

IATT Webinar: 2016 Paediatric HIV Modelling and Estimates
June 7, 2016

A total of **88 participants** from DRC, Senegal, Switzerland, South Africa, Mozambique, Namibia, Tanzania, Zimbabwe and many other countries attended the webinar to learn about changes made to the Spectrum model and the 2015 paediatric HIV estimates. These data are the model inputs that generate the estimates used to measure performance against globally recognized indicators related to the elimination of Mother-to-Child transmission of HIV (EMTCT) and paediatric HIV. The changes made to the model were driven by new evidence that improves the outputs. The main message was that we now have **a better understanding of the probability of MTCT rates**, which are lower than previously thought, **and better data on what age children start antiretroviral treatment (ART)**. Both of these factors contributed to the reduction in the number of children living with HIV (CLHIV) and subsequent higher rates of pediatric ART coverage. Revisions to the assumptions in the model produced three main changes in results:

- Slight decrease in the number of new paediatric infections year over year (the model is applied to all previous years so that years are comparable to each other)
- Significantly fewer children living with HIV due to the lower number of new infections over time, the aging out of children from <15 to >15 years of age and from death;
- Slight decreases in paediatric AIDS-related deaths.

Overall, the webinar provided a better understanding of what the numbers mean, how the estimates are calculated, and the challenges and uncertainties involved in calculating them.

Presentation 1: Improving Paediatric Estimates: Process and Milestones, Martina Penazzato, Paediatric Advisor, HIV Department, WHO

- Drawing on the work of the UNAIDS Paediatric Reference Working Group, which was tasked with conducting a scenario exercise to: estimate the number of children living with HIV by 2020, and better understand other dimensions of the paediatric HIV epidemic it was concluded that Spectrum may not be as sensitive to changes as previously thought.
- This lower sensitivity was thought to potentially impact the number of children living with HIV. Therefore, the group identified the need for more accurate estimates on paediatric HIV.
- The working group convened technical consultations, to refine and adjust Spectrum, with epidemiologists, modelists and technical paediatric HIV experts to discuss the natural history of children on ART and programmatic experience from countries. The first meeting held in October 2015 reviewed the proposed structure, parameters and data sources for the modelling approach. It was agreed to build on Spectrum, which is an established model that countries rely on.
- Consensus was gained on what key drivers were to be used to estimate the number of children living with HIV. These included:
 - **New paediatric infections and survival rates:**
 - New paediatric infections are driven by:
 - Fertility differentials in women living with HIV (on ART) and changing patterns over time, and concentrated epidemics
 - Breastfeeding (BF) patterns in HIV-infected vs. the general population
 - HIV drug resistance (HIVDR) impact on Mother-to-Child transmission rate
 - Adherence to interventions
 - Length of first line regimen that may impact transmission in pregnant women

- Paediatric survival is driven by:
 - Child's median age at identification and at initiation of ART
 - Survival off ART
 - Survival on ART, by age at initiation and time since initiation
 - Adherence and retention
 - Failure by line of treatment, and time from initiation
- As the Spectrum models are being refined, the scale up of Option B+ contributed to a significant decline in the number of new HIV infections among children.
- Going forward, it is clear that Spectrum may need to better capture programme realities, such as retention and adherence, which affect parameters included in the model.
 - We may need a more granular approach to modeling (e.g., what is the history of individuals on ART, especially in terms of survival).
 - There is a strong link between the need to improve forecasting of paediatric ARVs, the development of a forecasting model in the context of a more granular structure.
- Funding is needed to support primary data collection, and conduct additional research and analyses.
- A follow up meeting (of the group of experts) is scheduled for the fall of 2016, to continue to refine pediatric HIV estimates.

Presentation 2 - 2016 Paediatric Estimation Methods, Mary Mahy, Division Chief, Strategic Information and Monitoring, UNAIDS Geneva

Background and Context

- HIV estimates are updated every year. This occurs for two reasons: 1) new surveillance and programme data are entered into the model; this can change HIV prevalence and incidence trends over time, including for past years; and 2) improvements are incorporated into the model based on the latest available science and understanding of the epidemic. This also means that historical data (up to 1970) are also updated on an annual basis. The 2016 estimates cover the years 1970 through 2015.
- It is important to understand the changes in the Spectrum model, and how these changes influenced the data or whether changes actually reflect differences in programme performance.
- UNAIDS along with partners (WHO and UNICEF) supports countries to annually update the models used to estimate the impact of HIV on their populations. The models are created using the Spectrum computer package, AIDS impact module (www.avenirhealth.org).
- Software development is guided by the UNAIDS Reference Group on Estimates, Modeling and Projections – a group of experts that advise on the methods used for the HIV estimates (www.epidem.org). The assumptions around the child estimates benefit from an additional working group that focuses specifically on paediatric HIV.
- The recommendations from the reference group are implemented in the software annually. Using updated models, country HIV estimates teams add their most recent programme and surveillance data to the models to produce annual HIV estimates. The models are sent to UNAIDS for review and eventually compilation for reports and to include in UNAIDS publicly-available database (aidsinfo.unaids.org). Every year the new set of estimates include revised historical estimates and estimates for the most recently completed year.

