Modelling Paediatric HIV and the Need for Antiretroviral Therapy: October 2015

Report and recommendations from a meeting of the WHO and UNAIDS in collaboration with the UNAIDS Reference Group on Estimates, Modelling and Projections, London, UK, 28-29 October 2015

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, 2015

Although remarkable progress has been made in scaling up efforts to eliminate mother-to-child transmission (MTCT) of HIV, the global burden of paediatric HIV remains a significant health challenge.

In order to improve as well as support the procurement and development of paediatric antiretroviral treatment (ART), understanding trends in paediatric infections and the need for ART is critical. Unfortunately, limited surveillance data on this population in many countries has hampered efforts to accurately assess the number of children newly infected with HIV, children in need of treatment, and AIDS related deaths among children. Consequently, country programmes are heavily reliant on modelling approaches to produce estimates of these indicators.

In order to review and update current parameters and methods of paediatric HIV estimation, the World Health Organisation and UNAIDS in collaboration with the UNAIDS Reference Group convened a technical consultation in October 2015. The overall objectives of thismeeting were as follows:

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

The UNAIDS Reference Group on Estimates, Modelling and Projections

The Joint United Nations Programme on HIV/AIDS (UNAIDS) Reference Group on 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 acts as an 'open cohort' of epidemiologists, demographers, statisticians and public health experts. It is able to provide timely advice and also address ongoing 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 meeting featured both presentations combined with group discussion to generate consensus recommendations. Thirty-one experts attended the meeting from seven countries (see Appendix II for a complete list of participants), each not only contributed data, insights and analysis but also produced a set of recommendation for UNAIDS and WHO drafted at the meeting. We would like to thank them for their attendance and contributions at the outcome and consensus reached during this consultation.

The recommendations drafted at these meetings give guidance on the assumptions for the parameters used to produce estimates of HIV/AIDS, provides opportunity to review current approaches and also helps to identify information needs (earlier reports are published on the Reference Group website). This transparent process aims to allow the statistics and reports published by UNAIDS and WHO to be informed by partial, scientific peer review.

Current Methods in Spectrum for Estimates of Paediatric Infection

John Stover provided a brief overview of the way in which paediatric estimates of HIV and HIV-related indicators are calculated using Estimation and Projection Package (EPP) and the AIDS Impact Module (AIM) in Spectrum. As it becomes increasingly important to better understand the size and health needs of HIV-exposed and infected children, several key updates have been implemented in Spectrum in order to strengthen these estimates and projections.

The estimates of HIV among children rely upon many other estimates and assumptions – estimates of adult incidence from EPP are fed into AIM and distributed by age and sex (sex ratio of incidence and age and sex-specific incidence rate ratios). These new infections are tracked by CD4 resulting in a pattern of HIV prevalence that is subject to age-specific fertility rates (reduced for HIV+ women not on ART) to determine the number of pregnant women in need of prevention of mother-to-child transmission (PMTCT). HIV outcomes of children born to HIV+ mothers are largely dependent on timing of infection, treatment and prophylaxis strategies.

CD4 Model for Children
A child CD4 compartmental model has been implemented in the AIDS Impact Model in Spectrum. As with the adult model, it is used to track progression from infection by CD4 and can be used to determine the number of children eligible for treatment at any point in time based upon their CD4 count. Most children newly infected with HIV 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 cause, (3) die from AIDS, (4) progress to the next lower CD4 category, (5) initiate ART, or (6) migrate out of the population (Stover et al., 2010).

Child survival in the absence of ART
The child CD4 progression parameters are fit to match estimated survival curves by timing of infection (Marston, et al) and the CD4 distribution of HIV+ children from the Paediatric Prognostic Markers Collaborative Study (Dunn, et al). Milly Marston conducted a recent analysis, reviewing the current available data for survival of children infected at older ages in order to inform updated child survival patterns. Data from haemophiliacs (from Europe, US and Australia) infected at ages 5-14 years, indicate higher survival compared with young adults infected with HIV at ages 15-19 (currently used to inform child survival past ages 2-3 years). John Stover noted that a re-estimation of the child survival curves to fit these data would not only increase survival but would also increase, and potentially overestimate, the overall number of children living with HIV.

