Future considerations for EPP & Spectrum and new approaches for generating estimates

Report and recommendations from a meeting of the
UNAIDS Reference Group on Estimates, Modelling and Projections
Seattle, WA, USA, 23-25 April 2014

REPORT & RECOMMENDATIONS

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

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

Kelsey Case, June 2014

Introduction

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 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 co-ordinated by a secretariat based in the Department of Infectious Disease Epidemiology at Imperial College London.

Aim of the meeting

To review and discuss new analyses, new data available, new approaches and considerations for generating estimates of HIV in order to better inform and improve the tools currently recommended by UNAIDS; and to review and discuss the development on novel methods and approaches.

Approach

The meeting featured presentations combined with group discussion to generate consensus recommendations. The list of participants is included in Appendix I and the meeting agenda is included in Appendix II.

The recommendations drafted at Reference Group meetings give UNAIDS and WHO 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.

Future considerations for EPP & Spectrum and new approaches for generating estimates

This meeting covered a wide range of topics. It began with a pre-meeting to review and discuss discontinuities in estimates (aka "the bump") followed by a review of declines in incidence in select country Spectrum files. The main meeting opened with a mortality session reviewing new GBD 2013 methods and comparisons of GBD 2013 estimates of mortality due to HIV with UNAIDS estimates. All-cause mortality, model parameters for mortality on and off ART and reconciling loss to follow-up were all discussed. Session 2 discussed the recent Latin American workshop which examined modelled estimates and country data and attempted new methods for generating estimates. Session 3 reviewed new ALPHA Network data to inform an updated pattern of age and sex-specific incidence rate ratios in Spectrum. The data closed with review and discussion of paediatric and child estimates. The final day considered longer-term approaches – joint estimation of survival and CD4 progression – and new methods for generating estimates including age-specific and hierarchical models. The following details the discussions and consensus recommendations generated at this meeting.

Pre-Meeting: Discussion on incidence declines

Previously, the UNAIDS Global Report has reported estimated incidence trends over a 10-year period categorised into declining, stable and increasing incidence. The purpose of this session was to review country Spectrum files and to discuss the robustness of these statements on incidence. It was discussed that with epidemic saturation, incidence declines are expected but the natural decline as a result of epidemic dynamics is different from declines due to behaviour change, treatment and other interventions. Treatment is an important factor and over-estimating numbers on treatment will overestimate survival which then results in under-estimation of incidence.

The utility of the incidence decline tool in Spectrum, used to categorise incidence declines for the Global Report, was discussed. This tool evaluates 1000 draws on incidence over a specified time period and for a specified decline in incidence. It was agreed that the curves generated do not represent the true range of possibilities (the data force the shape curves generated) thus use of this tool may give a false precision.

It was also discussed that the categories used to define estimated incidence trends should be re-considered to better guide priorities and recommendations. For example, countries with "stable" but very low incidence will likely have different priorities and recommendations than countries with stable incidence at a high level. Overall, it was agreed that UNAIDS will be able to make general statements about incidence declines and countries will need to investigate and test these declines in greater detail.

Recommendations for UNAIDS:

1. **Redefine the categories (e.g. declined to low level, declined to stable)**
2. **Presentation : Consider breaking up the 10 year period – first half and 2nd half (large declines in 1st, and then differences in the 2nd half)**
3. **Sensitivity Analyses *(especially for countries on "the edge")***
    - **Further investigation into rural fitting in countries with limited early rural data and ambiguity surrounding the shape of the rural curve - *What happens when an ANC trend is removed (i.e. misclassification)?***
    - **Numbers on ART – inflated? *Effect on incidence with over-reporting of ART?***
    - **Sex worker turnover (or other pops)**

- **Changing the impact of ART on transmission**

Age pattern on ART: Internally, Spectrum has the pattern on ART, compare this pattern with data from WHO – ART by sex and age (5 year groups) – and also South Africa and IeDEA data.
Follow-up: UNAIDS to send data available to John Stover for comparison

Pre-meeting: Discussion on discontinuities in incidence ("the bump")

There are several factors that can contribute to discontinuities in incidence in EPP and Spectrum, including population projections, the prevalence adjustment in Spectrum (to match EPP prevalence) and patterns of ART scale-up. Much of the discussion focussed on the parameter used to quantify the effect of ART on transmission.

Effect of ART on transmission in Spectrum
High ART coverage combined with a high assumed effect of ART on reducing HIV transmission (92%) can readily result in discontinuity and thus "bumps" in estimated incidence. It is unlikely that all individuals on ART are virally suppressed thus the transmission effect is probably too high. Numbers on ART may also be overestimated. A recent publication quantifies viral suppression at approximately 80% in a sub-Saharan Africa population. It is likely this effect will vary over time. One solution is to revise the ART model with the infectivity reduction based on suppressed viral load (CDC and WHO are recommending VL data collection). Another option is to simultaneously estimate this parameter.