- Inputs for Spectrum include: demographic data; programme statistics; epidemic patterns, which provide demographic and epidemiological calculations; and surveillance and survey data, which inform prevalence to incidence trends.
- A detailed description of the Methods for Deriving UNAIDS Estimates can be found [here](#). While this webinar focuses on the estimates related to children living with HIV and pediatric ART coverage, please visit www.epidem.org for more general information on the calculation of all HIV-related estimates.

How does the model currently work?

- Estimating the number new HIV infections among children:
 - The total fertility rate, age distribution of fertility, and number of women of reproductive age are included, which informs the number of births to women living with HIV. This includes for both women on ARVs and not on ARVs, as the fertility rate varies.
 - Programme data on ARVs and BF patterns then allow for the calculation of the number of new HIV infections among children. These data also allow for better recognition of the difference in effectiveness at prevention mother-to-child transmission of HIV (PMTCT), depending on ARV regimen and BF patterns.
 - New child infections, and the distribution of CLHIV at different CD4 percentages.
- Survival patterns (on and off ART):
 - Data on paediatric deaths show the patterns of survival by timing of infection, and by CD4 percentage groups.
 - Children who are infected during pregnancy are less likely to survive, while older CLHIV (further away from delivery) are more likely to live longer. This is the survival probability.

Data on survival while on ART is taken from International Epidemiological Database to Evaluate AIDS [leDEA](#), a consortium of ART providers that provide access to various cohorts of HIV-related data

- Research analysis was performed to look at the current understanding of MTCT probabilities who provided data on patients on ART. These data show the survival rates of children of different age groups and gender, for different time periods. (Mortality is higher among children with a lower CD4 % level.)

Changes made to model and discussing the results

Three main changes in results:

- Slight decrease in the number of new paediatric infections year over year (the model is applied to all previous years so that years are comparable to each other)
- Significantly fewer children living with HIV due to the lower number of new infections over time, the aging out of children from <15 to >15 years of age and from death;
- Slight decreases in paediatric AIDS-related deaths.

What accounts for these differences and how were estimates improved?

- This was last done in 2012, and there are now more data available to improve understanding of MTCT probabilities. Looked at leDEA data on the distribution of when children were actually starting ART.
 - It was previously assumed that the distribution of ART initiation reflected proportionately to when children became eligible for ART. This previous approach did not account for delays in starting treatment until older age.
- Looked at the drop-out rate of women on ART during the BF period, and whether new infections taking place during BF were not being captured in the model.

- Test results also suggest that there are many fewer children living with HIV as well.

Updated transmission probabilities between a mother and children:

- The model assigns a probability of transmission from a mother to her child based on whether or not the mother received antiretroviral medicines to prevent transmission to her child and, if she did receive medicine, which regimen she received.
- The last review of the probability of transmission was conducted in 2012 (Rollins et al. *Sex Transm Infect* 2012;88:i44-i51).
- The most important difference from the updated analysis was in the transmission risk among women who seroconverted during their pregnancy. The probability of transmission among women who seroconverted during pregnancy is now believed to be 18% while previous analysis suggested it was 30%. (Please note that these percentages reflect only changes to the model and not the results or indicators).
- This change in the transmission risk has implications in the estimated 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) start ARVS earlier, which means that the probability of MTCT per month is lower.
- The previous transmission probabilities resulted in an overestimate of the number of children newly infected with HIV (figure 1) and, consequently, the number living with HIV (figure 2).