It was discussed that from a programme perspective, it is problematic to have changes in estimates due to model parameter changes, particularly with all the investments to reduce mother-to-child transmission (MTCT). In addition, countries still cannot find the children they are estimated to have already, let alone additional children. It was further discussed that the data from haemophiliacs are not necessarily representative of sub-Saharan Africa where the majority of children infected with HIV are.

Child survival on ART
Countries enter the total number of children under 15 years on ART, and Spectrum has to allocate ART by age, sex and CD4 with limited information to inform this allocation for specific countries. Therefore data from the IeDEA Consortium are used to inform patterns of mortality by region, sex, age and CD4 can be used if countries do not have national data.

John Stover noted that early infant diagnosis (EID) has also been added to the model to indicate what percent of children are started on ART by 8 weeks, but it had minimal effect in the 2015 model.

Comparing Modelled Estimates and Survey Results of HIV in Children
There are limited data from national surveys to compare with the modelled estimates. The available national survey data from Kenya (2012), Botswana (2008) and Swaziland (2006-7) were compared with the Spectrum estimates and do not provide further clarity (compounded with very large confidence intervals). In general the Spectrum estimates appear reasonable, but are higher (Kenya), lower (Botswana) and comparable (Swaziland, but both higher and lower across ages) compared to the survey prevalence.

Outstanding Challenges with Current Prevention of Mother-to-Child Transmission (PMTCT) Estimates

Mary Mahy examined how the adult surveillance and survey data utilized by Spectrum to inform adult estimates of infection affect the estimates of coverage of prevention of mother-to-child transmission (PMTCT). That is, the total number of women counted by the programme to be receiving antiretroviral therapy, versus the total number of HIV+ pregnant women.

In the 2014 UNAIDS estimates, a number of countries with high quality PMTCT programme data, including Namibia, South Africa, Rwanda and Swaziland, had estimates of PMTCT coverage of 100% or more . Moreover, a number of concentrated epidemics had PMTCT coverage over 100%. Further investigation is required to reduce double counting (Malawi has adjusted their historical data following an evaluation that reduced double counting). In some countries the values over 100% might be due to double-counting, however, given that some countries with high quality data, such as South Africa and Rwanda, are still estimating 100% PMTCT coverage, there is a need to further interrogate the methods used. Other potential factors include:

- HIV prevalence among reproductive age women,
- Age-specific patterns of fertility
- The differential in fertility among HIV- and HIV+ women.

Estimates of HIV Prevalence by Age and Need for PMTCT
John Stover demonstrated that careful attention to the age pattern of HIV prevalence can potentially improve estimates of PMTCT coverage. Adjusting the incidence rate ratios (IRRs) by age in AIM to match patterns of HIV prevalence by age from national survey data can result in improved estimates of PMTCT coverage in some instances. However this is a fairly un-intuitive adjustment. It might be possible to include a tool in Spectrum to help make these adjustments.

Fertility among HIV+ Women
There may be changes in fertility among HIV+ women in the ART era. In previous rounds of estimates, many countries have removed the fertility discount for HIV+ women. In the 2014 round, the adjustment was removed for the proportion of women receiving treatment. Thus, the model assumed there is no difference in fertility between HIV+ women receiving treatment and HIV- women. This modification is based on the hypothesis that the much earlier commencement of treatment in the ART era will potentially negate HIV-related subfertility (but is not backed up by data at present).

Recommendations

- ***Countries should review total fertility rate and age distribution provided by UN Population Division. (UNAIDS to add to guidance) Furthermore, they should revise the demographic inputs if they have more recent and accurate data.***
- ***Avenir Health to investigate automating adjustment to incidence rate ratios to match to prevalence from national survey.***

- ***UNAIDS to provide guidance to ensure countries review prevalence by age (validation tools).***
- ***Avenir Health to add EID to the validation page so that countries can triangulate EID results against treatment results.***

Fertility in the Era of ART

The current Spectrum model assumes that subfertility for untreated women is a function of age, thus inferring that the age-adjusted fertility rate as compared with HIV- women will remain constant over the course of the epidemic. For HIV+ women on ART, Spectrum assumes there is no fertility discount.

Basia Zaba used the Bongaarts' proximate determinants of fertility framework, to consider the underlying mechanisms through which ART may impact the fertility of HIV+ women. She postulated that although HIV has been shown to reduce the fertility at both the individual and the population level, the scale-up of ART access has influenced both the biological and behavioural determinants of fertility among infected women.

