
Estimating Paediatric HIV and the Need for Antiretroviral Therapy

Report and recommendations from a meeting of the WHO, UNAIDS and
UNICEF in collaboration with the UNAIDS Reference Group on Estimates,
Modelling and Projections, New York, USA
09-10 November, 2016

REPORT & RECOMMENDATIONS



The meeting of the WHO and UNAIDS in collaboration with the UNAIDS Reference Group on Estimates, Modelling and Projections was organised by the secretariat of the Reference Group (www.epidem.org) based at Imperial College London. Participants of the meeting are listed at the end of this document.
Soraya Rusmaully, 2017

Although tremendous progress has been made in scaling up services for the prevention of mother-to-child transmission (PMTCT), the global burden of paediatric HIV remains a significant health challenge. As efforts to expand paediatric testing and treatment increase, a larger proportion of children are expected to survive and be in need of antiretroviral therapy (ART). In order to support the development and procurement of ART an understanding of the trends in paediatric infection at a national and global levels is critical. Unfortunately, limited surveillance data on this population in many countries have hampered efforts to accurately assess the number of children in need of ART or predict the update of current treatment recommendations. As such, forecasting the demand of paediatric drugs and formulations remains a challenge potentially undermining treatment outcomes.

The World Health Organisation and UNAIDS in collaboration with the UNAIDS Reference Group on Estimates, Modelling and Projections convened its third technical consultation to review and update current parameters and method of paediatric HIV estimation. The overall objectives of this meeting were as follows:

- To improve country and global estimates of the number of children newly infected with HIV
- To estimate the number of children in need of 1st and 2nd line regimen ART up until 2020 and explore the size and age of this population.

The UNAIDS Reference Group on Estimates, Modelling and Projections

The Joint United Nations Programme on HIV/AIDS (UNAIDS) Reference Group on Estimates, Modelling and Projections exists to provide impartial scientific advice to UNAIDS and other partner organisations on global estimates and projections of the prevalence, incidence and impact of HIV/AIDS. The Reference Group serves as an 'open cohort' of epidemiologists, demographers, statisticians and public health experts. It is able to provide timely advice and also address on-going concerns through both ad hoc and regular meetings. The group is coordinated by a Secretariat based in the Department of Infectious Disease Epidemiology at Imperial College London.

Approach

The recommendations drafted at Reference Group meetings give UNAIDS guidance on how best to produce estimates of HIV/AIDS, provides an opportunity to review current approaches and also helps to identify information needs (earlier reports are published on the Reference Group website www.epidem.org). This transparent process aims to allow the statistics and reports published by UNAIDS and WHO to be informed by impartial, scientific peer review.

The meeting featured both presentations and facilitated discussion to generate consensus recommendations. Thirty-one experts from seven countries attended the meeting – each contributed data, insights and analysis to produce a set of recommendations on the HIV estimates. We thank them for their attendance and contributions.

I. Current Methods of Paediatric Infection Estimation in Spectrum AIDS Impact Model

Empirical measures of HIV prevalence, incidence and mortality are currently developed using the AIDS Impact Module in Spectrum. The Estimation Projection Package fits user-supplied prevalence data from HIV surveillance systems to generate a prevalence projection and then calculates associated incidence for adults aged 15-49 years. The resulting fits are fed into Spectrum and distributed by age and sex. New adult infections are then tracked by CD4 count resulting in a pattern of HIV prevalence that is subject to age-specific fertility rates to determine the number of pregnant women in need of PMTCT. To calculate HIV in children, transmission from mother-to-child (MTCT) is divided into transmission during pregnancy and birth and transmission through breastfeeding, with the model assuming no new infection from other sources other than MTCT among children less than 15 years.

To determine the number of children eligible for treatment, Spectrum tracks the progression of the infection by CD4 count. Most children newly infected enter the model with CD4 counts of above 500, but some may start at 350-500. In each time step those in a CD4 category may (1) stay in that category (2) die from a non AIDS-related cause (3) die from AIDS (4) progress to the next lower CD4 category (5) initiate ART or (6) migrate out of the population¹. All surviving children are then transitioned to the adult model aged 15 years.

Following recommendations made at the [2015 WHO/UNAIDS Paediatric Estimates Meeting](#) and the [2016 Spring UNAIDS Reference Group Meeting](#) several modifications were made to the child model, resulting in important differences in paediatric estimation:

(a) *Updated probabilities of MTCT*: Following an updated review of MTCT transmission probabilities it was found that the probability of transmission among women who seroconverted during pregnancy has been revised to 18% from 30%.