Figure 1: Number of children (0-14 years) newly infected with HIV, globally, 1990-2015

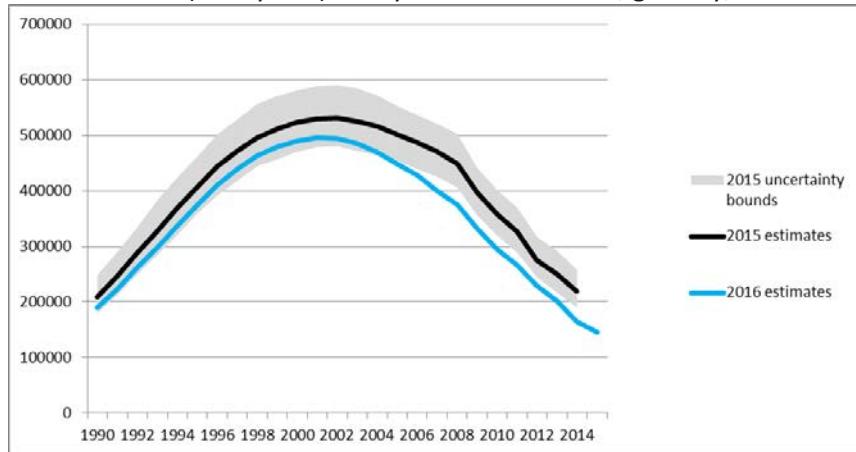
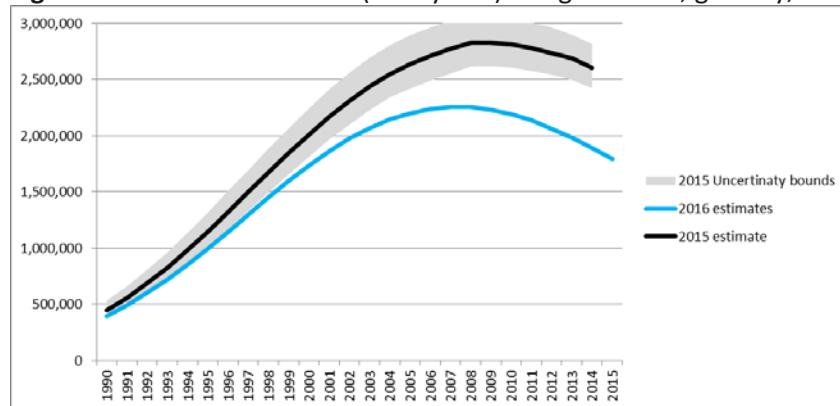


Figure 2: Number of children (0-14 years) living with HIV, globally, 1990-2015



Median age of paediatric ART initiation:

- Determining the survival patterns of children who are infected with HIV it is necessary to know at what age they start ART
- It was known that the age distribution of *when* children started ART was not fully accurate, but these data were not widely available in countries. The previous model assumed that children were started according to when they became eligible for treatment based on national guidelines.
- UNAIDS contacted IeDEA is able to provide these data (2002 - present) until countries have age disaggregated antiretroviral data available. If these data are available at country level, those values are inputted. Where these data are not available, default values now reflect the regional values provided by the IeDEA network sites. IeDEA now provides ART initiation by single year age groups (0-14) for 3 regions (Asia, Africa and LAC). Additionally, these data are supplemented by programme data from South Africa and Tanzania for data triangulation (this is allowed as it reflects the same year).
- 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**, improving 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 because of the adjustment to the transmission probability mentioned above. However the rate at which children living with HIV died was higher.)

Impact on ART coverage among children

- 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 is similar to coverage among adults (figure 4).

Figure 3: Distribution of age at which children are initiated on ART by age, globally, 2014

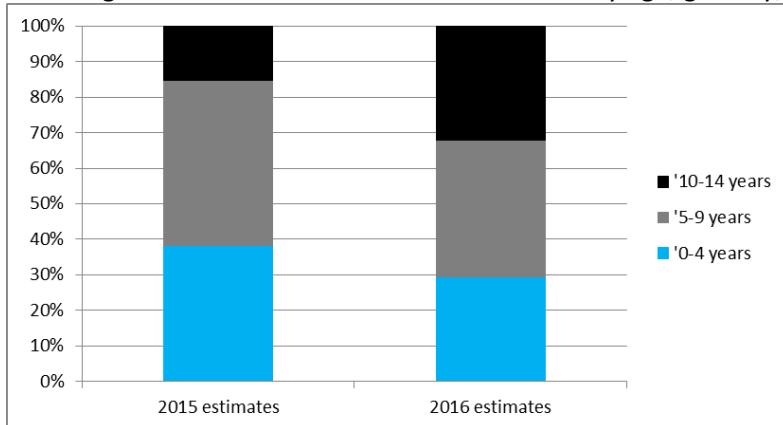
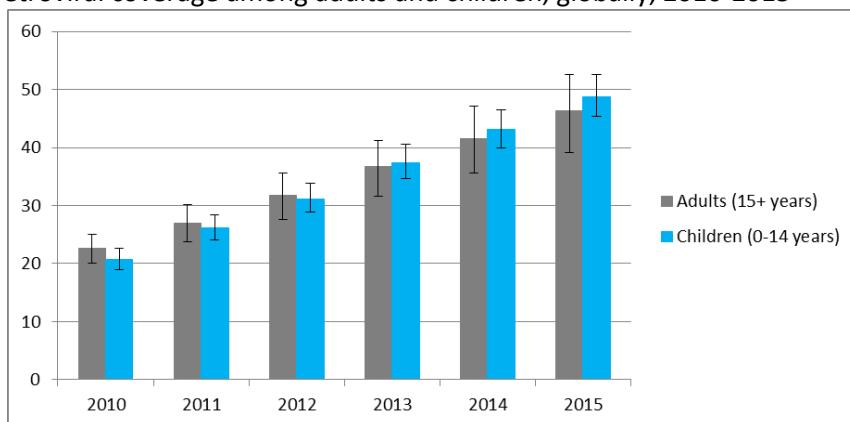