A systematic review by Sara Yeatman found that there has been an increase in fertility of HIV+ women in the ART era which appears to increase with time on ART. However, from the published literature available, HIV+ women still have reduced fertility compared to HIV- women (Yeatman, et al, forthcoming). Analyses from ALPHA network data illustrated similar findings with fertility disparities between HIV+ and HIV- women narrowing over time (fertility "rebound"), but still remaining.

Jeff Eaton and Milly Marston proposed a new method which aims to better represent the effects of HIV and ART on fertility by incorporating subfertility by age and stage of HIV infection in Spectrum. Unlike the current model which estimates subfertility by age, modelling reduced fertility associated with disease stage endogenously captures the consequences for fertility of women at later disease stages. Data from three ALPHA network sites (Rakai, Masaka and Kisesa) were used to estimate, fertility rate ratios (FRR) of HIV+ women (relative to HIV-) by age and duration of infection, in the pre-ART era (1998-2005). Regression analyses were adjusted for differences in age-specific fertility rates according to the respective study sites as well as the population fertility trend over time.

Regression results found that FRR declined with duration of infection for untreated women. The residual age pattern (following adjustment of duration of infection), demonstrated that among younger women aged 15–19 years, fertility was higher among HIV+ women than HIV-, while among women aged 40+ fertility was lower among HIV+ women than HIV-, indicative of widowhood or volitional effects. The fertility trend by duration of infection was used to derive FRRs associated with each stage of infection such that the model simulation for fertility by duration of infection matched the regression results, illustrating that the observed data were consistent with decreasing fertility with each CD4 stage.

Given these findings, Jeff Eaton suggested that this approach should capture the FRR by stage of infection. Additionally, some baseline assumptions are required about fertility while on ART. It was assumed that ART will have no effect on fertility during the first year of treatment (same fertility as women in CD4 stage from which ART is initiated). Following the first year of ART, age-adjusted fertility of women on ART was assumed to be 0.8 that of HIV- women, based on evidence from Malawi that fertility of women on ART was higher than untreated women, but lower than HIV- women.

It was illustrated that when applying these assumptions to the Spectrum epidemic model, the model predicted a narrowing of TFR between HIV- and HIV+ women at the population level, consistent with longitudinal data from the ALPHA network. Thus it was concluded that we can represent the natural dynamics of PMTCT need as ART scales up in the current Spectrum model structure – as it captures both fertility among women on ART and the consequences not on ART.

Recommendations

- ***Further testing of this approach, incorporating the new adult progression parameters that are being incorporated into Spectrum in the upcoming round.***
- ***It was also recommended that Jeff Eaton compare the results with the Chen and Walker (2010) results, and to provide an appropriate representation of uncertainty.***
- ***It was agreed that pending these modifications, Avenir Health would implement Jeff Eaton's proposed calculation in time for the upcoming round of estimates.***

Estimates of the probabilities of Mother-to-Child-Transmission of HIV

Lynne Mofenson updated the PMTCT probabilities calculated in the 2011, Nigel Rollins et al paper (Rollins et al., 2011) These probabilities inform the model parameters for the probability of transmission of HIV from mother-to-child depending on stage of infection of the mother, the duration of breastfeeding, and the prophylactic regimen. The update was necessary because of new research on mother to child transmission by different regimens and because a probability was needed for women who started on ART irrespective of CD4 count (Option B+)

Lynne's analyses found some changes to the probabilities based on the latest research. In particular, the probability of MTCT during incident HIV infection was much lower. She noted that initiation of ART prior to conception could have a transmission probability as low as 0.019%.

The transmission probabilities for each scenario were calculated as the mean average of each study and were not weighted according to the study sample size. Moreover, children that were lost to follow-up were not accounted for. It was agreed that the UNAIDS Reference Group Secretariat to identify someone to re-conduct a weighted meta-analysis of these probabilities. The resulting estimates would then be formatted and entered in to Spectrum as defaults values for the next round of estimates. Mary Mahy noted that past estimates of the transmission probabilities were determined using the median value of reported data due to the limited data available at that time and the subsequent variability across studies. It was agreed that with the data available now, it is no longer necessary to use median values.

Recommendations:

- ***Implement updated MTCT values based on revised systematic review, but pending meta-analysis coordinated by the Reference Group***

Postpartum HIV Transmission

Current WHO guidelines for ARVs recommend the use of ARVs to prevent postnatal transmission of HIV throughout the breastfeeding period. Where national authorities promote breastfeeding and ARVs, mothers known to be HIV-infected are recommended to breastfeed their infants until at least 12 months of age.