Recommendations:

- **Test the effect of changing the ART reduction in EPP and how well it will work to simultaneously estimate this parameter as part of MCMC.** *Follow-up: Tim Brown & Le Bao*
- **Investigate how best to incorporate the infectivity reduction - in EPP and in the work going forward (new models).** *Follow-up: All modellers*
- **In the immediate term, it is reasonable for countries to consider reductions in the parameter for the effect of ART on transmission to more appropriately reflect national programmes.** *Follow-up: UNAIDS to provide guidance where necessary*

Recommendations for individual analyses of discontinuities in incidence in EPP:

- **Identify the year of discontinuity**
- **Examine pattern of ART scale-up**
- **Examine individual incidence trends for each sub-population**
- **Check populations sizes for discontinuity (*_surv.csv file has a population table)**

Guidance regarding model to use for curve fitting - classic, spline, r-trend
UNAIDS currently provides specific guidance for the recommended model to use for fitting in EPP based on data available. The newer models (r-trend and spline) are less structured than EPP classic and intended to provide flexibility to follow the data in the post-peak period, for example the upticks in prevalence in Uganda and Kenya. As more countries now have repeated surveys over time, variability in prevalence patterns has emerged (e.g. Kenya, South Africa) and it may be unadvisable to allow the flexibility to follow the data if these fluctuations are not real ("overfitting").

Recommendations:

- **Short term: First, re-evaluate the risk of overfitting and potential solutions. One potential outcome is to re-conduct the formal model comparison (spline, r-trend and EPP classic). Also re-consider use of EPP classic in countries where additional structure is needed (i.e. countries with multiple surveys where the additional flexibility can lead to discontinuity).**
- **Longer term: New models and methods (see Session 8)**

Session 1: Mortality

GBD 2013: Estimates of mortality due to HIV, *Chris Murray*

IHME will soon release the GBD 2013 update (papers under review now, expected publication summer 2014). For estimates of mortality due to HIV in generalised epidemics, IHME has coded a modified version of Spectrum but with altered assumptions for mortality in the absence of ART, mortality on ART and CD4 progression from seroconversion. The altered assumptions for CD4 progression are very similar to those used by UNAIDS and the mortality parameters are fairly similar but uncertainty is much larger in the GBD work (very wide ranges on mortality parameters).

Mortality in the absence of ART (GBD): Median survival across all age groups is 3.6 to 29.5 years. Estimates of age-specific survival (4 age groups) calculated based on a systematic review, data extracted from 13 studies with survival from seroconversion.

Mortality on ART (GBD): Systematic review on studies of mortality and LTFU, parameters modified using methods that closely follow those of Egger[1] and Verguet[2] (nomogram approach) to adjust for LTFU. Key findings from this work include:

- Heterogeneity in treatment outcomes – very different survival across programmes, overall it is unlikely that there is achievement of optimal ART effect.
- Important differences for survival on treatment in LMIC compared to Africa require the need to separate out LMIC.
- Improved survival 24+ months on treatment which may be important to include.

Matching with demographic analysis of all-cause mortality

For the GBD 2013 work, the gaps are minimised for the country estimates of AIDS deaths in generalised epidemics that are greater than 80% of all-cause mortality (by age-sex group). A thousand incidence curves are taken from EPP, the parameter distributions for all input parameters are randomly sampled to obtain 10,000 epidemic curves (incidence, prevalence, deaths by age and sex) and then 250 Spectrum curves and all-cause mortality curves that are consistent are matched. The effect of this matching for some countries (e.g. Zimbabwe, Uganda, South Africa) is selecting curves at the very low end of this distribution which then have very long survival. This is important because it changes the age-pattern of mortality, shifting to an older epidemic over time. This is exemplified in the GBD estimates for South Africa where the longer progression results in a much older age pattern of mortality due to HIV that is not in agreement with national survey data.

West & Central Africa:	Close match, very little gap
Southern Africa:	Substantial gap (Botswana, South Africa, Zimbabwe)
East Africa:	Minimal gap

Concentrated epidemics

For concentrated epidemics with vital registration (VR) data, the incidence curve (from modified Spectrum) is recalibrated to fit VR data corrected for misclassification of deaths. This method works very well for many, but not all, countries (e.g. Mexico is still an issue). For some countries, the timing of ART and VR is incongruent and it is difficult to disentangle whether ART scale-up is off or the VR data are off.

[1] Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. *PloS Medicine*. 2011;8(1):e1000390.

[2] Verguet S, Lim SS, Murray CJ, Gakidou E, Salomon JA. Incorporating loss to follow-up in estimates of survival among HIV-infected individuals in sub-Saharan Africa enrolled in antiretroviral therapy programs. *Journal of Infectious Disease:* 2013; 207(1), 72-9.

Russia is a GBD 2013 example of difficulty correcting HIV and TB reassignment – if all TB deaths are re-assigned to HIV, there are too many HIV-related deaths. For GBD 2013, direct testing of TB-HIV cases is used to inform the reassignment. The bulk of HIV-related deaths in Russia come from reassignment, but it is believed these estimates are more credible than previous estimates.

Key differences – GBD 2013 estimates of mortality due to HIV compared to UNAIDS
Most of the differences (approximately 2/3) are observed outside sub-Saharan Africa with the majority of these differences occurring in concentrated epidemics. The largest differences, in terms of overall numbers, are observed in Eastern Europe (Russia, in particular) and Southeast Asia. There are also differences in Latin America, but because the population sizes are small they account for a small portion of the difference.

GBD 2013: All-cause mortality, *Haidong Wang*
The mortality envelope is generated in a multi-stage process. Child (5q0) and adult (45q15) mortality are estimated, and then for HIV-affected countries, HIV-free morality (country-year-sex) is first estimated, and excess HIV mortality is added (distributed across age groups), and finally there are HIV corrections to fit the all-cause mortality envelope.