- This change in the transmission risk has implications on the reduced number of children infected with HIV since the start of the HIV epidemic. There were also small reductions in the transmission probability for different regimens and for women who received no prophylaxis. For example, single-dose nevirapine (Sd-NVP) change which women received in early part of epidemic and pregnant women living with HIV (PWLHIV) initiate ART earlier, which means that the probability of MTCT per month is lower.

(b) *Implementation of a new default distribution of ART initiation in children by age*: Due to the lack of country-level data, the model previously assumed that ART initiation would occur in accordance with national eligibility criteria. It was agreed that the International Epidemiology Databases to Evaluate AIDS Consortium (IeDEA) would provide age disaggregated antiretroviral data until country level data becomes available. Default values now reflect the regional values by single year age groups (0-14) for 3 regions (Asia, Africa and LAC).

- These updates resulted in an upward shift in the mortality rate among children living with HIV because children were not started on ART at a young age, which would improve chances of survival.
- This upward shift in the mortality rate results in fewer children living with HIV. The actual number of AIDS deaths among children is lower in the current round because there were fewer children living with HIV due to the adjustment to the transmission probability mentioned above. However, the rate at which children living with HIV died remains high.

¹ Stover, J., Brown, T. and Marston, M., 2012. Updates to the Spectrum/Estimation and Projection Package (EPP) model to estimate HIV trends for adults and children. Sexually transmitted infections, 88(Suppl 2), pp.i11-i16.

- The lower number of children living with HIV implies that there are fewer children who should be receiving antiretroviral therapy. While in previous years' considerable attention was drawn to the gap in antiretroviral coverage between children and adults, the new estimates show that coverage among children may be similar to coverage among adults.

Chewe Luo acknowledged that while the new estimates are more accurate than previous rounds, the implications of 27% fewer children living with HIV in 2014 than the 2015 model will have significant programmatic implications at the country-level. She recommended that UNAIDS provide guidance to assist countries to better understand the assumptions that have led to such a significant downward revision. In addition to this, she highlighted the need to better understand the impact of the epidemic on the adolescent community. Thus, it was agreed that adolescent-specific topics should be recommended by the group for inclusion in the agenda for the next meeting.

Recommendation:

- **Adolescent-specific topics of discussion to be included in the next meeting (WHO, UNICEF and UNAIDS, October 2017).**

II. Estimating HIV-Positive Pregnant Women

Reviewing PMTCT Coverage: An Analysis of Spectrum model inputs that affect national and sub-national PMTCT coverage estimates

In the 2016 UNAIDS estimates, a number of countries with high quality PMTCT programme data had estimates of PMTCT coverage of 100% or more. Following recommendations made at the 2016 Spring UNAIDS Reference Group Meeting, Anna Radin conducted a comprehensive review to identify the Spectrum model inputs that were contributing to this overestimation. Female population (projected by Spectrum using UN data), HIV prevalence and population of HIV positive females (modelled in Spectrum with EPP, based on national surveys, ANC sentinel surveillance data and program data) and total fertility rate reduction for HIV positive females not on ART were all identified to be the model inputs prone to the greatest error and were predicted to be contributing to overestimation of PMTCT coverage. Thus, further analyses were conducted to assess the degree to which changing the source of these specific model inputs would affect PMTCT coverage.

The analysis yielded the following results:

- HIV prevalence among pregnant women was identified as the largest potential source of error in the Spectrum PMTCT coverage model. When replaced by prevalence data from a recent survey or DHS, the model projected lower PMTCT coverage estimates. However, this association was less clear at the sub-national level where HIV prevalence estimates had wider confidence intervals. Given that in most cases, HIV prevalence estimates among pregnant women in Spectrum were substantially lower than HIV prevalence estimates in recent surveys, it was agreed that the current Spectrum estimates of HIV prevalence would be reviewed and revised accordingly.
- Use of World Population Prospects (WPP) population data yielded PMTCT coverage estimates that were sometimes higher and sometimes lower than the coverage estimates using Spectrum-projected population, and the magnitude of change was small relative to the other inputs (HIV prevalence and total fertility rate (TFR) reduction). Thus, it was agreed that we should continue to use Spectrum-projected population data in the PMTCT coverage estimation model.
- Although only 4 out of 12 countries included in the analysis had national files which used non-default data for TFR reduction, PMTCT coverage estimates were found to increase when Spectrum default assumptions for TFR reduction (reduction in total fertility rate among women living with HIV not on antiretroviral therapy) were used.

