Improving estimates of national HIV burdens and ART need, and modelling the impact of prevention programmes

Report of a meeting of the UNAIDS Reference Group for Estimates, Modelling and Projections held in Athens, Greece, December 13-15th 2005

TECHNICAL REPORT AND RECOMMENDATIONS

UNAIDS

The meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections (the 'Epidemiology Reference Group') was organised for UNAIDS by the UK secretariat of the reference group (http://www.epidem.org) based at Imperial College London. Participants of the meeting are listed at the end of this document. The recommendations in this document were arrived at through discussion and review by meeting participants and drafted at the meeting.

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Introduction

The Reference Group

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 the World Health Organization (WHO) 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, Imperial College London (www.epidem.org).

Aim of the meeting

The aim of this meeting was to bring together experts to produce recommendations on a range of topics, including using the BED assay to estimate HIV incidence, improving estimates of nation burdens of HIV and ART need, and the epidemiological impact of (male) circumcision, PMTCT regimens, ART and cotrimoxazole prophylaxis.

Approach

The meeting featured both presentations of recent data and group discussions, which focused on specific technical issues. Presentations included details of the BED assay and its application to specific data-sets; reports of trials of (male) circumcision and modelling of its impact on HIV transmission; updated guidelines on provision of ART; the effect of ART on survival; HIV prevention and treatment in children; ante-natal clinic surveillance; and updated methods of estimation of uncertainty in estimates of national HIV burdens (see Appendix I for a complete list of presentations).

The meeting was attended by 44 experts from 9 countries (see Appendix II for a list of participants). Each contributed, not only data, insights and analysis, but also worked hard to produce a set of recommendations for UNAIDS and WHO, drafted at the meeting. We would like to thank them for their hard work and attendance at the meeting.

The recommendations drafted at Reference Group meetings give UNAIDS and WHO guidance on how best to produce estimates of HIV/AIDS, an opportunity to review current approaches and also help 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.

BED assay and incidence estimation

1. Background

Measurement of HIV incidence is important in monitoring the HIV epidemic, assessing the success of control programmes, and determining where prevention needs lie. Incidence data are contemporary, whilst prevalence data report on the history of the epidemic. Furthermore, incidence data are more easily communicated and interpreted than prevalence data.

However, incidence is much more difficult to measure than prevalence, due to the time dimension. There is considerable interest in estimation of incidence from cross-sectional surveys using 'de-tuned' antibody assays to distinguish weak antibody responses to HIV, which occur early in infection, from strong responses, which occur later, to determine what proportion of HIV-positive samples came from recently-infected individuals. This analysis could be applied to samples already being collected through prevalence-based surveillance systems, such as through ante-natal clinics (ANCs) and voluntary counselling and testing (VCT) services. It should be noted, however, that, because the window period is $\sim 1/20$ of the duration of HIV infection, very large sample sizes would be needed for robust incidence estimation.

In principle, a test for recent infections could:

- identify risk groups in an emerging epidemic and shifts in patterns of incidence;
- act as an early-warning system of a concentrated epidemic occurring/increasing;
- identify the stage of an epidemic;
- improve surveillance in developed countries, that is based on case-reports;
- improve estimates of incidence used in power calculations for vaccine trials.

However, the 'de-tuned'-assay approach requires validation and calibration, both of the laboratory assay itself and of the statistical analysis of its data. With regard to the laboratory assay, there are a number of factors to consider, including the time from infection to detectable antibody response occurring, and time from then until a strong antibody response occurs (called the 'window period'). This window period may differ by subtype (with mid-point estimates ranging from 115 days for subtype E in Thailand to 181 days for subtype C in Zimbabwe), and amongst populations (mid-point estimates for subtype C were 167 days in Ethiopia and 181 days in Zimbabwe). A weak antibody response can also be caused by late-stage infection as the immune system deteriorates, leading to overestimation of the proportion of infections that is recent, and hence an overestimation of incidence. The assay indirectly measures levels of HIV-IgG antibodies as a proportion of total IgG, so its performance will be affected if total IgG levels are raised by other infections.

2. Studies presented at the meeting

Several studies from different countries were presented at the meeting, reporting that the current use of the BED assay was resulting in substantial over-estimation of HIV incidence. To make this important information available as soon as possible, a statement was issued by the meeting, and is reproduced below. The findings of these studies will be published in academic journals and so they are not reported in detail here. However, recommendations on current use of the BED assay, and further work that is required are reported below.

