~20% of those LTFU could not be traced).

This review show that there is limited paediatric data on ART interruption, and that available tracing studies are mostly small-scale, restricted to African cohorts and varying in the estimated true disengagement from care/ART interruption. Results suggest a trend toward falling disengagement rates in recent years, perhaps with more silent transfers. Implementation of unique identifiers and national registries will be needed to fill this knowledge gap. In the meantime, more community tracing studies correcting LTFU rates for

undocumented mortality and silent transfers are needed to inform ART interruption assumptions.

Patricia Agaba presented on **PEPFAR programme data on adult and child treatment interruption.** Data completeness of interruption in treatment (ITT) varies so results should be interpreted with care. PEPFAR defines interruption in treatment (IIT) as no clinical contact for 28 days after the last scheduled appointment or expected clinical contact. This is equivalent to the WHO concept of loss to follow up (LTFU) and therefore could include unknown deaths and silent transfers. In general, % ITT is higher for settings with more complete reporting. Agaba showed that for Q2 2022 - Q1 2023 IIT was 2-2.5% per quarter for adults and 2.2-2.8% for children. Total % IIT by age in 2022 for various countries is shown in Figure 3, indicating highest IIT among children <5.

Total % IIT by Age, CY22

Total % IIT by Age

Note that data is presented by OU, not country

	<5 yrs				5-14 yrs				15+ yrs			
OU	2022 Q2	2022 Q3	2022 Q4	2023 Q1	2022 Q2	2022 Q3	2022 Q4	2023 Q1	2022 Q2	2022 Q3	2022 Q4	2023 Q1
Angola	14.87%	10.66%	9.23%	15.25%	11.49%	11.01%	8.90%	13.11%	5.50%	6.61%	6.55%	10.47%
Asia Region	6.84%	4.30%	5.66%	6.08%	3.71%	2.34%	2.85%	1.91%	2.90%	2.79%	3.23%	2.65%
Botswana	0.61%		1.89%	1.26%	0.98%	0.80%	1.60%	1.04%	0.54%	0.70%	0.60%	0.57%
Burundi	0.66%	0.33%	2.36%	1.29%	1.32%	0.50%	0.59%	0.92%	1.63%	1.19%	1.36%	1.39%
Cameroon	1.54%	1.68%	1.98%	2.14%	1.02%	0.72%	1.08%	0.74%	1.25%	0.95%	0.97%	1.14%
Cote d'Ivoire	1.48%	2.11%	2.41%	2.69%	1.31%	2.12%	1.59%	2.11%	1.81%	1.82%	1.72%	1.73%
Democratic Republic of the Congo	1.25%	0.97%	1.55%	1.35%	0.95%	0.79%	1.55%	1.75%	0.73%	0.71%	1.21%	1.45%
Dominican Republic	6.45%	6.45%		10.53%	4.67%		4.20%	7.25%	7.82%	5.87%	4.82%	5.32%
Eswatini	5.02%	2.84%	2.73%	3.87%	2.79%	4.27%	1.92%	3.58%	3.96%	4.27%	2.30%	3.59%
Ethiopia	3.55%	3.65%	2.82%	3.13%	1.03%	1.27%	1.02%	1.09%	1.45%	1.21%	1.23%	1.23%
Haiti	1.84%	2.50%	3.29%	4.47%	1.54%	1.41%	1.87%	3.02%	2.41%	2.86%	3.88%	5.48%
Kenya	1.61%	2.22%	1.81%	2.72%	0.70%	0.90%	0.78%	1.24%	1.11%	1.31%	1.17%	1.89%
Lesotho	1.88%	1.04%	1.97%	2.01%	0.87%	0.71%	0.84%	0.82%	1.23%	1.17%	1.36%	1.23%
Malawi	5.00%	5.09%	4.32%	5.51%	2.94%	2.66%	2.43%	2.97%	3.11%	2.80%	2.60%	3.01%
Mozambique	4.26%	3.96%	3.72%	4.74%	2.84%	2.39%	2.39%	3.05%	3.66%	3.02%	2.90%	3.51%
Namibia	7.41%	9.62%	10.79%	8.76%	4.93%	4.57%	5.29%	5.89%	5.40%	5.29%	5.65%	6.31%
Nigeria	2.77%	2.87%	1.08%	1.94%	2.25%	2.01%	0.70%	1.32%	1.48%	1.36%	0.60%	1.03%
Rwanda	0.59%		0.41%	0.82%	0.11%	0.19%	0.04%	0.08%	0.26%	0.30%	0.27%	0.33%
South Africa	6.86%	7.04%	7.25%	9.31%	3.72%	3.74%	3.54%	4.91%	3.71%	3.84%	3.51%	4.53%
South Sudan	5.33%	7.65%	4.59%	6.30%	4.29%	5.88%	6.76%	7.05%	5.36%	5.93%	4.87%	4.94%
Tanzania	3.36%	2.42%	1.80%	1.93%	2.20%	1.80%	1.21%	1.11%	2.69%	1.89%	1.27%	1.08%
Uganda	2.99%	2.88%	2.52%	2.84%	1.88%	1.73%	1.31%	1.63%	2.45%	2.07%	1.97%	2.20%
Ukraine	5.62%	10.96%	9.02%	5.26%	4.49%	11.01%	7.21%	2.64%	5.50%	9.43%	5.25%	4.57%
Vietnam		1.06%		2.00%	0.36%	0.33%	0.11%	0.22%	1.32%	1.47%	1.40%	1.25%
West Africa Region	4.33%	1.99%	6.64%	2.52%	8.43%	2.00%	1.86%	2.21%	9.37%	2.02%	1.55%	2.44%
Western Hemisphere Region	3.51%	3.13%	1.96%	5.21%	3.03%	3.03%	2.15%	1.82%	5.46%	5.65%	5.35%	6.73%
Zambia	3.16%	4.28%	3.31%	5.39%	2.09%	1.90%	1.78%	3.16%	2.30%	1.94%	1.91%	3.58%
Zimbabwe	0.39%	0.59%	0.44%	0.66%	0.61%	0.42%	0.30%	0.44%	0.72%	0.65%	0.56%	0.69%