An additional suggestion was made to compare PMTCT coverage (the percent of HIV+ pregnant women receiving PMTCT) to ANC1 coverage (the percent of all pregnant women attending at least 1 ANC visit) since PMTCT services are delivered through antenatal care.

Additional Comment Added After Meeting: However, PMTCT coverage and ANC coverage are based on different denominators and are not directly related. ANC coverage is not necessarily greater than or equal to the percent of HIV+ women receiving PMTCT. If HIV+ women have different ANC attendance patterns -- which is likely if they know or suspect their HIV status -- a higher or lower percentage of HIV+ women could be receiving PMTCT medicines. For example, if ANC1 coverage is 90% and HIV+ women seek out ANC services because they know their status the PMTCT coverage might be 95%. On the other hand, if HIV+ women avoid services due to stigma PMTCT coverage might be 85%.

Although the meeting participants recommended adding a comparison of ANC1 to the Spectrum validation page, this recommendation was not implemented due to the lack of ability to meaningfully validate results based on the ANC coverage indicator.

Adjusting Incidence Rate Ratios to Fit to Survey-Based Estimates of HIV Prevalence by Age

Currently, the AIM module uses incidence rate ratios (IRRs) to disaggregate HIV incidence by sex (time varying) and age (constant over time). Although, the age-specific IRRs reflect specific epidemic patterns over time, a “one-size-fits-all” method to fit age-specific HIV prevalence data may not be representative of survey data. A more systematic approach was proposed by Robert Glaubius in which he aimed to assess the impact of incorporating the ability in AIM to automatically adjust age-specific IRRs to fit AIM projections to HIV prevalence estimates from national surveys.

27 countries with at least 1 national HIV prevalence survey and a 2016 national AIM file were included in the analysis. The age-specific IRRs were modelled as shifted longitudinal densities and then optimized IRR to fit survey-based data. The resulting findings showed that fitted age-specific IRRs may improve the accuracy of AIM HIV prevalence projections - time-varying (as compared with static) IRRs modestly improved the accuracy of AIM HIV prevalence projections in some countries (Lesotho, Sierra Leone, Swaziland, Zambia and Zimbabwe), but were prone to increasing the likelihood of overfitting. Robert demonstrated that the improved fidelity to HIV prevalence data results in a redistribution of prevalence by age, which drives the observed changes in the estimates of PMTCT need and coverage. That is, with static IRR correction, PMTCT coverage fell by approximately 4.6 percentage points, after fitting IRRs in 80% of countries, whereas dynamic IRR adjustment on the other hand decreased coverage by 5.1 percentage points.

Given these findings, it was agreed at the UNAIDS Reference Group meeting, prior to this meeting that Improvements to age-specific IRR's through an additional fitting step in Spectrum will be should be implemented to better match to prevalence data. Further, it was recommended that Avenir Health conduct a method evaluation with all country files and recommend application of either static or dynamic time-variant IRR's, on a country-by-country basis.

Recommendation:

- **Automatic fitting of age-pattern of incidence to induce better agreement between model and available age-pattern of prevalence to be implemented (Avenir Health, December 2016)**

Sub-Fertility By Stage Of HIV Infection

Fertility trends among HIV-positive women are important for estimates because there is a need to, i) plan for PMTCT services needed and evaluate coverage and, ii) understand how to generalise prevalence trends among pregnant women to general population prevalence. Jeff Eaton and Milly Marston in collaboration with colleagues at the ALPHA Network previously proposed a new model to

represent effects of HIV on fertility. The advantage of such an approach is that it captures the effects of ART on the relationship between HIV and fertility, which removes the need for ad-hoc parameter adjustments in the ART era. The model predicts a narrowing (but not removal) of fertility differences over time between HIV-negative and HIV-positive women, in line with data from the ALPHA Network. However, this approach was not implemented because it exacerbated the problem of PMTCT coverage overestimation.

This work has now been further extended to directly estimate subfertility by the stage of infection in the current Spectrum Model. The fertility rate ratio (FRR) of women in each CD4 category is estimated relative to those with a CD4 count greater than 500. This is done by calculating the probability of CD4 stage over time using individual HIV status, survival information and Spectrum CD4 progression parameters (Markov model). Observed fertility events are then used to estimate the fertility rate in each stage based on probable state distribution (Poisson process). This approach directly estimates subfertility by age and duration of infection from cohort data.