3. Statement of the UNAIDS Reference Group on Estimates, Modelling and Projections on the use of the BED assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring

See next page.

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UNAIDS Reference Group on Estimates, Modelling and Projections' statement on the use of the BED-assay for the estimation of HIV-1 incidence for surveillance or epidemic monitoring

On 13 December 2005, the UNAIDS Reference Group on Estimates, Modelling and Projections reviewed results of the application of the BED-assay for estimation of HIV-1 incidence in surveillance settings, and in selected validation studies. Data were presented from studies in Côte d'Ivoire, South Africa, Rwanda, Zambia, Kenya, Uganda, Ethiopia, and Thailand, and from additional laboratory validation studies.

The comparison of BED-assay derived measures of incidence with directly measured prevalence and with estimates of incidence based on different methods consistently suggests that the current BED-based method overestimates incidence. Several studies show BED-derived incidence of a third to half the prevalence. This is inconsistent with the pattern of growth of the epidemic and data about survival of people infected with HIV-1. In studies that compare different measures of incidence, BED-assay derived incidence appears 2-3 times higher than that found using other methods (e.g. HIV-1 incidence measured directly in prospective studies, or derived from prevalence surveys in young people [15-24 years old] by single year of age or modelling using the Estimation and Projection Package and Spectrum or the Asian Epidemic Model).

There is evidence that the above discrepancies arise because the BED-assay captures not only recent infections, but also late stage HIV infection (with or without antiretroviral therapy) when the levels of antibodies fall. Additionally, there may be an impact of sample storage conditions on assay results. There is evidence that assay characteristics vary by HIV-1 subtype.

Based on the above-summarised evidence, the Reference Group recommends that at present the BED-assay not be used for routine surveillance applications, neither for absolute incidence estimates, nor for monitoring trends. In addition, the BED-assay should not be applied in national surveys, and sample sizes of planned national surveys should not be increased solely for the application of the BED-assay.

The Reference Group also calls for more research on the validity of the BED assay for estimating incidence, as well as for exploring alternative laboratory assays or modelling methods. The validation of the BED-assay should go beyond seroconverter panels, and include analyses in cohorts (looking at both early and late HIV infection) with exploration of reasons for false positives and evaluation in cross sectional studies as appropriate.

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4. Recommendations

The BED assay should not be used at present

The BED assay is currently unvalidated, and there are different window periods for different HIV subtypes. Evidence presented at the meeting suggests that its current use overestimates incidence, at least in part because it also captures late-stage HIV infection.

The BED assay should not be used for absolute incidence estimates. It should not even be used to monitor trends in incidence, because the degree to which it overestimates incidence may change – e.g. due to a shift in HIV subtypes, or due to a changing incidence of late-stage disease occurrence. Until the assay has been validated, it should not be used, so training in its use – and any planned implementation – should be halted.

Alternative approaches to estimating incidence include (i) the use of pooled PCR; or (ii) estimation from age-specific prevalence data.

Further research

Further research is needed in to the validity of the assay. Note that HIV-surveillance data may not be the most suitable for this validation, and that data from cohort studies of early and late infection would be preferable. It is recommended that DHS data are not used for validation, since the sample sizes required to obtain statistical power would be unfeasibly large and therefore expensive.

The reasons for false positives (i.e. false recent infections) need to be investigated, requiring data on:

- demographics (age, sex) and behaviour;
- CD4 count;
- HIV subtypes and subtype mixture;
- current treatment (ART regimens);
- quality assurance, including freezing and thawing of specimens;
- total concentration of IgG antibodies.

Specificity may be improved by using a two-test algorithm, using BED in conjunction with another assay (e.g. the avidity assay). Testing for CD4 level would assist in identifying late-stage disease. Additionally, data collected with the sample should include age and symptoms of late-stage disease so that samples that may appear to the BED assay to be incident infections could be identified.

Factors that may affect the window period, including age, mode of transmission, HIV subtype, and pregnancy, need to be investigated, as well as how the window period may vary amongst populations, and over time within populations. Age- and sex-distributions of BED-derived incidence estimates should be compared with patterns derived from other means of estimation.