Nigel Rollins showed that in most high prevalence countries (19 out of the 21 priority countries), breastfeeding with ART is recommended. Moreover, there is some data to suggest HIV+ mothers are

exclusively breastfeeding more than uninfected mothers, perhaps due to the support and guidance being provided by HIV services. It also appears that attitudes and patterns of breastfeeding have changed over time and may continue to change. The Mma Bana Study in Botswana, a country where formula had been a default recommendation for mothers living with HIV, found in a 2010 study investigating the efficacy of ART during breastfeeding that only 8.8% declined enrolment in the study in favour of formula feeds (Shapiro et al., 2010).

Breastfeeding practices among HIV+ women may continue to change. As a result, the use of breastfeeding patterns from DHS data, which are not disaggregated according to HIV status, may become increasingly unreliable for informing the duration of exclusive breastfeeding among HIV+ women in Spectrum,. In addition, these patterns may change over time.

Finally, there is great uncertainty surrounding both retention in care (PMTCT) and adherence, including adherence to ART and adherence to postnatal prophylaxis regimens. Both of these issues will affect estimates of mother-to-child transmission.

Priscilla Idele reported back on the IATT meeting on monitoring Option B+. She outlined the mother and infant tracking that countries are using to monitor retention. She highlighted that Zambia had implemented an electronic Smartcare Card and unique identifiers to monitor mother and child pairs, while most other countries have remained dependent upon the use of longitudinal ART and ANC cohort registers. Better integration is needed between ART and PMTCT monitoring to obtain national data on retention disaggregated by pregnancy and breastfeeding status. In addition, it was suggested that final outcome data for children, may be suitable proxies for estimating programme impact during the postpartum period.

Recommendations

- ***Standardised definition for retention/attrition is needed. Follow-up: IATT Monitoring and Evaluation Working Group***
- ***The IATT Monitoring and Evaluation Working Group also agreed to look into other countries (e.g. Kenya, Rwanda) with possible data on retention among breastfeeding women, to better inform the assumptions currently used for the default monthly dropout rate of postnatal prophylaxis***
- ***Lynne Mofenson also highlighted that the first 6 months is the critical time for dropout. However, the monthly dropout rate assumed in Spectrum was calculated by taking the 12 month drop-out rate from Malawi and spreading this out evenly over 12 months. Given that in the data observed there is a higher initial dropout rate, then a lower dropout rate (ie it is not constant over time) – John Stover mentioned he would look into the Malawi data and see if he could better inform this assumption. Andrea and the IATT Monitoring and Evaluation Working Group will look into other countries with data to inform this assumption.***

An Evaluation of the Spectrum Model of Breastfeeding Transmission of HIV and an Alternative Model

Peter Johnson (CDC) provided an overview of the current Spectrum methods for calculating breastfeeding transmission and proposed an alternative method. He highlighted that in the current model, the denominator of the MTCT rate only includes the number of HIV+ mothers who have given birth; however, HIV- mothers who get infected are at risk of incident infection of their children. In addition, the placement of new child infections by age and time period is not correct, Spectrum assumes that the breastfeeding transmission rate is a linear function of weighted risks of transmission over four segments of the breastfeeding period, and incident infections are treated

similarly to other risks (incorporated into the breastfeeding transmission rate in the four breastfeeding segments).

Peter Johnson suggests a new model which tracks mother-child pairs. This approach allows for better tracking of mother child pairs with different risk of transmission to the child, it attempts to place new child infections in the correct child age and time period, it allows assessment of exposure to risk and new infections by group, and incident infections are straightforward. Further work and development of this approach is ongoing

Recommendations

- ***Avenir Health agreed to liaise with Peter Johnson, to discuss the current issues identified in Spectrum, and consider the use of an alternative breastfeeding code.***

Treatment Initiation and Survival of Children and Adolescents on ART

The estimates of child mortality on ART in Spectrum are derived from data from the International Epidemiologic Databases to Evaluate AIDS (IeDEA). These estimates vary by CD4 age, duration on treatment and across region. The WHO treatment guidelines for ART eligibility among children have changed over time and these changes are reflected in the data will illustrates 2013 an evident decline in the average age at ART start from 2004 to 2012, in East, West and Central Africa as well as the Asia Pacific region. The median age at ART initiation in children <5 years is approximately 3 years for East, West and Central Africa and 2 years for Asia Pacific and CCASAnet, but has been changing over time (earlier initiation) in response to the changing guidelines.