Jeff highlighted several key advantages of incorporating such an approach into Spectrum:

- It allows for the direct estimation of subfertility by stage of infection from cohort data with rigorous statistical uncertainty versus the ad-hoc calibration to the regression model that was presented previously.
- It directly utilises the Spectrum CD4 progression and mortality parameters.
- It leverages data about mortality in the calculation of the probable CD4 stage over time. This allows us to infer stage of infection, when they became infected and when they die.
- It also accounts for the correlation between HIV and fertility in the handling of the unknown HIV seroconversion interval.

Although the group acknowledged that updated data is still urgently needed regarding the fertility of HIV-positive women in the ART era, it was agreed that a CD4-based method for representing sub-fertility would be a reasonable synthesis of currently available data and allows the changes over time in the stage of infection of HIV-positive women to be captured. However, it was noted that correction of FRR's to allow for agreement between the model and data on HIV prevalence among pregnant women, would have implications on the historic pattern of the epidemic, and thus, the numbers of paediatric infections historically. The group recommended testing the updated method in Spectrum such that the implications on all indicators can be assessed, with a view of adoption of this method.

Recommendations:

- **CD4-based method for representing sub-fertility to be incorporated into the model for testing so that implications on all indicators can be assessed (Avenir Health, Jan-Feb 2016).**
- **Correction of FRR's to allow for agreement between the model and data on HIV prevalence among pregnant to be implemented in the model (Avenir Health, Jan-Feb 2017).**

III. Retention in Care

Uptake of ART during pregnancy has improved with the introduction of ART services integrated into antenatal care (ANC). It has also resulted in earlier ART initiation, increasing the time on treatment prior to delivery and further reducing the risk of MTCT. Unfortunately, poor ART adherence and disengagement from care undermine the potential benefits of maternal ART use during pregnancy and/or breastfeeding and confer increased risk of MTCT as well as maternal morbidity and mortality.

Fatima Oliveira Tsiouris (ICAP, Colombia) and Shaffiq Essajee (WHO) presented the increasing evidence of reported loss to follow-up (LTFU) among HIV-positive pregnant women between ANC registration and delivery. Retrospective evaluation of 186 primary healthcare facilities in Uganda found that greatest LTFU occurs following initiation with 25% (n=2000) of women who did not return

following their first ANC visit. Similarly, in Kenya, it was found that women newly diagnosed with HIV in pregnancy were more likely to have disengaged from care (25% within 3 months of initiation) compared to women who had been diagnosed earlier. While the move to Option B+ simplifies the guidelines for ART by recommending that all pregnant women, regardless of CD4 count or clinical stage, begin lifelong ART; an implementation science study conducted in Swaziland by ICAP found that retention during the antenatal period still remains less than optimal at 61% - although a higher proportion of women overall were retained with B+ compared to Option A (68% versus 54%).

Fatima noted that despite the limitations of programmatic data, such early losses will likely impact rates of MTCT. Highlighting that antepartum LTFU is not accounted for in the model – it is currently assumed that all HIV-positive pregnant women who have initiated ART remain adherent until delivery – she raised the question of whether there is a need to assess such early losses as ‘failure of uptake’ rather than LTFU to better inform model parameters. Although John agreed antepartum LTFU could be incorporated into the model – Lynne Mofenson (Elizabeth Glaser Pediatric AIDS Foundation) and Constantin Yiannoutsos (IeDEA Consortium) highlighted that our quantitative understanding of these losses is fundamentally challenged by lack of robust data. They added that, in setting a default value of antepartum LTFU for countries who are not capturing this data could have a greater impact on MTCT. As such, the group agreed that there is the need to balance the importance of including these factors, against availability of data and risk of an inappropriate assumption leading to misleading results.

Accordingly, the group suggested an expert group be tasked with developing a recommendation for a default value as well as guidance on how country teams can synthesise the data that may be available. In particular, the group should consider the difficulties of interpretation of those data, by examining (i) the extent to which loss to follow up can be incorporated into probabilities of transmission that are used in the model and (ii) whether ancillary data can be used to detect if current projections do in fact, underestimate transmission risk overall (children 12-24-month population survey), and recognizing the impact of mortality on those data. In addition to this, it was suggested that a systematic review be conducted, to consolidate and better understand the growing body of evidence on this issue.