Figure 3: Total % IIT by age in 2022, PEPFAR data

John Stover presented on **the impact on child estimates of assuming similar interruption among adults and children in Spectrum.** Of 208 Spectrum files created in 2023, 130 assumed zero ART interruption for both adults and children but 58 files had zero for children, and an average of 5.5% for adults. Using these adult LTFU rates as the proxy for paediatric LTFU had negligible impact on child estimates. He concluded that interruption rates are important at the individual level, but that rates so far entered into Spectrum for adults would be too low to make much difference to child estimates. Interruption will impact on age distribution of children on ART, but such results were not shown.

Leigh Johnson presented on **fitting ART initiation to age distribution of children currently on ART in Thembisa.** Spectrum has to match programme data on total numbers of children on ART. This presentation explored the advantages to calibrating Spectrum to data on the age distribution of children on ART. Age distributions of children on ART are determined by levels of peri- vs post-natal infection, timing of paediatric HIV testing, survival on- and off-ART, initiation of and retention on ART, and temporal changes in these.

Calibrating a model to age distribution data may help to reduce uncertainty associated with these factors.

He used an example of Thembisa to demonstrate addition of age distribution data to the calibration. Data of total numbers of children with laboratory evidence of being on ART, by age were obtained from the National Health Laboratory Service (NHLS), for 2011-2018. The uncertain parameters in the calibration were average breastfeeding durations, rates of untreated HIV disease progression, and rates of ART initiation. The likelihood function was defined to indicate goodness-of-fit for total number of children on ART, the age distribution of children on ART, and HIV prevalence in children (from 4 household surveys).