Key changes (GBD 2010 vs GBD 2013)

- Data bias adjustment for child mortality (GBD 2010 did not apply bias adjustment process – assumed constant bias over years)
- Functional forms between income, education, HIV/AIDS and mortality rates
- Unified standard life table selection process
- Excess mortality due to HIV (adults) allocated to detailed age groups
- Coherent model outputs with Spectrum and codCorrect

Estimates of child mortality
UNAIDS estimates of child mortality are higher than GBD. Key differences occur in children ages 5-9 and 10-14 years. One hypothesis is that children who survive to age 5 in the absence of ART may have better survival than reflected in the current Spectrum parameters.

All-cause mortality from ALPHA Network, *Emma Slaymaker*
All-cause mortality: A key trend in the ALPHA Network data is a decline over time in mortality rates (by age and sex) in both sexes and occurring in both HIV+ and HIV- individuals.

All-cause mortality, comparison with Spectrum: Spectrum all-cause mortality is slightly higher than the most recent ALPHA Network data. ALPHA sites may be performing well thus lowering mortality or Spectrum all-cause mortality may be slightly high.

All-cause mortality rates in HIV+ by treatment stage: Mortality rates by treatment stage from ALPHA sites are as expected with early increases in mortality due to slow rollout of ART and decreasing mortality rates over time. A direct comparison with Spectrum is needed to fully understand any differences with the main caveat that ALPHA prevalence is different from the national prevalence which will affect the comparison.

A key caveat (relevant to all ALPHA analyses) is how to pool the data - sites started at different times, data collection occurs at different times, sizes are different. Deaths are enumerated via demographic surveillance (different methods across sites) and the upper age limits have changed over time to allow HIV testing in older ages.

Mortality on ART and ART drop out from ALPHA Network, *Georges Reniers*

Data from ALPHA Network sites also find changing trends over time for mortality after treatment initiation, with much lower early "bumps" in mortality and lower levels of mortality on ART in the more recent cohorts compared to past cohorts. It was discussed that there have been improvements in service uptake and it is likely that changes to ART guidelines (earlier treatment) also play a role. Lower mortality following ART interruptions was also observed for the more recent cohorts. Overall, men had worse outcomes than women with higher mortality on ART, higher pre-treatment mortality and higher prevalence of treatment interruption. Differences by region were not straightforward – substantial heterogeneity is observed across sites (for treatment initiation, mortality on ART in the first year and mortality over time), but it is not clear what is driving these differences.

Mortality on ART and disengagement from care, *Elvin Geng*

Unknown patient outcomes account for a substantial proportion at each step of the treatment cascade. Loss to follow-up (LTFU) will include patients who have died, those who have stopped treatment but are still alive and those who have switched clinics and re-entered care. To better understand and address these unknown outcomes, a sampling-based approach was used at IeDEA sites in East Africa, identifying a small but randomly selected sample (appx 15-20%) of those lost for intensive follow-up. The outcomes of this random sample can then be incorporated to produce revised estimates of mortality after treatment initiation and retention in care.

Initial findings using this approach found that retention in care pre-adjustment (69%) matched a 2010 systematic review,[3] but was much actually much higher (~79-86%) with corrected estimates. In analyses of predictors of mortality, using only known deaths overlooked associations (age, weight, year of ART initiation) and had spurious associations (male sex) that were identified with inclusion of the resampled outcomes.

For generalizability, this approach was applied across 18 clinical settings in Uganda, Tanzania and East Africa. A key finding was the large variation by site which is difficult to explain (and holds when adjusted for CD4, age, etc). This heterogeneity across programmes was observed for both mortality and the rate of re-entry to care. The differences in mortality after ART initiation across programmes are comparable in magnitude to factors like CD4 and WHO stage at ART initiation. Despite similar packages of care, there are substantial differences in the comparative effectiveness of ART treatment across programmes. Overall, the effectiveness of ART is at sub-optimal levels.

The importance of understanding what is driving these differences was discussed – quality of care, clinical processes, community engagement. All were IeDEA sites and affiliated with NGOs and other programmes. It was discussed that for Spectrum, an average across the sites will likely be required.

The sampling-based approach used by EG was discussed in comparison to the nomogram approach (used by IHME and Egger[4]). The validity of the nomogram approach is driven by the fraction of those LTFU that you are able to obtain which varies widely. The nomogram approach is also unable to represent uncertainty. The sampling-based approach is systematic and uncertainty can be represented (bootstrap).

[3] Fox M.P. and Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. *Tropical Medicine & International Health*; 2010: 15, 1–15.

[4] Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. *PloS Medicine*. 2011;8(1):e1000390.