It was highlighted, that there are differences between the country-level data and the regional estimates. Given this variability and uncertainty regarding the quality of the data at the country-level, is was agreed that at present regional data may be more representative general population trends.

Recommendations

- **To implement median age at ART initiation from IeDEA data (by region) into Spectrum and compare the result. Follow-up: John Stover, Constantin Yiannoutsos after triangulating those data against any available national data or PEPFAR data**

CIPHER

Mary Ann Davies gave an overview of the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), aimed at optimising clinical management and delivery of services to infants, children and adolescents affected by HIV in resource-limited settings through advocacy and research promotion. She spoke specifically of its cohort collaboration, which comprises 12 networks and over 100 individual cohorts. She outlined two key projects:

1. *Time on first-line ARV's in children: The aim of this project is to estimate incidence of treatment switch to second line ART by: age, CD4 per cent and AID status at ART initiation, initial regimen, calendar year, country/region and country income group.*
2. *Adolescent Epidemiology: The aim of this project is to describe the global epidemiology of perinatally HIV-infected adolescents and compare outcome across regional and patient-level contexts.*

Speaking specifically in relation to the adolescent population living with HIV, Mary Ann Davies highlighted the work of Leigh Johnson (2012) – the number of children on ART has changed significantly since 2000 and is likely to continue to do so. As we look forward at projections for 2020

for South Africa, Leigh Johnson has shown that the burden of paediatric HIV will have shifted to the adolescent age, as a result there will be a much larger proportion on ART.

Comparisons between data in 2008 and 2014, in South Africa from IeDEA, nearly a quarter of children aged 10 years and above are recorded to have some follow-up. Among this population we see very low mortality among those on ART. However, this is still four times the mortality of the HIV uninfected population. A high LTFU has also been identified - it was suggested that we may need to inflate current mortality rates, so as not to miss the deaths that may be occurring as a result of LTFU. However, Mary Ann Davies noted that up to the age of 15 years, the cohorts have linked LTFU to deaths recorded at the death registry.

ICAP and PHIA

On behalf of Chloe Teasdale and Elaine Abrams, Fatima Tsouris provided an overview of multi-country data from the Optimal Models cohort of the CIPHER network, focusing specifically on retention of children and adolescents in ICAP supported HIV treatment programmes.

She highlighted that the key challenge in obtaining and understanding data pertaining to children on ART is retention in care. Approximately 27%-39% of cohorts of children in Uganda, South Africa and Mozambique have been lost to follow-up following their first clinic visit (initial diagnosis). For example, in Mozambique, 17% children under the age of 15 years were shown to have no recorded visits following the date of enrolment into care. In addition, several published analyses have not accounted for these figures and are thus, are contributing to underestimates of lost to follow-up.

Consequently, many children are not being initiated on ARV therapy; in the Optimal Model Ethiopia cohort, between 2006 and 2013, almost 20% of 2090 children were LTFU before ART initiation. And, under 50% of children under the age of five years (n=2567) were initiated on ART. And as we move along the care continuum there continues to be further LTFU following ART initiation. It was agreed that ICAP should investigate time trends in these analyses, ie to look at the most recent period as opposed to entire time series pooled together.

Cumulative incidence of LTFU and death post-ART initiation among children under 15 years in Kenya, Mozambique, Rwanda and Tanzania over a five year period (2005-10) showed that almost 75% of children had died or were LTFU by 2 years on ART – with the median age of survival at 4 years. Furthermore, this is a likely underestimate given that there may be undocumented deaths due to LTFU.

Although children appear to be at highest risk of LTFU, high rates have been recorded among adolescents aged 10-19 and youth aged 20-24, both before and after ART initiation. Unlike younger children, adolescents and youth have different needs. Adolescents are often children that were perinatally infected children who have aged into adolescence. They are likely to be sicker overall as they enter care. Youth on the other hand tend to represent behaviourally infected individuals – a large proportion of whom are young women, who are identified as a result of pregnancy. Unlike adolescents, they are likely to be in better health which may contribute to LTFU.