Recommendations:

- **An expert working group to be assembled: UNAIDS and WHO to coordinate to develop a terms of reference to support a consultant to complete task (Feb, 2017)**
- **A systematic review of to be conducted to consolidate studies of reported loss to follow-up (LTFU) among HIV-positive pregnant women between ANC registration and delivery (ICAP – Feb, 2017).**

Loss to Follow-Up in Children Starting Antiretroviral Therapy

Mary-Ann Davies (UCT) presented details of LTFU among children initiating ART taken from analyses of the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). The analysis sought to assess the probability of a ‘first episode’ of disengagement/LTFU from care (defined as ‘the first gap in visits of more than 365 days, without documented transfer out or death) in children starting ART before the age of 15 years, irrespective of whether they are subsequently re-engaged at the same or a different site. The resulting analysis shows that approximately 30% of children were LTFU following ART initiation – with particularly high rates of LTFU observed in the African regions. Further, it would appear the LTFU is significantly higher in the younger age groups, but this decreases with increasing age. However, Mary-Ann noted there is a concerning longer-term trend in those aged 10-15 years.

An analysis of the IeDEA South Africa cohort found that among 45,409 children approximately 69% had a gap in visits of greater than 180 days, ultimately meeting the definition of LTFU. Yet of that 73% of them would re-engage in care at the same site. And, approximately 53% reengaged within 6-9

months. Although, a gap of 180 days between visits would seem rather large, it would seem that the longer you leave the gap from LTFU this decreases the chance of misclassification.

Given that the accurate categorization of a patient as either active or LTFU presents unique challenges, the group agreed that an updated analysis should be conducted using the definitions consistent with the current model, to determine those “lost” after an initial visit using a shorter definition of “lost”, and looking at amount of time actually spent “alive and lost.” On review of this, the group will consider the best way to represent this in model – either implicitly, with a simplified model, or a more elaborate model with parameters for transition and mortality represented.

Recommendations:

- **An updated analysis of LTFU among children initiating ART to be conducted using shorter or standardized definition of “lost” following initial visit. Further analysis, should also include a review of time spent “alive and lost” (UCT, July 2017)**
- **Incorporate findings of the review into the model (Avenir Health, December 2017).**

III. Age at Start of ART in Children

- Due to a lack of country level data, a default distribution of children starting ART disaggregated by age using leDEA data was implemented in Spectrum in 2016. Jeannie Collins presented details of analyses conducted to assess whether the CIPHER cohort collaboration (including data from leDEA and non-leDEA networks) in resource limited settings could provide similar age distributions as leDEA estimates. The resulting findings show Spectrum’s age distribution for Africa to be comparable to CIPHER; the majority of estimates for the proportion of children starting ART aged 4-9 is within a 2% margin of difference, and is relatively consistent over the observed calendar years (2004-14). The greatest differences were observed in estimates of proportion of children starting ART aged younger than three years. It was suggested that this observed divergence may be led by the Southern African regions (South Africa and Botswana) given the differences in access to infant HIV diagnosis. Further, differences observed among older children may be in part due to the inclusion criteria of enrolment. John agreed that this analysis could be used to update default values in Spectrum for children over the age of three years.

Switch to Second-Line ART in HIV-Infected Children

Data on the durability of ART regimens is critical to inform clinicians, policy makers and programme planning, particularly in HIV-infected children and adolescents who, according to the new 2015 WHO Consolidated Guidelines, have been recommended for initiation of immediate therapy and in need for life-long treatment. However, data on the probability of switch to second-line in children are limited, and definitions of what constitutes “second-line” treatment vary. Jeannie Collins presented a global analysis to better understand the observed trends in data on time to switch from first-line to second-line ART in children.

A switch to a second-line regimen was defined as a (i) change of at least one NRTI-based regimen (ii) change from single to dual PI; or (iii) an addition of new drug class. And, time to switch was assessed using cumulative incidence curves with death and loss to follow-up (LTFU) considered as competing risks. Individual-level data pooled from 12 paediatric HIV cohort networks within the CIPHER and not restricted to resource-limited settings. Of the 93,213 children who met the inclusion criteria, 21.8% were from South Africa and 68.1% were from rest of Sub-Saharan Africa (SSA). Overall, 89% of children initiated on an NNRTI-based regimen, 11% on a PI-based regimen, with wide variations across regions. In South Africa, approximately 86.7% of children who started treatment before the age of 3 years,

approximately 86.7% were initiated on LPV-based regimens as outlined in the guideline recommendations. The rest of SSA, however continue to initiate on NPV – based regimens. Overall cumulative incidence of switching at 3-years after ART start was calculated to be 3.1% (95% CI 3.0% to 3.2%). However, significant variation across regions was observed, from 1.6% (95% CI 1.5,1.7) in SSA to 26.8% (20.6,33.3) in North America. Further, a higher incidence of switch was observed among those initiating on NNRTI-based regimens versus PI in all regions except for rest of SSA, where the proportion initiated on PI was low, and those initiated on PI appeared to have higher incidence of switch, possibly associated with stock outs or programmatic guidelines.