Figure 4: Antiretroviral coverage among adults and children, globally, 2010-2015



New 2016 Results:

- Significant decline in the number of new HIV infections among children - not as high as in the past.
- Child ART coverage has increased and is much closer to adult coverage than previously thought (in some cases it is slightly higher than adult coverage). Given that historically it was reported that there has been a widening gap, messaging this new information will need to be carefully developed so as not to confuse further.
- The number of AIDS deaths declined among children:
 - The majority of pediatric AIDS deaths are among 0-4 year olds and that trend line has drooped steeply
 - 5-9 years have been declining since 2008
 - 10-4 years olds starting to decline
 - And 15-19 years olds are increasing slightly
 - The reduction in pediatric AIDS deaths (trend line) is due to the wave of children historically infected peri-natally and more recently the scale-up of more effective ARVs for PMTCT.

Conclusions and Next Steps:

- The IATT monitoring and evaluation working group (MEWG) will help identify potential countries that have data on ART retention and/or drop-out rates.

- Examine IeDEA data to see if information on pregnant women available to inform assumption about drop-out rates.
- The reference group will discuss how to best understand what is happening during the BF period among women (e.g., ART retention) to determine post-partum transmission probabilities. Given the information available on poor retention of women in the breastfeeding period, greater data is needed to support the assumption of potential increased probability of MTCT during the child's exposure during this period, which is currently not factored into the model output.
 - While there was no change made to the model assumptions on drop-out retention rates, the group acknowledges that limited data may result in an underestimation of new child infections. This will need to be considered going forwards.
- Additional information is contained in the [Global Plan Report](#), which includes data for the 21 priority countries. (India has not provided estimates.) Country specific data will be found at aidsinfo.unaids.org.
- If you have further questions, please send an email to estimates@unaids.org.

Q&A

- 1. Have you considered looking at data from large test and treat trials such as SEARCH in Kenya to inform the models and estimates?**

We [UNAIDS Reference Group on Estimates, Modelling and Projections] have pulled data from other trials but we have not looked at the Kenya SEARCH estimates and we'd be glad to look into the data. We often look at the larger household surveys but the confidence intervals are so wide that it is hard to interpret the data. I agree that the SEARCH Study is a good option. Thank you.

- 2. Did you change any assumptions in the model about cotrimoxazole (CTX)?**

No. The CTX assumptions remained the same. The use of CTX along with ART results in a 30% reduction in child mortality. We ({he UNAIDS Pediatric Reference Working Group} discussed this in detail because over the past 3 years data from randomized control trials (RCTS) pointed to the impact CTX has on child mortality and new guidelines that recommend CTX be used for all children living with HIV.

- 3. When Spectrum is revised it is difficult to compare the progress on some indicators at country level. How can we handle this issue?**

It's a challenge between the science, improving the models and our understanding and the communications of those changed results. When we update our estimates, we update the whole series of estimates. We want to use the same model to compare the historical numbers. We can explain to our partners and programme managers why the new estimates are better and why we should use the new one over the previous ones. This can be difficult because this is fairly technical. **The key messages that can be used to discuss the changes in country are: we have a better understanding of probability of MTCT rates which is lower than thought and better data on when children living with HIV start ART.**

- 4. How do you define mothers needing PMTCT and does this include CD4 cut off points?**

Any woman living with HIV and is pregnant needs PMTCT and is eligible for treatment according to the current WHO Guidelines so there is no CD4 count involved. Women with CD4 counts will have different transmission probabilities, the model assumes all women living with HIV need PMTCT.