Recommendations:

1. **Learn from GBD work where possible, contribute as appropriate**
2. **Propagating uncertainty in natural history model:**
    - **Short term: Implement the variation around mortality used in GBD in Spectrum the (as opposed to the 5% currently used).**
      Follow-up: Katrina Ortblad to send ranges used for mortality, additional notes on methodology, details for data sources/lit reviews for mortality on/off ART, April 2014
    - **Long term: Improved uncertainty with the joint estimation of progression and survival from the natural history model (see Session 8)**
      Follow-up: Tara Mangal work, review progress June/July 2014, results Dec 2014
3. **Estimates of mortality due to HIV in children:**
    - **Review of HIV survival curves for children and trends in all-cause data available to inform (e.g. South Africa).**
    - **Consider commissioning updated review on effects of paediatric ART and ART allocation** *(TBD after June 2014 WHO meeting)*
      Follow-up:
        - ✓ *UNAIDS, WHO and Reference Group to participated at WHO paediatric estimation meeting June 17-18, London*
        - ✓ *Review of recent literature for updated data to inform child survival*
        - ✓ *Contact IeDEA to identify data to inform child survival*
        - ✓ *Contact researchers in this field to identify additional data that may be able to further inform.*
        - ✓ *IHME to follow-up with data used to inform, Katrina Ortblad, April 2014*
        - ✓ *ALPHA Network meeting on HIV in children*
4. **ART drop out and mortality on ART:**
    - **Compare Elvin Geng approach to previous Constantin Yiannoutsos approach, quantifying the difference between methods (likely small).**
    - **Add disengagement from care into Spectrum (pooled estimates) but with revised mortality on ART (later period) - review and compare for a sample of countries.**
    - **Consider adding input for annual new ART initiates in Spectrum (note the data are needed historically); request countries to bring these data to the workshops.**
    - **Outcomes of disengagement in care are important for contributing to surveillance and programme management – performance and impact. Data collection needed at the local level (programme).**
    - **Contribute as needed to the WHO guidelines process for data collection for the treatment cascade.**

Session 2: Estimates in Latin America and use of alternative methods for fitting

In Latin America many countries have detailed cause-specific mortality data over time and HIV case report data but more limited and sporadic data on HIV prevalence. Previous EPP/Spectrum estimates of HIV prevalence have yielded higher AIDS mortality estimates compared to measured mortality. As a result, a workshop was held in Latin America discuss data, data quality and estimates in this region.

At this workshop, Futures Institute created an alternative approach for fitting – initially scaling incidence down to match to level of mortality observed from VR data – but ultimately came up with a revised method to fit incidence to match the three key national-level indicators: AIDS deaths, PLWHIV and new HIV cases. This method was proposed as an alternative simple approach, fitting

incidence to all three indicators by generating a family of national incidence curves, calculating a score for each (closeness to indicators) and taking the best fit from these scores. The rationale for this approach is that many countries have not recently conducted surveillance and population size estimates, and prevalence data are of limited quality, but the programme and case surveillance data are greatly improved. Note that uncertainty is not captured with this method.

Another approach was presented by Juan Vesga which follows Ard van Sighem's method of using case report data to estimate incidence, illustrated for Colombia. Data quality is a key issue for use of this approach which necessitates a detailed understanding of the data, for example, understanding the case detection rate and how this has changed over time. By risk group, the validity of the case report data by mode of transmission is a key area to address. Note that ART is not currently included. Presently, this approach needs to be applied on a case by case basis.

A combined approach was considered during the discussion with the agreement that the end result would be a complicated model with a substantial fitting process. It was also discussed that for the simple approach, it is possible to bypass the EPP process (and dividing into sub-populations, entering surveillance data) but that this will then lose the process of thinking critically about key populations.

Recommendations:

- **Shorter-term solution from John Stover: Investigate in detail for a few countries, driving results from mortality and from implied case report data, comparing both processes and the results ("forwards" and "backwards" approach).**
- **Long-term solution from Juan Vesga: Adding ART and integrating the available data sources including the use of adjusted mortality data for simultaneous fitting to all data available.**

Follow-up: John Stover to investigate both potential options, review Aug 2014
Follow-up: Juan Vesga to present results, Nov/Dec 2014

Session 3: Incidence rate ratios from ALPHA

Age and sex-specific incidence rate ratios in Spectrum are informed by pooled data from the ALPHA Network sites. New rounds of data collection provided the opportunity to update these parameters. Analyses of changes in incidence rates over time from site-specific and pooled data from the ALPHA Network do not show the same clear temporal trend observed in the mortality data. Note that while the Tanser paper[5] shows a decline in incidence over time, this finding is sensitive to how the data are viewed (year of boundaries).

A key consideration for use of the combined data is how to pool the data. The sites began in different years, collect data in different ways, are of very different sizes (with site size not related to population size), have different testing protocols, and changes in these protocols over time. In addition, the largest sites have the highest HIV prevalence and mortality rates but the shortest history of HIV testing.

Recommendation: Implement revised sex and age-specific pattern of incidence in Spectrum (IRRs). The optimum method for pooling the data is not readily apparent, but will be investigated.
Follow-up: John Stover and Emma Slaymaker to liaise for implementation, May 2014

[5] Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science;* 2014*:* 339 (6122), 966-971.

Session 4: Child estimates and coverage of PMTCT

Publication of estimates of PMTCT coverage in concentrated epidemics, *Mary Mahy*

For many countries, estimates of PMTCT coverage are close to, or greater than, 100%. There are several factors that affect these coverage estimates – prevalence estimates, programme data (data quality and validity, i.e. de-duplication, avoiding double counting) and the model parameters, including age-specific incidence rate ratios, the sex ratio of incidence and fertility in HIV+ women. In the past, UNAIDS has not published coverage estimates of PMTCT in concentrated epidemics.