The effect of (male) circumcision on HIV transmission

1. Background

In areas of Africa where circumcision is common HIV prevalence tends to be lower, suggesting a protective effect. A meta-analysis (Weiss *et al.* 2000) found that circumcision reduced the risk of HIV acquisition in men by 58% (95%CI: 46-66%).

In an observational analysis using data from the Rakai study of discordant couples, circumcision was found to be protective both against acquisition of HIV by the circumcised male (reducing incidence by 47%; 95%CI: 13-67%), and against transmission of HIV (reducing incidence by 60%, with no instances of transmission having occurred from a circumcised male with an HIV viral load of <50,000 copies/ml) (Gray *et al.* 2000). *T*ransmission of *Trichomonas vaginalis* and HSV2 from male-to-female were also reduced (relative risk 0.75).

A prospective randomised controlled trial in Orange Farm, South Africa (ANRS1265), reported a 60% (95%CI: 32-76%) reduction in the incidence of HIV among circumcised men, despite reported sexual risk behaviour (i.e. numbers of sexual partners) having been higher in the circumcised group. That is, circumcision was still strongly protective despite a potential disinhibiting effect. This trial involved the general population (aged 18-24 years), and so the results are expected to be applicable to the population that would receive the intervention if it were implemented. No data on male-to-female transmission rates were obtained.

Prospective randomised trials of circumcision are also underway in Rakai, including analysis of male-to-female transmission rates in discordant couples. Another trial, in Kisumu, Kenya, is underway, with scheduled completion in September 2007.

2. Mechanism of action

Circumcision may protect against both HIV acquisition by the circumcised male and HIV transmission from him.

Circumcision's protective effect may occur 'directly', or may be mediated via reduced risk of acquisition of other STIs which are known to promote HIV acquisition and/or transmission. This means that the effectiveness of circumcision as an intervention would be dependent upon the prevalence of these other STIs in the particular setting.

Circumcision can involve removing different amounts of the foreskin, which may affect the degree of protection offered. The protective effect of circumcision presumably occurs through the removal of mucosal membranes which are rich in HIV target cells and more prone to micro-tears than the strongly keratinised skin of the rest of the penis. Additionally it promotes more-rapid drying which reduces the likelihood of bacterial infections, which in turn reduces the risk of acquisition of HIV.

3. Potentially harmful effects

Potential adverse events include excessive bleeding, infection, excessive pain, anaesthetic-related problems, too much skin being removed, damage to the penis, cosmetic problems, erectile dysfunction, psycho-behavioural problems, penile amputation, and death.

In the short-term, circumcision may *increase* the risk of HIV acquisition and transmission through the creation of the wound: typically patients are advised to abstain from sex for 4-6 weeks.

The impact of circumcision on risk behaviour needs to be examined, since the knowledge that it is protective against HIV may lead to *behavioural disinhibition* – i.e. increases in risk behaviour, including an increase in the number of sexual partners or a reduction in condom use. This may reduce the power of intervention trials, and be a serious problem for any intervention.

4. Implementation of circumcision services

There are now 11 studies of acceptability of circumcision in 8 African countries with 45-80% of uncircumcised men reporting acceptance if circumcision is safe and affordable.

The age at which circumcision occurs is important: prior to sexual debut maximises the period of protection, but there are ethical issues regarding consent. Neonatal circumcision would obviously ensure that the entire period sexual activity was protected, and there may be less behavioural disinhibition. Also uptake may be higher. However, the availability of safe of neonatal services would have to be considered.

Rates of complications and speed of wound-healing needs to be monitored in trials and intervention programmes.

There are potential synergies with other HIV prevention services including male and female condom distribution, behavioural change programmes, HIV counselling and testing, STI treatment, empowering women, and poverty reduction.

In economic evaluations of the impact of provision of circumcision, the discount rate applied will be important, since benefits accrue over the long term, whilst costs are up-front as this is a single-event intervention (in contrast to ART provision, where treatment of the individual patient is on-going).

5. Epidemiological effects

It is important to emphasise that circumcision is not just (partially) protective of circumcised males: their female sexual partners are also protected, 'indirectly' through a consequent reduction in the prevalence of HIV in the male population, and potentially 'directly' through a reduction in the infectivity of HIV-positive circumcised men. Additionally, circumcision may reduce transmission of other sexually-transmitted infections (STIs) that promote HIV transmission, which would also protect both males and females from both these STIs and HIV. Circumcision would also have an indirect protective effect on uncircumcised men.