Among PEPFAR supported countries, Cameroon, Cote d'Ivoire, Ethiopia, Kenya, Swaziland, Tanzania and Zambia, Jamie Houston highlighted as of the 2015 reporting period there are approximately 218,048 children on treatment, 25% of those on treatment are under five and 75% are between 5 and 14 years. The total number of newly initiated on ART during the reporting period was approximately 29,000 – 38% were under five, 30% were 5-9 years and 32% were 10-14 years.

Given the wealth of data from CIPHER, PEPFAR and leDEA to inform trends on time to switch from first-line to second-line ART in children, Tim recommended that countries take a hierarchical approach in reporting; If data for all time periods is available, then countries should assess the national breakdown of the number of children initiating ART. If this is unavailable, PEPFAR data should be used together with observational data for historical estimates. And, in the absence of observational data one of two stereotypical profiles should be used based upon the CIPHER analyses.

Recommendations:

- **Update default values in the model for children aged 3 years and over from CIPHER analyses: Jeannie Collins (UCL) to provide date to Avenir Health, December 2016.**
- **Data entry screen to be incorporated into the model to allow countries to enter numbers of children starting on ART, dating back to 2013 (Avenir Health, December 2016)**
- **Guidance to be provided to countries on use of a hierarchical approach to report switch from first-line to second-line ART in children (UNAIDS and WHO, Feb-Mar 2017)**

IV. Paediatric ART Forecasting

While the HIV community has made significant progress over past years in improving access to paediatric ARTs, treatment coverage for children continues to be low. Unfortunately, the paediatric ART market is small and fragmented, often failing to provide sufficient incentives to manufacturers (both originator and generic) to overcome the specific challenges of producing paediatric ARTs, such as co-formulation, palatability, and dispersibility. With anti-retroviral treatment (ART) scale-up set to continue over the next few years Martina Penazzato (WHO) highlighted that it is of key importance that manufacturers and planners in low- and middle-income countries (LMICs) are able to better anticipate and respond to future changes to treatment regimens, generics pipeline and demand, in order to secure continued access to all ART medicines required.

John Stover provided an overview of the current methods used to provide suppliers and pharmaceutical companies with a global forecast of the estimated demand for active pharmaceutical ingredients (APIs) so that they can manage their manufacturing capacity accordingly. Three forecasting approaches are used to project the demand for ART, expressed as the number of people on treatment through 2020 using best available evidence. These projections are presented annually at the AMDS Manufacturers meeting co-hosted by WHO and UNAIDS.

- **Linear Projections:** The linear projection estimates the annual increase in the number of people receiving treatment for 154 countries from a linear regression line fitted to the number of adults and children receiving ART from the past 3 years as reported in the on the 2015 WHO

survey on ART drug use. John highlighted that short-term forecasting is more tactical given that it provides vital data on commodity requirements and costs for annual budget allocations on which specific supply plans and procurement contracts are developed, and actual orders are placed.

- Country Target Projections: Most countries set their own targets for the number of people they expect to be receiving ART – as such, the country target model reflects the reported programme goals of national programmes;
- Fast-Track Projection: For comparison purposes, a fast Fast-Track projection is also included. This projection assumes that, by 2020, 90% of all people living with HIV know their HIV status, 90% of the people who know their HIV-positive status are accessing treatment and 90% of the people receiving treatment have suppressed viral loads. John noted that although long-term forecasts are more strategic; they provide critical information for national governments and international funders for multi-year budgeting and resource mobilization, they can be considered by manufacturers to be less precise given their larger scope.
- Clinton Health Access Initiative (CHAI) Projections: For 153 countries, the potential number of children on ART are projected and disaggregated by those who might be on first and second line therapy. The different mix is then projected and the total volume of demand for ARTs is estimated accordingly. Given that pharmaceutical companies are often focused on the short term – linear extrapolations of past trends of actual numbers receiving ARTs are used to estimate the volume of ART required.