Recommendations:

- **Evaluate for each country – estimates in some countries may be of high enough quality to report a range of PMTCT coverage.**
- **For countries with estimates of lower quality it may be advisable to not publish PMTCT coverage estimates.**
- **Liaise with programme managers regarding the validity of coverage estimates.**
- **Consider using prevalence from ANC for coverage in countries where the ANC prevalence is likely to be fairly representative.**

Child prevalence – survey data vs Spectrum estimates, *Mary Mahy*

There are limited empirical data available to compare with estimates of HIV prevalence in children. From the national survey data available, Spectrum underestimated prevalence in children 5-9 years across all three surveys in Botswana, and the 2005 survey in South Africa (with better agreement in the 2008 and 2012 surveys). For Kenya (2012), Mozambique (2009) and Swaziland (2006) there was good agreement. In kids 10-14 years there was less agreement, with Spectrum underestimating prevalence compared to all surveys except Kenya (2012).

See recommendations from Session 1 regarding research plans to improve child prevalence and mortality estimates.

Fertility in HIV+ women, *Basia Zaba*

Analyses of fertility trends over time from ALPHA Network data illustrate fertility of HIV infected women continues to be lower than uninfected women for women 20+ years of age. While these lower levels of fertility have been rather stable over time, this ratio (of fertility in HIV+ women compared to HIV-) appears to be tending toward 1 in the ART era. There were slight geographical differences in the ALPHA data with the ratio of fertility in HIV+ women compared to HIV- much closer to 1 in South Africa, but still less than 1 in East Africa.

Recommendation: Advise countries to us the most recent DHS to inform this reduction, allow this adjustment to vary over time.

Session 5: Spectrum & EPP – future considerations

New updates in Spectrum include TIME, the suite of TB tools (data, estimates, impact and economics which links to One Health); the separation of country data files from the install file (to reduce the size of the Spectrum install); the collation of Spectrum manuals into a single manual and help file; and the collation of all projection files into a single *pjnz* file.

Future considerations for both Spectrum and EPP that were discussed included:

> Median CD4 count at ART initiation**:** Including this input will allow Spectrum to adjust the distribution of ART across new initiates in a more robust manner.
> **Recommendation: Test the implementation of this method, identify default values to include in the absence of data to inform and investigate options for the projections.**
> *Follow-up: Futures Institute, review Aug 2014*

HIV+ Adolescents in EPP**:** Currently, HIV+ 14 year olds are not being included in EPP (i.e. not ageing in at age 15).

Recommendation: Spectrum to pass annual number of HIV+ 14 year-olds to EPP to include in the fitting.

Follow-up: East-West Center and Futures Institute, review in Aug 2014 if necessary

Use of PMTCT surveillance data in EPP: Many countries will soon stop ANC surveillance and switch to PMTCT surveillance which will affect estimation. CDC is working on the guidelines for this transition, which are anticipated in June, 2014. Within EPP, this issue raises several questions including the ability to handle changes in data quality (and sample size), the statistical implications of substantially increasing the number of sites (and potentially the geographical distribution), and methods to use to transition from use of ANC to PMTCT data.

Recommendation: In EPP, use separate data entry pages for PMTCT and ANC and separate calibration constants (bias parameters) for fitting. Continue to investigate how to best implement in EPP.

Follow-up: East-West Center to implement, review in Aug 2014 if necessary

R-trend model in EPP: The r-trend error was implemented with an equation error which resulted in less optimal fitting of the pre-data period.

Recommendation: Review the countries that used r-trend for fitting, identify how widespread this issue is and then address on a case by case basis, comparing the difference in model fitting.

Follow-up: East-West Center to implement, UNAIDS to review country files, May 2014

Dump files in EPP: A variety of dump files are obtainable with shortcut keys within EPP.

Recommendation: Create shortlist for generating dump files in EPP

Follow-up: East-West Center to implement, May 2014

Cyrillic names: Cyrillic file names have been causing issues (not recognised)

Recommendation: Program Spectrum and EPP to allow for Cyrillic file names if needed

Follow-up: Keith Sabin to consult with countries, East-West Center and Futures Institute to liaise if programming required, May 2014

Session 6: CD4 progression

Nikos Pantazis presented an updated analysis of CD4 progression from the pooled cohort data focusing on regional variation. Linear mixed models were fit to CD4 data by region using estimates of fixed effects and random components to derive the CD4 distribution after seroconversion at any point in time. By region, similar rates of CD4 loss were observed for North American cohorts and non-Africans in European cohorts, but slower rates in African cohorts and faster rates in Asian cohorts. Baseline CD4 was also lower in Asian cohorts compared to all others and estimated time from seroconversion to reach a 200 CD4 cell count (estimated in the absence of treatment) was substantially shorter in Asia compared to all other cohorts. These results highlight the importance of re-considering the CD4 and progression parameters for Asia.

It was discussed that there are empirical data for survival by age in Africa which gives greater confidence in matching the progression patterns, but these data are not available for Asia thus comparison and validation of regional progression patterns for Asia will be limited.

Joint estimation of HIV CD4 progression and survival, *Tara Mangal*

Hidden Markov models allow joint estimation of CD4 progression and time to death with the key advantage of jointly estimating model parameters instead of calibrating to separate models of CD4 progression and survival.