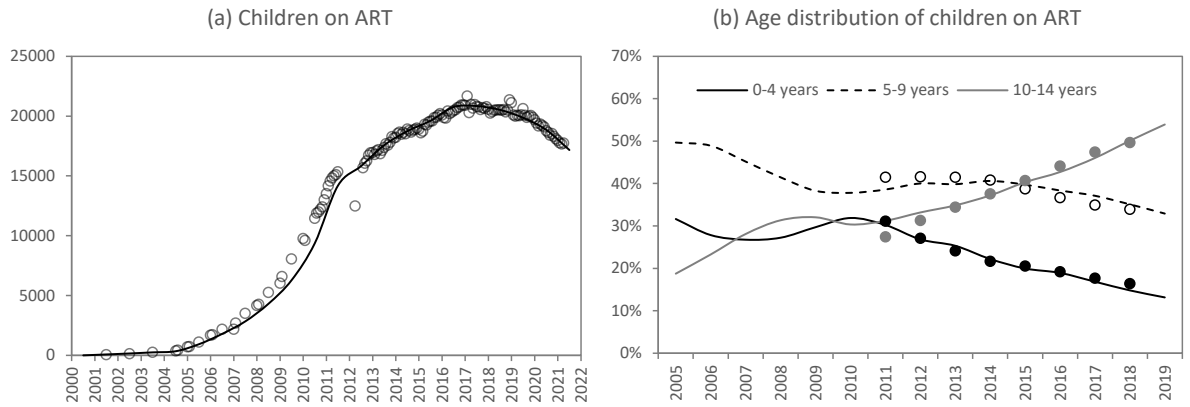

Figure 4: Thembisa model fit to data from the Eastern Cape. Source: Thembisa 4.5, www.thembisa.org

The fitted Thembisa results compare well to earlier calibrations that had not considered ART age distribution, but the new estimates have narrower confidence intervals, reflecting reduced uncertainty in parameters.

Johnson furthermore noted that age distributions in laboratory data were quite different from age distributions in the national electronic medical record (EMR) data and the model was not able to match the pattern in the South Africa national EMR data. In the EMR, the proportion of children on ART aged <5 was increasing over time, the opposite of what would be expected, and not consistent with NHLS data and Thembisa). This may be a problem if Spectrum were to attempt fitting to these data.

Shirl Smith presented **PEPFAR data on the indicators 'newly initiated' and 'currently on treatment' for children versus adults.** She started by noting that PEPFAR data may not be representative of national programmes because PEPFAR programmes have varying subnational coverage and are often in higher burden districts. Mozambique, South Africa, Uganda, Tanzania and Nigeria are among PEPFAR-supported countries with highest numbers of newly initiated on treatment among children <1 years over 2020 to 2022. Adults currently on treatment increased over the 2020 to 2022 period, while children on treatment declined.

Rob Glaubius presented **updated breastfeeding patterns among women with HIV incorporating new PHIA data.** Postnatal mother-to-child transmission in Spectrum depends on breastfeeding (BF) duration among mothers with HIV and these durations are

estimated from household survey data. Since the previous analysis of the data in 2020, 6 additional PHIA data sets (3 Eastern and 3 Southern Africa) as well as one DHS data set from Western Africa have become available. However, the 2020-21 Botswana PHIA survey was excluded, since in this country only, guidelines encourage a maximum of 6 months BF to mothers with HIV. Compared to the previous analysis, the updated parametric survival analysis suggests that *initial breastfeeding %* among mothers with HIV decreased more slowly over calendar time in Eastern Africa and may have been stable or increased with calendar time in Southern Africa. The updated *median breastfeeding duration* was similar to the previous analysis in Central, Western, and Eastern Africa. Among mothers with HIV in Southern Africa, the updated analysis suggests a slower decline in *median BF duration* over time. Spectrum with these updated breastfeeding patterns estimates ~10% more new infections in Rwanda in 2021, ~5% in Lesotho, Madagascar and Namibia, and ~15% in Eswatini. The number of CLHIV in these countries in 2021 increased proportionally. Glaubius noted as limitation of the data, the inability to stratify the mothers with HIV by knowledge of status. If mothers with undiagnosed HIV infection breastfeed longer than mothers who know their HIV-positive status, Spectrum may produce biased estimates of new child infections as knowledge of status improves. Future work related to the BF model is to incorporate BF duration data from household surveys that did not include HIV testing (MICS/DHS), which will include precision of breastfeeding assumptions for countries with only such surveys.