- 5. How can you explain that children ART coverage is similar to adults?**
We think that the model are much more accurate. As a result, the denominator for children living with HIV is lower. As countries have increased the number of children receiving ART, when put over a lower total number, the percent coverage goes up. We need better data to validate the model and better measures of HIV prevalence among children in smaller age groups which may be available in the data coming out of the SEARCH trial. There is no good evidence to say that the previous estimates of low coverage were correct. Anecdotally, programme managers discussed the challenges in case finding i.e. finding all the children who were not being treated. However, additional validation is always welcome. Coverage is calculated based on real data coming from countries to calculate the numerator i.e. the numbers of children being treated on programme data, while the denominators are calculated by Spectrum.
- 6. Significant drop in total number of children living with HIV and increase paediatric ART coverage is likely to result in overstocking of ARVs and poses challenges at country level.**

This is a valid point and helps us to reflect on programmatic implications of these numbers. This specific issue may not be a problem everywhere and we recognize that paediatric ART has not scaled up as rapidly as desired. If countries are shifting to treating all children living with HIV at this point in time we are not concerned about overstocking drugs. The situation may be different in Accelerating Children's Treatment Initiative priority countries but we don't expect this to be an issue in all countries as more children will be starting on treatment and drugs available in country can be used.

- 7. We saw a reduction in the number of new HIV infections peri-natally for almost all categories of ARV remaining between 2014 and 2016 and an increase of those initiated on ART in 2016. How can this be? (see slide on peri-partum transmission)**

These are probabilities of transmission which are the inputs into the model – not the results. We previously misunderstood the probability of transmission. In 2015, we estimated it to be too low vs. in 2016 which is higher. The PROMISE Study and other studies showed that the probability of transmission is higher than initially thought when starting ART in pregnancy. The other items circled in red had a greater impact – historically there were more incident infections among pregnant women, which outweighed the impact of the increase in the number of women starting ART in pregnancy and more women received Sd-NVP historically. These have a larger impact than the recent increase in the number starting ART in pregnancy.

- 8. If there is an estimated 60% of new infections coming from the BF period couldn't the lack of data on adherence make a significant difference in the estimated number of children living with HIV and paediatric ART coverage?**

Yes. That is one of the reasons that we still included this in our discussion even though we did not change the model, because we wanted to raise awareness that we need more data to inform any revision to the model. It depends on what data we can obtain and it may mean we potentially underestimate the number of new infections. We hope that the IATT MEWG may support us to gather programmatic data, look at it more critically and develop a

default value that can be used for countries that still don't have that information. That default value would be based on the few countries that are able to collect that data.

9. Lower estimates that come from both the success of PMTCT and lower survival because of later ART initiation – can you estimate the relative contribution to the decrease in the number of new HIV infections among children?

From the change in the transmission probabilities we estimate a 30% reduction and the percent change in the ART data reflect a 10% increase, but it is not necessarily relative. We would have to go back and calculate that for you.

10. Can you expand upon the substantial reduction in the estimated risk of transmission after incident HIV during pregnancy?

Lynne Mofenson was kind enough to have done this analysis for us. There is a number of studies that went into this analysis.

The DRAKE meta-analysis was used to inform the reduction in the transmission probability of incident HIV during pregnancy which showed that the rates with incident infection were lower than were reported in smaller case reports, which primarily drove the reduction of transmission rate during incident pregnancy. We can share these reports and resources.

Lynne Mofenson - I was fixated on the data for ART start during pregnancy because it doesn't look consistent with what we discussed. The transmission probability for ART during pregnancy was 2% in the 2015 model and the data suggested lower risk – the PROMISE study showed 0.6%. The change there was for children who are breastfed and children who are not breastfed. We went with the option of children who are breastfed since the vast majority of children in our models are breastfed. That was our final conclusion to use that value. Following the results of the Promise Study, we changed the transmission probability to 0.95 during which was what was actually used by countries in the workshops for transmission probability at 6 weeks in 2015. The 2016 model used 1.9% among breastfeeding populations through 6 weeks. Even though those women may not continue to breastfeed, the assumption was that peri-partum transmission is higher.

11. What are the median ages of initiation of CTX and ART and do these vary by regions?

We don't have CTX by age captured in the model. If the child is on CTX and ART the mortality is reduced. We do have the median age at ART initiation. Keep in mind that starting on ART is a distribution by single year age group so when we calculate the median it is a simplification of the full amount of data and will be different for each country. While I showed a rough line for Africa, it will vary by each country based on the proportion of children on ART and the age distribution of children in each country. It would be a country specific response. We could provide data by regions as needed but it would be a further step.