Key model parameters include:

1. Initial state probabilities (fraction who start in each CD4 bin after seroconversion)
2. Transition rates between CD4 compartments
3. Death rates

This approach is faced with many potential difficulties: natural variation in CD4 cell count measures; accounting for ART initiation, different study designs for each cohort (e.g. hospital recruitment where patients are likely to be quite ill); limited data at low CD4 counts; background (non-AIDS) mortality; and distinguishing between fast vs slow progressors. Methods are being developed to address each of these difficulties.

It was discussed that in order to include this approach in Spectrum the CD4 bins would need to match. The CD4 bins in Spectrum were created to account for ART eligibility and changes over time.

Recommendations:

- **It would be ideal to have regional patterns of CD4 decline in Spectrum.**
- **Short term: Consider separate pattern for Asia based on analyses conducted by Nikos Pantazis (and the ALPHA survival from Todd et al) and investigate the effects of implementing this revised pattern.**
- **Longer term: Joint estimation of survival and CD4 progression from Tara Mangal**

Follow-up: Test effect of implementing separate pattern for Asia, Nikos Pantazis & John Stover

Follow-up: Review Tara Mangal's work, December 2014 (update end June)

Session 7: Sub-national estimates

HIV prevalence from survey data varies widely at the sub-national level. Estimates and indicators at the sub-national level are greatly needed for efficient programme planning and service delivery. There is substantial support for sub-national estimates - from the Global Fund, PEPFAR and the UN. Many countries have attempted sub-national estimates in the current estimation round.

Kenya has generated provincial level estimates in the past but the recent devolution to the county level (47 counties) necessitated estimates at this level for resource allocation decisions. County estimates were reconciled to match provincial totals (but only minimal adjustments were required) and a large spread sheet of indicators was created detailing all of the county estimates. Programme data at the county level were used to calculate estimated ART and PMTCT coverage.

Nigeria needed sub-national estimates at the state level (37 states). UNAIDS provided support to the 13 high priority states to help develop the files. Key issues included data availability at the appropriate level (state), file quality and underlying demographic data and. At the state level, there was far more limited data available for fitting and very limited programme data. The quality of fitting for each state was variable. Comparison of the aggregate file to the national estimation file showed fairly large differences with migration a key factor (challenge of appropriately describing demographic projections at the sub-national level).

Moving forward, it will be important to address these quality issues. Currently, UNAIDS conducts a very thorough file review process which may be difficult to maintain if there are substantial

increases in files as more countries generate sub-national estimates. It was also discussed that uncertainty will be much larger in the aggregate file compared to a single national file.

HIV Modelling Consortium meeting on methods for describing sub-national HIV patterns

In March 2014, the HIV Modelling Consortium held a meeting in Nairobi to review and discuss methods for describing sub-provincial variations in HIV epidemiology. Groups working on these methods, across diseases, were invited to participate and apply their proposed approaches to standardised datasets for selected countries. Pre-defined metrics were used for internal and external validation. While there was a wide range in the level of complexity, results from all methods were fairly similar. **Recommendations were made for a short-term method (PrevR) and a longer-term approach for development (Oxford Group).**

The discussion concentrated on data vs computational methods and the very sophisticated approaches conducted with limited and often poor quality data. There still remains a need to focus on improving the quality and use of programme and feeding this information back to the programmes and the local level.

Recommendations for sub-national estimates:

- **Sub-national estimates are greatly needed with main caveat that the data are not necessarily at the appropriate level of quality (and availability) thus solutions have been developed for both the short and longer term with different levels of complexity.**
- **If countries have adequate data available, recommendation for sub-national estimates (e.g. Tanzania).**
- **Data quality and data use are paramount – recommendation for continued strengthening of data collection and use of data at the programme level.**

Session 8: New models, new ideas

Hierarchical model for EPP/Spectrum, Le Bao

A hierarchical model can be used to share information across areas, "borrowing" information from high-quality data-rich areas to inform data-poor areas. Le Bao has been working on a hierarchical model for use in EPP for generalised and concentrated epidemics.

Generalised epidemics: Countries with high quality datasets (16 in SSA) were used so the posterior distribution was driven by the data and not the prior distribution and to easily evaluate the prediction performance.

Three potential methods were considered for implementation in EPP/Spectrum:

1. Fit datasets simultaneously (very time consuming)
2. **Fit datasets separately** (easy to implement without too much additional computing cost)
    - Caveat – may not have enough unique samples when all datasets are high quality
3. Fit high-quality datasets separately
    - Caveat – users have to identify which datasets are high/low quality

The recommended approach is to fit the datasets separately, evaluated for 3 controlled scenarios – high quality datasets, mixed datasets (high and low) and low quality datasets (removing data to create this scenario). Substantial improvements in fitting the low quality dataset were observed for the mixed data scenario providing evidence of the utility of this approach. When all datasets were of low quality, there was little improvement using the hierarchical model.

Sub-national estimates: A generic hierarchical approach can be used for sub-national estimates. This method was able to improve fitting at the sub-national level in South Africa and Malawi.

Concentrated epidemics: The hierarchical model was evaluated for use in data-rich concentrated epidemics. Across the different epidemics and across sub-populations (i.e. risk groups) there were few similarities observed and very limited high quality datasets. While a hierarchical model can be used, there is not enough evidence to be convinced of improved fitting using this approach.