One effect may be to increase the *proportion* of all HIV infection that occurs in females, since there may be a greater protective effect on males than females, since circumcised males are protected 'directly' whilst females are protected 'indirectly'. However, circumcision would reduce the total *number* of infections occurring in both sexes, and therefore also protect females.

The impact of an intervention to provide circumcision will depend in part upon the current prevalence of circumcision in the intervention setting. Data from Demographic

and Health Surveys (DHS) show that the prevalence of circumcision varies amongst countries, and within countries by religious group (typically close to 100% in Muslims and lower in other groups) and ethnicity (which may be associated with religious group). It may also vary by age-group and over time, and there may be recent changes – e.g. in Burkina Faso, the average age at circumcision was higher in fathers than their sons, indicating a shift to earlier circumcision; there was also a shift towards circumcision being performed by medical staff rather than a traditional practitioner.

Since HIV is present even in areas where circumcision is universal, provision of circumcision alone is unlikely to eliminate HIV, even with very high uptake. However, combining circumcision with other interventions such as ART provision may produce much larger reductions in HIV transmission.

6. Mathematical modelling studies

Mathematical modelling can be used to predict the reduction in HIV incidence and prevalence that may occur due to provision of circumcision, and the timescale over which changes may occur. These predictions are an essential component of economic (e.g. cost-effectiveness) evaluations.

The relationships between the reduction in the per-sex-act transmission probability and the incidence and prevalence of HIV are non-linear, and made even more complex by heterogeneity in risk behaviour. Therefore predicting the impact of increased circumcision is complex. Additionally, the nature of the HIV epidemic – whether it is concentrated or generalised, nascent or mature – will affect the magnitude and dynamics of the impact.

Models need to consider the patterns of risk behaviour – including heterogeneity, including commercial sex – in the population and the background prevalence of circumcision and the increase following the introduction of the intervention. The impact of circumcision on risk behaviour needs to be considered. Additionally, interactions between other STIs and HIV, and the impact of circumcision on those STIs should be considered.

Key questions to be addressed by modelling include:

- What is the potential impact of rolling out circumcision programming in sub-Saharan Africa (SSA)? How much does it depend on the:
  - speed at which circumcision services are rolled out
  - circumcision prevalence level before and after roll-out (numbers of additional circumcisions performed and coverage achieved)
  - countries in which it takes place
  - underlying dynamics of the HIV epidemic in various settings
  - sub-populations that might be initially targeted.

- From an epidemiological perspective, what is the most effective age range to have the biggest impact on the epidemic (context specific as it depends on the peak incidence): neonatal, pre-pubescent, pubescent, 18–24 years old, all males, before or after sexual debut.

- What would be the relative benefit of targeting higher-risk groups, e.g. mineworkers, truck drivers, high-HIV-prevalence communities, low-circumcision-prevalence communities?

- What role do sexual networks play in determining steady state HIV prevalence and what is the relative impact of circumcision (and other interventions) in different network contexts?

- What are the possible synergies between HIV, HSV-2 and circumcision given that circumcision appears to have only a small impact on HSV-2 (OR ≈ 0.8–0.9) but the association between HSV-2 and HIV is very strong?

- What are the benefits of circumcision to women? To what extent do the benefits for women depend on the age of men and women? HIV prevalence in SSA is already higher in women than in men. What does circumcision do to this differential impact of HIV?

- How much of the variability in HIV prevalence in sub-Saharan Africa can be explained by differences in circumcision practices and prevalence?

7. Further research

Questions for further research include:

Biological factors and determinants of transmission

- How does the protective effect depend upon the amount of foreskin removed? Is there a direct linear correlation between extent of remaining Langerhans cells and HIV acquisition risk?
- Can further analysis be done on the Orange Farm data in order to better understand other important determinants of transmission?
- Why does circumcision appear to be most protective in the highly exposed?
- Impact of circumcision on male to female transmission: data from Uganda trial.