There are a number of limitations with the current programme data. Paper systems are most commonly used; however, most retention data is often reported from electronic systems. As such, it is unclear what percentage of the HIV population is actually being captured by these systems. Furthermore, there are significant issues with data quality and missing data.

ICAP has been funded by CDC to carry out Population HIV Impact Assessments (PHIA). The goal is to implement household based HIV focused national surveys within the general population of 15-20

African countries over a five year period (2014-19). The results will be used assess national and regional cascades and guide the use of resources and future efforts to control the epidemic. Zimbabwe and Malawi have just launched PHIAs which include infants, adolescent and children. Fatima suggested that this would be particularly relevant in updating Spectrum given the current lack of data to parameterise the child Spectrum model.

First and Second Line ART in Children

Using data from trials and cohorts as well as ongoing analyses of EPPICC and IeDEA data Intira Jeannie Collins (UCL) examined the estimations for expected duration on first line ART in children as well as the estimated need for second line ART.

Recommendations

- ***Despite discussions during the main Reference Group meeting and this meeting regarding whether adolescent results should be displayed in Spectrum, it was suggested that the results would need to be reviewed given changes with the new parameters (from IeDEA) before we choose to commit to this. It was agreed that the results would likely be reasonable given we have fairly reliable distribution of children on ART. John Stover to conduct this with systematic testing during December/January.***
- ***CIPHER, others to pull together analyses on disengagement from care, alive (as opposed to transfer, death) for Spectrum and determine whether varies by: duration on ART, age at initiation, CD4 count and region.***
- ***ICAP to investigate age-specific time trends in LTFU following ART initiation, i.e. to look at the most recent period as opposed to entire time series pooled together.***
- ***2014 Guidelines recommend use of Cotrimoxazole for all children and adolescents living with HIV irrespective of ART status and CD4 count – this needs to be updated in Spectrum.***

Forecasting and Programme Planning

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 Ciaranello 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.

Projected Demand for Paediatric ARV's

Vineet Prabhu from CHAI provided a useful overview of the challenges around the paediatric ARV market. Although the paediatric ARV market is much smaller than the adult market – it is far more complex. Unlike adults, where ARVs may be as simple as one pill once a day – among the paediatric population, there are multiple ages, weight-bands and regimens that need to be accounted for when

developing and producing formulations. As such, these complexities are often considered to be problematic for the market.

In particular, suppliers are limited by minimum batch requirements – manufacturers produce a minimum quantity of a particular product at a time. A product will not be produced until orders meet the minimum batch requirement; otherwise, supplier risk incurring losses from carrying stock which fall below a country's shelf-life requirement. CHAI produces a global ARV forecast using Spectrum outputs combined with ARV and lab prices, operational and human resource costs, treatment norms and testing algorithms, then generates different scenarios to produce estimates of patient numbers and costs under these scenarios.

In collaboration with CHAI and several other partners, WHO and UNAIDS published the "Antiretroviral Medicines in Low and Middle Income Countries: Forecasts of Global and Regional Demand for 2014 -18". The purpose of this effort was to project the future demand for ARVs in children, to inform manufacturers and suppliers and ensure there is sufficient supply,

The main data sources used for this effort are:

- the Global AIDS Response Progress Reporting online country reporting tool
- WHO ARV survey – country reports of the regimens currently used in countries. Typically, the survey receives fairly good coverage – in the last year 85 countries participated.
- Procurement – data reported to WHO which aids in validating the other databases.

Projections are made 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 ARVs is estimated accordingly. Given that pharmaceutical companies are often focused on the short term – linear extrapolations of past trends of actual numbers receiving ARVs are used to estimate the volume of ART required. The same analyses are also conducted for diagnostic tests i.e. EID tests.

Recommendations

- ***While more detailed modelling is currently out of the scope of Spectrum the group highlighted that it would be helpful to have drug forecasting all coordinated in a single model (additional module in Spectrum that can be turned on/off). This module would build upon additional modelling work including CEPAC and CHAI.***

Next Steps

The next round of estimates will be produced in the first half of 2016. Software will be available to countries in early February and they are expected to submit their updated files in early April. Specific updates to the software include:

- Adjustment to the fertility discount to reduce fertility based on time since infection and age instead of age only
- Guidance to countries to check basic demographics of fertility and population distribution and a tool to adjust incidence rate ratios to match resulting prevalence to survey data by age and sex.
- Revised transmission probabilities including the probability for transmission regardless of CD4 value
- A new default distribution of children starting ART by age group based on data from IeDEA which is validated against national estimates or programme estimates.
- Review code for calculating breastfeeding transmission based on comments from Peter Johnson, and specifically on start time of breastfeeding transmission.