Recommendation: Further explore the use of Le Bao's hierarchical model at the sub-national level testing with the countries that completed sub-national Spectrum files.
Follow-up: UNAIDS to provide files for Le Bao, review results December 2014

Age-structured model, *Sam Clark*

Methods for developing an age-structured model for HIV have been published in three papers (plus two more available soon). These include:

Establishing the age-structured demography with estimation of consistent past trends in age-specific mortality, fertility, age structure and sex ratio at birth. A cohort component model of population dynamics was used to ensure consistency between vital rates, migration and age structure.[6]

Estimating age-specific HIV incidence in East Africa consistent with the population dynamics.[7][8] The demographic cohort component model was expanded to incorporate HIV (very large matrix) providing an organised method to ensure consistent population and disease dynamics.

The next steps are to add ART and to consider incidence scenarios and sex-age mixing (complex and adds many parameters). Key data required are sex and age-specific prevalence and ART data. It was discussed that it is possible to have different levels of structure in order to have a model that works in different areas. Many parameters can be fixed, keeping the model as simple as possible but with potential to expand and add the additional complexity.

HIV trends in pregnant women and the general population in the ART era: implications for estimates and surveillance, *Jeff Eaton*

A comparison between EPP prevalence fits and DHS prevalence data for countries in southern Africa raises the question of whether EPP is overestimating prevalence declines in recent years. This brings back the often posed question of whether trends in ANC have become less representative over time. One hypothesis is that the effect of ART in an ageing epidemic may, over time, shift the burden of prevalence into older, less-fertile age groups.

Trends in age-specific ANC data compared to survey data in South Africa show recent increases in prevalence from survey data but almost no change in ANC prevalence during the same time period. Analysing the ANC data by age illustrates the increasing prevalence over time in older age groups but declining prevalence in the younger age groups. When the age distribution from the South African ANC data is compared to that of the general female population, it is apparent the ANC data are not reflecting the age-structure of the population (missing older women). Adjusting the ANC data to reflect the age distribution of the general female population results in obtaining a similar trend to that observed in the household survey with increases in prevalence over time. An analysis of HIV prevalence in pregnant women from DHS data compared to the general female population (DHS) in

[6] Wheldon MC, Raftery A.E, Clark SJ., and Gerland P. Reconstructing past populations with uncertainty from fragmentary data. *Journal of the American Statistical Association*. 2013; 108 (501): 96-110.

[7] Clark SJ, Thomas J, Bao L. Estimates of Age-Specific Reductions in HIV Prevalence in Uganda: Bayesian Melding Estimation and Probabilistic Population Forecast with an HIV-enabled Cohort Component Projection Model. *Demographic Research*. 2012;27(26):743-74.

[8] Thomas J, Clark SJ. More on the Cohort-Component Model of Population Projection in the Context of HIV/AIDS: A Leslie Matrix Representation and New Estimates. *Demographic Research*. 2011;25(2):39-102.

SSA shows that some countries have divergent trends. In particular, southern Africa exhibited greater declines in prevalence in pregnant women compared to the general population women.

Proposals to investigate this potential bias in the short term:

1) **Age-adjusted ANC prevalence data**: Uses existing model structure, requires age-structured ANC data
2) Calibrate to "derived ANC prevalence": Leverages EPP/Spectrum assumptions, user blind to input data changes, requires software development

The longer-term aim is a flexible model for age-structured incidence that includes spatial structure with a hierarchical model to share information, which captures uncertainty around progression and mortality and incorporates additional data sources into the likelihood (e.g. mortality).

Recommendations for age-structured models (SC, LB, JE)

- **Age-structured models will only be applicable for generalised epidemics (require detailed demographic and national survey data).**
- **Advocate for collection of age-structured data to inform these detailed models in the future – ANC, PMTCT, ART.**
- **Encourage further development of seemingly highly promising approaches from SC, JE, LB and others.**
- **Further explore Jeff Eaton proposal for short-term solution using age-adjusted ANC data (requires available ANC data disaggregated by age)** *Follow-up: Review in July, 2014*

Appendix I: List of Participants

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Appendix II: Meeting Agenda

Future considerations for EPP & Spectrum and new approaches for generating estimates

23-25 April 2014

Pre-Meeting: Discussion on discontinuities in incidence ("the bump")

Effect of patterns of ART scale-up and "the bump"			
1230	40	Discussion re investigations into "the bump" *(including discussion on assumptions for ART reduction)*	Led by Tim Brown & John Stover
1310	20	Recommendations	ALL
1330		Coffee	

Pre-Meeting: Spectrum File reviews

Start	Duration	Subject	Speaker
Country file reviews (Chairs: Peter Ghys & Tim Hallett)			
1330	*30*	*Coffee and light snacks*	
1400	15	Introductions and aims of session	Peter Ghys, UNAIDS
1415	75	Group review of approximately 10 country files including: - incidence - prevalence - meta-data Focus: Countries with newly declining epidemics, changing epidemics, surprising curves	Led by Mary Mahy, UNAIDS
1530	20	*Coffee break*	-
1550	75	File review continued	ALL
1705	25	**Recommendations**	Led by Tim Hallett, Imperial College
1730		*Close*	