Key points from discussion:

- Data on child age distribution at treatment initiation are available from countries' programme data and should be considered instead of IeDEA data to inform Spectrum (Eaton).
- This links to Maggie Walter's presentation in the October 2022 meeting where the age at ART initiation was higher in programme data than in Spectrum. This is caused by the Spectrum not capturing interruption and reinitiation appropriately (Eaton).
- Non-zero default interruption rates in Spectrum will encourage more careful reflection by countries about changing that number to zero (the current default) or to another, hopefully locally justified value (Stover).
- Further discussion is captured in the recommendations in **Appendix A**.

Session 3 – Mortality assumptions

This session chaired by **Mary Mahy** reviewed existing assumptions about mortality among children living with HIV and identify additional data to improve estimates.

Maggie Walters presented **sources of uncertainty on Spectrum paediatric HIV estimates.** Walters explored assumptions that could lead to incorrect estimation of paediatric HIV incidence rate, HIV mortality rate among CLHIV and paediatric HIV prevalence. The Spectrum uncertainty analysis considers four sources of uncertainty in the paediatric model (1) numbers of births to women with HIV, (2) children receiving ART, (3) the effectiveness of cotrimoxazole, and (4) MTCT transmission probabilities. She conducted Shapley decomposition analysis to attribute proportions of uncertainty to each source of uncertainty.

Walters noted that the current approach to uncertainty analysis in the Spectrum paediatric model does not incorporate uncertainty about paediatric survival and HIV natural history, which are likely the most uncertain parameters. On the other hand, the decomposition analysis demonstrated that most uncertainty arises from maternal prevalence, which is relatively precisely observed in many settings through routine antenatal HIV testing prevalence. The large uncertainty in Spectrum from maternal HIV testing is because the full range of uncertainty in population HIV prevalence is propagated to uncertainty about HIV prevalence among pregnant women. Conditioning on the observed HIV prevalence among pregnant women from ANC for each prevalence uncertainty draw (similar to fitting to observed ANC prevalence in Spectrum AIM) would likely substantially reduce the uncertainty from this source.

John Stover presented the **impact of adjusting off-ART AIDS mortality for child ART coverage.** Spectrum's adult mortality model assumes that the characteristics of PLHIV off ART change as ART coverage increases, such that increasingly, those closest to death are more likely to get on ART than those without serious symptoms. Spectrum achieves this by adjusting off-ART mortality downward as ART coverage increases. This presentation investigated whether the same should be done for off-ART paediatric mortality. Adjusting off-ART AIDS mortality among children resulted in a global 34% decrease in paediatric AIDS-related deaths and a 22% increase of CLHIV in 2021. The adjustment moves estimated HIV prevalence among 0-14 years closer to PHIA estimates in 3 of 12 countries where the initial Spectrum estimated prevalence was initially below PHIA but enhanced the discrepancy in 9 of 12 where the initial Spectrum estimate was already above the PHIA's (Figure 5).