- Consider adding a dropout rate that is variable over duration of breastfeeding since retention is much worse during the first 6 months of breastfeeding.

These modifications are likely to have important impacts on the estimated number of children infected, the number of children living with HIV, and AIDS related deaths. In the previous versions of Spectrum the children receiving ART was spread evenly across all age groups. Evidence from multiple sources suggests that children were not started on ART until they were much older potentially skewing the number of AIDS deaths. A clear technical description of why these changes happened will be needed.

To improve future inputs to the models primary data on breastfeeding practices is still needed, particularly from countries who have adopted the B+ option. In addition the IATT M&E working group was asked to follow up on two items:

- Develop a standardized definition for retention among pregnant women and breastfeeding women.
- Identify a few countries with good data on retention to use as default data until more reliable data are available.

Overall the group recognised the need for funding to support the activities of this paediatric working groups as well as related specific projects to improve data input and background assumptions.

References

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Appendix I

In Collaboration With The UNAIDS Reference Group On Estimates Modelling And Projections
Modelling paediatric HIV and the need for ART

	Time	Agenda Item	Presenter/Moderator
October 28h (DAY 1)		**Chair: Tim Hallett**	
	9:30 – 9:40	Opening remarks	Timothy Hallett (Imperial College London) Txema Garcia-Calleja (WHO)
	9:40 – 10:00 10:00 – 10:20	• Summary of previous meeting • Overview of the child model in Spectrum	Martina Penazzato (WHO) John Stover (Avenir Health)
	10:20 – 10:30	Outstanding challenges in Spectrum	Mary Mahy (UNAIDS)
	10:30 – 11:00	Coffee Break	
	11:00- 11:45	**Session 1: HIV prevalence** • HIV prevalence by age groups • Trends in prevalence among adolescents	John Stover (Avenir Health) Priscilla Idele (UNICEF)
	11:45- 13:00	**Session 2: The interaction of fertility and HIV** • Fertility and ART • Literature review • Empirical data from ALPHA • Sub-fertility by stage of HIV infection	Basia Zaba (LSHTM) Sara Yeatman (LSHTM) Milly Marston (LSHTM) Jeffrey Eaton (Imperial College London)
	13.00- 14.00	Lunch	
	14:00 - 15:30	**Session 4**: **MTCT transmission** • Updated transmission probabilities • BF duration: impact on HIV transmission • Estimating breastfeeding transmission • Retention among BF women • Postnatal period: potential data input (feedback from the B plus framework meeting)	Lynne Mofenson () Andrea Ciaranello (CEPAC) Peter Johnson (US Census) Nigel Rollins (WHO) IATT M&EWG
	15:30 – 16.00	Coffee Break	

	16:00- 17:00	**Session 5: Mortality and treatment**
		
		• Age at start of ART initiation among kids
		• Country perspective
		  ○ High prevalence
		  ○ Low prevalence
			Costantin Yiannoutsos (IeDEA)
			Wilford Kirungi (MOH Uganda)
			Mutsa Mhangara (Zimbabwe
			Naoko Ishikawa (WHO)

	17:10 –17:30	Discussion and next steps	Timothy Hallett (Imperial College London)

	TIME	AGENDA ITEM	Presenter/Moderator
October 29th (DAY 2)		Chair: Simon Gregson	
	9:00 – 9:10	**Summary Day 1**	Mary Mahy (UNAIDS)
	9:10- 10:30	**Session 7: Disease progression and treatment sequencing** – Modelling disease progression – 1st and 2nd line regimens – CIPHER data to inform models – Retention across the age spectrum	Andrea Ciaranello (CEPAC) Jeannie Collins (CTU-MRC) Mary-Ann Davies (UCT-IeDea) Fatima Tsiouris (ICAP)
	10:30 – 11:00	Coffee Break	
	11:00 – 12:30	**Session 8: Improving forecasting** – Current approach to global paediatric forecasting – National forecasting challenges and needs High prevalence Low Prevalence	John Stover (Avenir Health) Vineet Prabhu (CHAI) Cordelia Katureebe/Wilford Kirungi (MOH Uganda) Mutsa Mhangara (Zimbabwe Naoko Ishikawa (WHO) Guo Wei (China)
	12:30 – 13:30	Lunch	
	13:30 - 15:00	**Session 9: Adolescents** • Pediatric ART data required for PEPFAR • Surival among vertically infected	Jamie Houston (CDC) Mary-Ann Davies (UCT-IeDea)
	15:00 –15:30	Coffee Break	
	15:30 –15:45	**Next Steps**	Martina Penazzato (WHO)
	15:45 – 16:00	**Closing remarks**	Mary Mahy (UNAIDS) Txema Garcia-Calleja (WHO)