DAY 1

830	30	Coffee and light breakfast available	
900	15	**Meeting opening - introductions, aims, key issues**	Peter Ghys, UNAIDS Tim Hallett, Imperial College London
Session 1 - Mortality (Chair: Geoff Garnett)			
Mortality by age and sex			
915	25	GBD 2.0: Revisions to the overall all-cause mortality envelope including methods for the age distribution of all-cause mortality	Haidong Wang, IHME
940	25	GBD 2.0: - Methods for re-classifying AIDS deaths from other causes, with examples from Latin American and Eastern European countries (e.g. Russian Federation) - Estimation of survival of people living with HIV in the absence of ART - Estimation of survival of people living with HIV on ART	Chris Murray, IHME
1005	25	ALPHA Network: All-cause mortality by age and sex (numbers of deaths) and HIV mortality rates by age and sex	Emma Slaymaker, LSHTM
1030	*30*	*Coffee break*	
1100	30	Discussion	-
ART drop out and mortality on ART			
1130	25	Disentangling ART drop out and mortality on ART	Elvin Geng, UCSF
1155	20	Disentangling ART drop out and mortality on ART from ALPHA; comparison with Spectrum for eastern and southern Africa	Georges Reniers, LSHTM
1215	30	Discussion	
1245	*60*	*Lunch*	-
Session 2 - Latin America (Chair: Txema Calleja)			
1345	10	Update from mortality workshop in Latin America	Keith Sabin, UNAIDS
1355	10	Spectrum tool using AIDS deaths from VR in LA to calculate changes in incidence required to match AIDS mortality from VR (and comparison to previous estimates from Spectrum)	John Stover, Futures Institute
1405	10	Questions	
1415	10	Alternative models for concentrated epidemics - Extension of Ard van Sighem approach, results from application in Colombia	Juan Vesga, Imperial College London

1425	30	Questions and discussion *To include:* *- Recommendations for countries to bring mortality data to workshops for fitting?* *- Recommendations for use of mortality data for fitting?*	
1455	*20*	*Coffee*	-
Session 3 - Incidence rate ratios (Chair: Tim Hallett)			
1515	20	Incidence rate ratios by age and sex from ALPHA Network	Emma Slaymaker, LSHTM
1535	20	Questions, discussion, recommendations *- Include discussion on country approaches/modifications to IRRs*	
Session 4 - Paediatric estimates (Chair: Tim Hallett)			
Generalised			
1555	15	Paediatric infections from Spectrum compared to DHS data; prevalence among pregnant women from DHS and ANC vs Spectrum	Mary Mahy, UNAIDS
1610	15	Changes in fertility with ART scale-up from ALPHA Network	Basia Zaba, LSHTM
1625	20	Questions, discussion, recommendations	
Concentrated			
1645	15	Estimates of PMTCT coverage in concentrated epidemics *Recommendations re publication*	Mary Mahy, UNAIDS
1700		Close	

DAY 2

Start	Duration	Subject	Speaker
800	*30*	*Coffee and light breakfast available*	
Session 5 - Spectrum & EPP: Future considerations (Chair: Simon Gregson)			
830	15	Spectrum - Issues for future consideration including: matching to child prevalence, effect of ART on child mortality, input for median CD4 at ART initiation	John Stover, Futures Institute
845	15	EPP - Status updates, key issues for future consideration	Tim Brown, East West Center
900	15	Questions and discussion	ALL
PMTCT vs ANC for fitting			
915	10	Update on PMTCT vs ANC surveillance, guidelines and country plans	UNAIDS
925	10	Statistical considerations for use of PMTCT data for fitting	Le Bao

935	20	Discussion *Including Kenya example*	
Uncertainty			
955	10	Comparison of confidence intervals in EPP vs AIM vs DHS	Kim Marsh, UNAIDS
1005	10	Proposed methods for combining draws in EPP for national uncertainty	*Concept note from Dan Hogan*
1015	25	Questions, discussion, recommendations	
1040	20	*Coffee break*	
Session 6 - CD4 progression (Chair: Tim Brown)			
1100	20	Updated analysis of CD4 progression from pooled cohort data	Nikos Pantazis, Univ of Athens
1120	20	Proposed methods for jointly re-estimating CD4 progressions and survival	Tara Mangal, Imperial College London (presented by Jeff Eaton)
1140	25	Discussion	
1205	55	*Lunch*	
Session 7 - Sub-national estimates (Chair: Basia Zaba)			
1300	5	Introduction	Peter Ghys, UNAIDS
1305	15	Kenya+C90 - experience generating sub-national estimates, confidence intervals	John Stover, Futures Institute
1320	10	Nigeria & Malawi - experience generating sub-national estimates, confidence intervals	Mary Mahy, UNAIDS
1330	15	Update and recommendations from Modelling Consortium meeting on generating sub-national estimates	Tim Hallett, Imperial College London
1345	30	Questions, discussion, recommendations	
1415	*30*	*Coffee break*	
Session 8 - New models, new ideas (Chair: Peter Ghys)			
1445	20	Review of preliminary results from hierarchical model	Le Bao, Penn State
1505	20	Age-specific model development – proposed methods, feedback & discussion	Sam Clark, Univ of WA
1525	20	HIV trends in pregnant women and the general population in the ART era: implications for estimates and surveillance	Jeff Eaton, Imperial College London
1545	25	Discussion	ALL
1610	15	Final comments	Peter Ghys, Tim Hallett
1625		Closure	