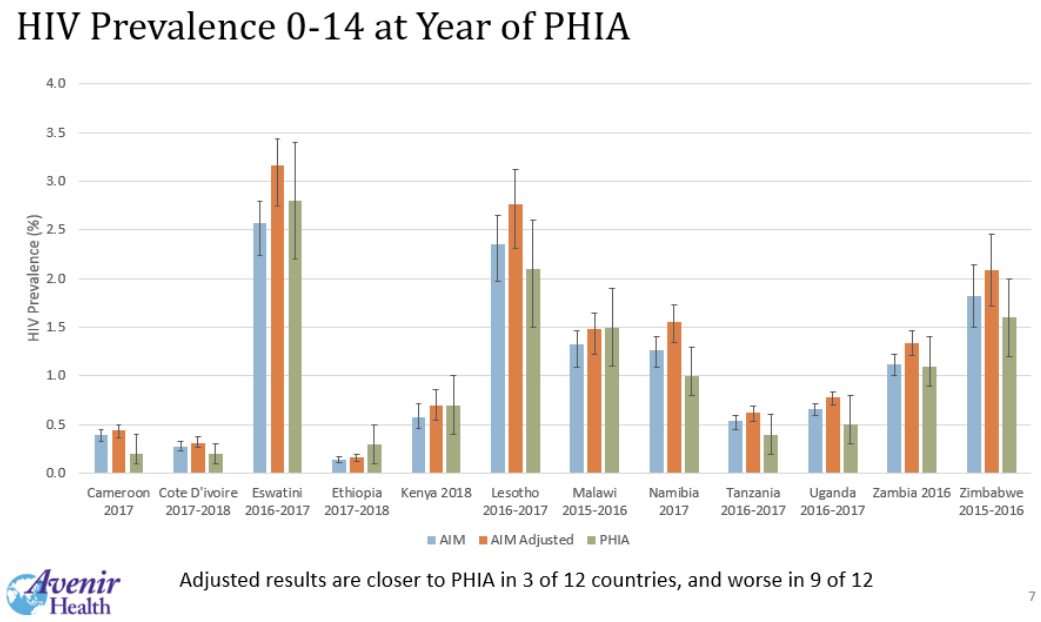

Figure 5: HIV prevalence among children aged 0-14. Source: Spectrum 2023 and PHIA surveys

Nicole McCann presented a **comparison of Spectrum, Thembisa and CEPAC-Paediatric estimates of infant mortality in the first year of life in South Africa.** Since both Thembisa and CEPAC use finer age stratifications for timing of HIV infection and ART initiation than Spectrum (By month in Thembisa, continuously in CEPAC, and one-year ages in Spectrum),

McCann assessed whether the broad age grouping in Spectrum biases model results**.** The approach first examined the estimated first-year all-cause mortality in all children with HIV**.** Populations under comparison were all infants with HIV (whether known or unknown, treated or untreated) born in 2008, 2013, 2016. The analysis divided the CEPAC-projected number of children who died with HIV by the total number of children who ever acquired HIV up to 1 year of age. For each year, this proportion was multiplied by the Thembisa-projected estimate for total number of children with HIV in the respective year.

Model	**2008**	**2013**	**2016**
Thembisa	14,558	1,858	738
Spectrum	15,035	2,123	1,101
CEPAC	17,284	6,159	3,485

Infant mortality estimates from Thembisa and Spectrum were similar, but CEPAC estimates higher, potentially due to difference in estimates of non-AIDS mortality, mortality parameters, and HIV cascade inputs (e.g., ART initiation probability).

Kyu Han Lee presented **findings from Child Health and Mortality Prevention Surveillance (CHAMPS) studies from 7 African countries over 2016 to 2022.** CHAMPS assessed causes of death among children under 5 by minimally invasive tissue sampling within the first 24 hours after death and performing a wide range of tests on the samples, as well as verbal autopsy, photographs and gross examination. HIV is an important cause of under-five deaths at 4 CHAMPS sites studied (~5% of all deaths) and worryingly, ~50% of all HIV deaths were not diagnosed premortem, as shown in Figure 6 below.

Country	Enrolled	HIV PCR-positive	Child diagnosed before death	Child on ART before death	Death preventable*
Kenya	482	34 (7%)	11 (32%)	11 (32%)	33 (97%)
Mozambique	543	33 (6%)	20 (61%)	20 (61%)	32 (97%)
Sierra Leone	395	13 (3%)	3 (23%)	1 (8%)	13 (100%)
South Africa	715	28 (4%)	19 (68%)	11 (39%)	26 (93%)
Total	**2135**	**108 (5%)**	**53 (49%)**	**43 (40%)**	**102 (94%)**