Vineet Prabhu (CHAI) further explained the way in which CHAI models are used to estimate patient numbers and cost under various scenarios. He informed the group that coverage rates have steadily increased over the years; only 21 percent of children living with HIV/AIDS were on treatment in 2010. He highlighted that at the global level, CHAI conservatively expects approximately 1.1 million children to be on treatment in all-low and middle income countries by 2020, based on 4-year average linear growth rates. However, he noted that as countries get closer to achieving the Fast Track 2020 targets and PMTCT initiatives continue to succeed, the distribution of the paediatric population is likely to change. That is, cohorts of younger age groups will shrink and older age groups will increase. In the absence of robust data to inform the demand and need of paediatric ARTs, Vineet Prabhu suggested that expert-recommended “archetypes” of age and weight distributions implemented in Spectrum could be useful. Rather than the default ‘one size fits all’ assumption a country with unreliable data could selectively determine their likely weight distributions for each age band according to a recommended estimate.

Aastha Gupta, also provided an example of the forecasting exercise conducted by Medicines Patent Pool (MPP) to model the future uptake of new ART drugs for children using the ‘likely use’ scenario. That is, where the WHO guidelines would accept and recommend new products using the treatment optimization framework, thus inferring a ‘good’ uptake. In this scenario, Efavirenz (EFV) and Lopinavir (Lpv) are introduced in first and second-line treatment, and Abacavir (ABC) becomes the main backbone in first-line ART. Due to the increased use of ABC in first line, this would result in zidovudine (AZT) becoming the preferred option in second-line treatment, and therefore Tenofovir (TDF) use would be likely to continue, though at a stable rate - as it has been observed to be in use in 27% patients in the last ART Use Survey. Although such a forecasting analysis is considered useful to manufacturers Aastha highlighted several limitations of the model. The use of the UNAIDS Fast Track target to estimate ART demand, would assume high PMTCT success and thus less children with HIV, which in turn may result in shortages of these types of drugs. Further, these estimation of the need for second-line regimens become increasingly unreliable.

The ACT Initiative & Country Perspectives

Josh Rosenfold OGAC/USAID, gave an update of the PEPFAR Accelerating Children’s HIV/AIDS Treatment (ACT) Initiative and its impact on paediatric ART formulation uptake. As part of the US-

Africa Leaders' Summit, the ACT Initiative was announced in August 2014. A public-private partnership between PEPFAR and the Children's Investment Fund Foundation, this initiative intends to double the number of children on treatment, by assuring that 600,000 children are on ART by the end of the program. Countries were selected based on their paediatric HIV burden, disparity between adult and paediatric coverage and, and on being PEPFAR Long-Term Strategy countries. Cameroon, Democratic Republic of Congo, Kenya, Lesotho, Malawi, Mozambique, Tanzania, Zambia and Zimbabwe successfully applied for and were accepted into the ACT program.

As of mid-2016, PEPFAR is supporting 592,107 children ages (91% of target) putting the ACT initiative on track to achieve its target of 600,000 children on treatment. Further, as of 2015 approximately 72% of ARTs used were on IATT optimal list.

V. Basis for Developing a Forecasting Module

While Spectrum can inform projections of the number of new child infections and those surviving at each age, more detailed clinical models can inform a wide range of ART failure and regimen switch scenarios (including 2nd and 3rd line). Andrea Ciarenello provided an overview of the CEPAC model which can be used to examine the way variations in key assumptions can alter projections of survival on ART or switch rates. The CEPAC model is a Monte Carlo simulation model of HIV. It differs from Spectrum in that it simulates individual patients from the time they enter the model (birth) through to death. The paediatric model simulates MTCT (intrauterine, intrapartum and postpartum), mortality among HIV-exposed uninfected children, HIV disease progression among infected children, response to ART (viral load and CD4 count), LTFU, return to care and during the first two years, feeding status and maternal vital status. The model is populated with data from cohorts and clinical trials – and it is used to project short term and long term OI risk, survival, ART use and costs. In addition, it is also used to compare clinical outcomes and cost effectiveness.

During the brainstorming session the group discussed whether there may be a need for single tool to assess and project for both quantification and demand of paediatric ART's. John agreed that addition of a forecasting module into Spectrum to would be a possibility but it may need to be customized.