Appendix II

In Collaboration With The UNAIDS Reference Group On Estimates Modelling And Projections
Modelling Paediatric HIV and the Need for ART

LIST OF PARTICIPANTS

Anouk Amzel USAID Washington DC, USA aamzel@usaid.gov	**Renaud Becquet** Bordeaux School of Public Health France Renaud.Becquet@isped.u-bordeaux2.fr
Lorna Benton University College London London, UK Lorna.Benton@phe.gov.uk	**Kelsey Case** Imperial College London London, UK k.case@imperial.ac.uk
Andrea Ciaranello Massachusetts General Hospital Boston, USA ACIARANELLO@mgh.harvard.edu	**Jeannie Intira Collins** CTU- Medical Research Council (UCL) London, UK jic@ctu.mrc.ac.uk
Mary-Ann Davies University of Cape Town Cape Town, South Africa Mary-Ann.Davies@uct.ac.za	**Jeffrey Eaton** Imperial College London London, UK jeffrey.eaton@imperial.ac.uk
Simon Gregson Imperial College London London, UK s.gregson@imperial.ac.uk	**Timothy Hallett** Imperial College London London, UK timothy.hallett@imperial.ac.uk
James Houston Centers for Disease Control and Prevention Atlanta, US vie3@cdc.gov	**Wilford Kirungi** Ministry of Health Kampala, Uganda wkirungi@starcom.co.ug
Peter Johnson US Census Bureau Washington DC peter.d.johnson@census.gov	**Cordelia Katureebe** Ministry of Health Kampala, Uganda katureebecordelia@gmail.com
Priscilla Idele UNICEF New York, US Pidele@unicef.org	**Chewe Luo** UNICEF New York, US cluo@unicef.org
Mary Mahy UNAIDS Geneva, Switzerland mahym@unaids.org	**Kimberley Marsh** UNAIDS Geneva, Switzerland marshk@unaids.org

Mutsa Mhangara Ministry of Health & Child Welfare Zimbabwe mutsa.mhangara@gmail.com	**Lynne Mofenson** EGPAF Washington, US mofensol@gmail.com
Vineet Prabhu, Clinton Health Access Initiative New York, US vprabhu@clintonhealthaccess.org	**Marie-Louise Newell** University of Southampton Southampton, UK M.Newell@soton.ac.uk
John Stover Avenir Health Glastonbury, CT, USA JStover@avenirhealth.org	**Guy Mahiane** Avenir Health Glastonbury, CT, USA gmahiane@avenirhealth.org
Basia Zaba London School of Hygiene and Tropical Medicine London, UK Basia.Zaba@lshtm.ac.uk	**Sara Yeatman** UC Denver Denver, US Sara.Yeatman@ucdenver.edu
Brian Rice London School of Hygiene and Tropical Medicine London, UK Brian.rice@lshtm.ac.uk	**Fatima Oliveira Tsiouris** ICAP – Columbia University New York, US fao2001@cumc.columbia.edu
Constantin Yiannoutsos IeDEA - University of Indiana Indiana, US cyiannou@iupui.edu	**Wei Guo** National Centre for AIDS/STC Control and Prevention, China Guowei_cdc@sina.com
Tim Brown East-West Centre Honolulu, Hawaii tim@hawaii.edu	**Eline Korenromp** Avenir Health Glastonbury, CT, USA EKorenromp@avenirhealth.org

Nigel Rollins Medical Officer MCA Department rollinsn@who.int	**Martina Penazzato** Medical Officer HIV/AIDS Department penazzatom@who.int
Jesus Maria Garcia Calleja Technical Officer HQ/SIP Strategic Information and Planning callejaj@who.int	**Ishikawa Naoko** WP/HSI Sexually Transmitted Infections, including HIV/AIDS Manila, Philippines ishikawan@who.int