Figure 6: CHAMPS data. Source: Inacio Mandomando CROI 2023

Jiawei He and Austin Carter presented on **an ongoing meta-analysis on mortality among children and young adolescents on HIV treatment.** The study has 3 main objectives:

- Conduct a systematic review and meta-analysis of mortality among children and young adolescents on-ART by age, time since initiation of ART, geography, and year using all available global data sources.
- Quantify the impact of modifiable risk and protective factors on the risk of on-ART mortality to explain variation in on-ART mortality across locations and inform priorities for interventions.
- Decompose the impact of changes in biomedical, behavioural, and structural factors on changes in new HIV infections and mortality among children and young adolescents between 1990 and 2020.

They'll share progress as the extraction process continues.

Key points from the overall closing discussion of the session:

- MTCT rates in Spectrum are based on the 2019 review by Lynne Mofenson, with uncertainty represented by a simple standard deviation set at 0.05 times the MTCT rate for each group. Recommendation is to do a formal meta-analysis with uncertainty estimation of the Mofenson review.
- Further discussion is captured in the recommendations in Appendix A.

Appendix A -- Recommendations

Recommendation	Lead person(s)	Timeline
Session 1: Estimating births to women living with HIV (chaired by Leigh Johnson) **<u>Objective:</u>** **• Review default assumptions about retention on ART among pregnant women**		
ART retention in pregnant and postpartum women		
• Review of retention during pregnancy: Focus on reviewing new studies on silent transfer/tracing, and studies that distinguished women on ART before pregnancy from women initiating ART during pregnancy. Assess evidence for changes in retention over time.	Caitlin Dugdale	
• Refer to "treatment interruption" rate in place of "loss to follow-up" rate in Spectrum input editors and HIV estimates guidance materials.	Avenir Health	2024 estimates
• Collect information from country HIV estimates teams that input different retention rates from default retention for information on what data their assumptions are based on. Compare this data with earlier cohort studies from Dugdale *et al.* meta-analysis to assess whether country data imply consistently different recent retention rates compared to earlier periods represented by studies in Dugdale *et al.*	UNAIDS	October 2023
• Encourage countries that are reporting 100% retention; countries that are still using very low (<80%) retention assumptions; and countries that are using defaults (e.g., WCA) to review locally available data on ART retention among pregnant and breastfeeding women and consider updating assumptions.	UNAIDS	2024 estimates
• Review new data regarding effectiveness of DTG in preventing MTCT.	TBD	
HIV prevalence in pregnant women		
• Association between HIV prevalence and access to ANC attendance and testing in WCA: Incorporate subnational ANC testing programme data into assessment of relationship between ANC testing coverage and HIV prevalence and evaluate impact on ANC HIV prevalence and coverage of PMTCT.	Jeff Eaton	

Recommendation	Lead person(s)	Timeline
• Assess impact of incomplete ANC attendance and incomplete ANC testing coverage in aggregate ANC model input trends. • Ensure consistency of ANC HIV testing data inputs across Spectrum and Naomi models – include greater disaggregation across districts (and sites where possible) to facilitate this. • Further analysis is needed to assess whether recently observed declines in ANC HIV prevalence are consistent with epidemiologic trends or reflect changes in data reporting or completeness.		
Conduct formal meta-analysis of MTCT rates based on Mofenson et al. review.	TBC	May 2024
Session 2: Estimates of children living with HIV and ART coverage (chaired by Jeff Eaton) **<u>Objective:</u>** **• Review Spectrum model assumptions about ART interruption and re-initiation and impact on paediatric HIV estimates**		
• Adopt proposed updated SSA breastfeeding duration estimates based on new survey data. • Excluding Botswana. Use custom pattern reflecting strict adherence to 6-month breastfeeding duration. • Develop statistical methods to incorporate breastfeeding duration data from household surveys that do not include HIV testing surveys (MICS/DHS), which will include precision of breastfeeding assumptions for countries with these surveys.	Avenir Health	October 2023