Accordingly, the group that in order to support procurement, forecasting at national/global levels and assess the market for future drugs and formulations – a new module will require the following inputs:

- The number of children on a given formulation at a given time, including the simplification strategies adopted, the age and weight at initiation of ART.
- The duration of time spent of a given formulation.
- The decisions considered when a switch to second-line is required i.e. regimen sequencing, age and weight at switch.
- Regimen used in the past as this will help projecting the sequence
- The adopted national guideline and if possible the projected change in national guideline
- As ~75% of the paediatric drug procurement is covered by GF + USAID + UNITAID + UNICEF + CHAI + SA, collect the procurement plans for those for the next 18 months

In order to inform these inputs, the group highlighted the potential data sources that are currently available:

- Programme data: although this may be data that is routinely collected – a dedicated periodic exercise may be useful to conduct.
- Spectrum input may be used if programme data is unavailable.

- Observational data such as the produced by CIPHER and the leDEA Consortium is already available on weight and age distribution, duration of 1st line by regimen and age at ART initiation etc.

Based on these discussions, it was agreed that members of the group would collaboratively draft a concept note to outline a project to develop a new forecasting module. Avenir, CIPHER and CEPAC were identified as they key groups to contribute to this work; CHAI, MPP, UNITAID and PEPFAR were highlighted as the key partners to work with under the umbrella of the Commitment to Action Initiative (CTA).

In collaboration with the UNAIDS Reference Group on Estimates, Modelling and Projections

Modelling Paediatric HIV and the Need for Antiretroviral Therapy

9-10 November, 2016

Labouise Hall, UNICEF, New York, NY

Day 1

TIME	AGENDA ITEM	Presenter/Moderator
Chair: Tim Hallett (UNAIDS Reference Group)		
9:00 – 9:45	Opening Remarks	Timothy Hallett, Imperial College London Chewe Luo, UNICEF
9:45 – 10:00	Summary of Previous Meeting And Objectives	Martina Penazzato, WHO
10:00 – 10:15	Results from 2016 and Remaining Challenges	Mary Mahy, UNAIDS
10:15 – 10:30	Overview of the Child Model in Spectrum	John Stover, Avenir Health
10:30 – 11:00	Coffee Break	
11:00 – 12:00	Session 1: Estimating HIV+ Pregnant Women <ul style="list-style-type: none"> - Results from review of PMTCT coverage and possible solution - Sub-fertility by stage of HIV infection versus empirical data Faciliated Discussion	Anna Radin, OGAC Robert Glaubius, Avenir Health Jeffrey Eaton, Imperial College London
12:00- 13:30	Lunch	
13:30 - 15:00	Session 2: Retention On ART <ul style="list-style-type: none"> - Dropout in pregnancy (& breastfeeding) - Drop out among children - Ability for countries to report these data Faciliated Discussion	Fatima Tsiouris, ICAP Mary Ann Davies, UCT
15:00 – 15:30	Coffee Break	
15:30- 16:30	Session 3: Age At Start Of ART <ul style="list-style-type: none"> - Age at start of ART initiation among kids - Data from CIPHER - Data from USG - Ability for countries to report these data Faciliated Discussion	Jeannie Collins, UCL Jamie Houston, CDC Arvind Pandey, India
16:30 – 17:00	Discussion and Next Steps	Timothy Hallett, Imperial College London

Day 2

TIME	AGENDA ITEM	Presenter/Moderator
Chair: George Siberry (OGAC)		
9:00 – 9:15	Summary of day 1 and objectives for day 2	Martina Penazzato, WHO
9:15 – 10:30	Session 1: Current Approach To Paediatric Forecasting And Quantification - UNAIDS/WHO - CHAI - MPP/WHO Facilitated discussion	John Stover, Avenir Health Astha Gupta, MPP Vineet Prabhu, CHAI Boniface Dongmo Nguimfack, WHO
10:30 – 11:00	Coffee Break	
11:00 – 12:00	Session 2: Country Perspective On Forecasting And Quantification - Lessons learnt from the ACT initiative - National forecasting challenges and needs Facilitated discussion	Josh Rosenfeld, USAID Country representatives (Kenya, South Africa, Brazil, DRC) Boniface Dongmo Nguimfack, WHO
12:30- 13:30	Lunch	
13:30 - 15:00	Session 3: Basis For Developing A Forecasting Module - Modelling disease progression and formulation need - CIPHER/leDea data to inform forecasting Facilitated discussion	Andrea Ciaranello, CEPAC Jeannie Collins, UCL Mary Ann Davies, UCT Martina Penazzato, WHO
15:00 – 15:30	Coffee Break	
15:30- 16:30	Session 4: Planning And Development Of Concept Note Facilitated discussion	Boniface Dongmo Nguimfack and Martina Penazzato, WHO
17:00 – 17:15	Wrap Up and Next Steps	Martina Penazzato, WHO Mary Mahy, UNAIDS

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