• Implement paediatric sub-model including paediatric ART interruption and re-initiation to produce output for previously treated population.
  • Allow users to specify interruption rates and relative re-initiation rates by 5-year age group.
  • Use output to furnish paediatric 'first 90' estimates in Spectrum and enable programmes to recognize and visualise importance of interruptions as part of the paediatric treatment gap.
  • Consider allowing programmes to input number initiated and number on ART to calculate 'programme observed' interruption.
  • This will require default assumptions about interruption by age.
	Avenir Health	October 2023

Recommendation	Lead person(s)	Timeline
• Compare ART interruption and silent transfer from Ghana data individually linked with national ID.	UNAIDS, Ekow Wiah	May 2024
Session 3: Mortality assumptions (chaired by Mary Mahy) **<u>Objective:</u>** **• Review existing assumptions about mortality among children living with HIV and identify additional data to improve estimates**		
Understanding sources of uncertainty in Spectrum paediatric HIV estimates • Update Spectrum Paediatric Model uncertainty analysis o Review decisions about selection of parameters included in Spectrum Paediatric model uncertainty analysis. o Consider reflecting uncertainty around paediatric disease progression and survival rates. o Consider representing uncertainty in paediatric programme data other than numbers on ART. o Reflect study uncertainty around parameters instead of assuming 5% relative standard deviation for all parameters. o Condition uncertainty about HIV prevalence among pregnant women on observed ANC routine testing prevalence data, where appropriate.	Avenir Health, Imperial College London	May 2024
Impact of adjusting off-ART mortality for child ART coverage • Recommend to not implement in SSA countries for all ages 0-14 years (in testing this resulted in increasing paediatric HIV prevalence, producing paediatric survey prevalence less consistent with PHIA survey prevalence). • Investigate impact of adjusting off-ART mortality for ART coverage only for older children (5+ years). • Investigate impact of this adjustment on mortality in high-income and concentrated epidemic countries; review whether this improves consistency of infant AIDS deaths with vital registration data.	Avenir Health	May 2024
Validation of Spectrum AIDS child mortality estimates with CHAMPS study data on child cause of death • Noting nearly 50% of infants who died with HIV were not diagnosed before death; review evidence about mother's	Imperial,	May 2024

Recommendation	Lead person(s)	Timeline
antenatal and postnatal testing, knowledge of status, and likely timing of infection (this information is collected during verbal autopsy). • Compare CHAMPS study results about antenatal cascade gaps resulting in paediatric deaths with Spectrum model results. • Triangulate CHAMPS data with local ANC, PMTCT, and postnatal testing programme data in the study areas. • Compare AIDS cause-specific mortality fraction (CSMF) to district-specific estimates on relative HIV burden to assess extent to which high AIDS CSMFs in CHAMPS studies are explained by study sites in particularly high HIV burden locations.	CHAMPS team	
<u>October 2022 recommendations still to be addressed:</u> Review literature on excess (non-HIV/AIDS) mortality among HIV uninfected children born to HIV-infected mothers (exposed uninfected), e.g., from the UK, US, or Canada	UNAIDS	May 2024
Review evidence on changes over time in the timing of ART initiation in the first year of life and potential magnitude of impact on paediatric AIDS mortality estimates during the first year. 1. Changes in age distribution at ART initiation over time (data from IeDEA, EID coverage estimates where available) 2. Implication of changes for child mortality	Mary-Ann Davies Avenir, Leigh Johnson, Andrea Ciaranello	May 2024

Appendix B -- Participants

Name	Organisation
In-person	
Akim Lukwa	SACEMA
Andreas Jahn	MoH Malawi
Cari van Schalkwyk	SACEMA
Deepa Jahagirdar	Avenir Health
Ekow Wiah	NAC Ghana
Eline Korenromp	UNAIDS
Faikah Bruce	SACEMA
Guy Mahiane	Avenir Health
Ian Wanyeki	UNAIDS
Jeff Eaton	Imperial College London
John Stover	Avenir Health
Keith Sabin	UNAIDS
Leigh Johnson	University of Cape Town
Maggie Walters	Imperial College London
Mary Mahy	UNAIDS
Mary-Anne Davies	University of Cape Town
Mathieu Maheu-Giroux	McGill University
Oli Stevens	Imperial College London
Ray Shiraishi	CDC
Reshma Bhattacharjee	USAID
Rob Glaubius	Avenir Health
Virtual	
Alex Vrazo	USAID
Amanda Novotney	IHME
Andrea Ciaranello	Harvard University
Anna YAKUSIK	UNAIDS
Annette Sohn	amFAR
Austin Carter	IHME
Chibwe Lwamba	UNICEF
Cynthia Whitney	Emory University
Edmond Brewer	IHME
Elizabeth Carter	CDC
Fatima Tsiouris	EGPAF
George Siberry	USAID
Hilary Wolf	CDC
Hmwe H. Kyu	IHME
Jiawei He	IHME
Jimmy Carlucci	Indiana University
Kimi Sato	CDC
Kyu Han Lee	Emory University

Maria Au	USAID
Mary-Ann Davies	UCT
Milly Marston	LSHTM
Neha Mehta	CDC
Nicole Buono	USAID
Nicole Mccann	Harvard University
Patricia Agaba	US Military HIV research programme
Rachel Esra	Imperial College London
Rebecca Anderson	Imperial College London
Sadhna Patel	CDC
Salome Kuchukhidze	McGill University
Savvy Brar	UNICEF
Shirl Smith	USAID
Tim Brown	East West Centre

Appendix C – Agenda

15 May 2023

All times are GMT+2 (Stellenbosch, South Africa)

Time	Duration (mins)	Topic	Presenter(s)
11.00	15	• Welcome and introductions • Review of 2023 estimates and pending challenges • Meeting objectives	Mary Mahy
11.15	10	Overview of Spectrum child model and LTFU assumptions	John Stover
Session 1: Estimating births to women living with HIV (chaired by Leigh Johnson) **Objective:** • **Review default assumptions about retention on ART among pregnant women**			
11.25	5	Review of retention on ART among pregnant women in 2023 estimates	Mary Mahy
11.30	10	Review assumptions of default LTFU among pregnant women	Caitlin Dugdale
11.40	30	Discussion	
12.10	10	Association between HIV prevalence and access to ANC attendance and testing in WCA	Jeff Eaton
12.20	10	Prevalence in pregnant women	Ian Wanyeki
12.30	30	Discussion	
13.00	60	LUNCH	
Session 2: Estimates of children living with HIV and ART coverage (chaired by Jeff Eaton) **Objective:** • **Review Spectrum model assumptions about ART interruption and re-initiation and impact on paediatric HIV estimates**			
14.00	20	Literature review to inform default paediatric treatment interruption rate in Spectrum	Jimmy Carlucci
14.20	10	PEPFAR data on adult vs child interruption	Patricia Agaba
14.30	10	Impact of assuming similar interruption among adults and children in Spectrum	John Stover
14.40	10	Fitting ART initiation to age distribution of children currently on ART in Thembisa	Leigh Johnson
14.50	15	PEPFAR data (newly diagnosed and initiated by age)	Shirl Smith
15.05	10	Updates to breastfeeding patterns based on new PHIA data	Rob Glaubius
15.15	60	Discussion	
16.15	15	BREAK	
Session 3: Mortality assumptions (chaired by Mary Mahy) **Objective:** • **Review existing assumptions about mortality among children living with HIV and identify additional data to improve estimates**			
16.30	15	Importance of different assumptions on estimates	Maggie Walters
16.45	10	Impact of adjusting off-ART mortality for child ART coverage	John Stover

16.55	10	Thembisa/CEPAC mortality assumptions in the first year of life	Nicole McCann
17.05	15	CHAMPS paediatric AIDS mortality fraction and comparison with UNAIDS estimates	Kyu Han Lee
17.20	15	IHME systematic review of child on-ART mortality	Jiawei He/ Austin Carter
17.35	60	Discussion	
18.35	25	Recommendations	
19.00		CLOSE	