Social context, behavioural norms, etc

- What are the cultural determinants of current circumcision practices and how might these affect uptake of services?
- How acceptable is circumcision in different communities and how likely will it be that males will access services if these are made available? Who will accept (differential uptake?) and in what environment will they accept? How does this vary among urban, peri-urban and rural communities? What differences can be anticipated by country?
- By what methods can circumcision be promoted most effectively?
- What role could be played by women in encouraging men to be circumcised?
- What is the prevalence of circumcision by geographical location, age, ethnic group, etc?
- Could male to female transmission be further explored by asking women in antenatal clinics (ANC) if their partners are circumcised?
- What information currently exists on the validity of self-report and partners' reports of circumcision status?
- Can we infer sexual mixing patterns from Demographic and Health Survey (DHS) data on number of sexual partners and obtain better data on the age at circumcision? Can we analyse female partner HIV status by male partner circumcision status?
- How much behavioural disinhibition may occur following adult male circumcision? What prevention methods are most effective in preventing it?

- How often does resumption of sex before wound healing occur and to what extent can increased susceptibility be demonstrated by higher HIV incidence in those who do resume sexual activity early?

Service delivery

- What is needed to provide circumcision as a routinely offered service (methods, infrastructure, training, medical personnel) and how would this vary by population: migrant workers, men in STI clinics, truck drivers, adolescents in youth friendly services, newborns?
- What service models are most acceptable and cost effective: vertical programmes, settings that focus more broadly on male sexual and reproductive health, other settings (e.g. PMTCT programmes)?
- What is the current incidence of side effects/adverse events by provider type and setting? How can these be minimised and at what cost?
- Current costs for male circumcision in different countries by provider and procedure.
- Safety issues: incidence of adverse events by provider, setting, etc.
- Feasibility: what proportion of uncircumcised males could be circumcised in 5 years by country? Current male circumcision prevalence, number of providers (role of traditional circumcision), potential for scale-up.
- What changes (training, licensing, regulatory, supply chain management, etc.) are needed to make current practices safer?
- What is the potential for training health workers other than doctors to provide circumcision services?
- Practical issues around scaling-up circumcision in urban, peri-urban and rural areas and in communities living in formal and informal housing.
- Empirical data on the impact of population level roll-out of circumcision services in one or more communities.

Anti-retroviral therapy (ART)

1. Background

A key issue raised by the roll-out of ART in developing countries requires is how to estimate current and future need for treatment. This depends upon the criteria for determining when an individual's ART provision should begin, the effect of ART on survival, and the trajectory of the HIV epidemic, including impact of ART-provision on that trajectory. As well as increasing survival of HIV-positive individuals (thus increasing current ART need), ART may reduce infectivity (thus reducing future ART need), but its provision may also lead to increased sexual behaviour of patients (due to improved health) and potentially behavioural disinhibition (particularly in HIV-negatives), leading to an increase in HIV incidence.

The criteria for ART-eligibility vary amongst countries; e.g. some use CD4-count data, whilst others use only signs and symptoms. Additionally, the speed with which ART-eligible people actually commence therapy will vary amongst countries, according to access to *diagnosis*, as well as availability of therapy. Therefore, the facility to reflect these national differences should be provided in EPP/Spectrum.

2. ART-eligibility criteria

In developing countries, sophisticated diagnostic methods are usually lacking; hence there is a need for simplified clinical management to determine when to commence ART, when to change regimen due to toxicity or failure and when to stop, to provide end-of-life care.

A new four-stage clinical scale (No symptoms, Mild, Advanced, Severe) has been defined, based on clinical and definitive indicators, which recognises that ART can reverse progression through the stages. The new guidelines recommend more strongly that ART should commence when patients reach clinical stage 3 (Advanced) or have CD4 levels in the range 200-350, rather than waiting for the count to decline below 200.

Measured CD4-percentage is a more reliable indicator of disease stage than simple CD4 count, particularly in children, although the latter is more widely-available. Total lymphocyte count can also be used as an indicator.

The revised guidelines also address management of toxicity and treatment failure.

3. The need for empirical data on the prevalence of stages of HIV infection

There is a programmatic and advocacy need for empirical data on the frequency distribution of infection stages and CD4 counts in HIV-positive populations, and CD4 counts in HIV-negative populations in the same countries (for comparison), which are currently lacking. These data are required for calculation of how changing ART-eligibility criteria affects ART-need, and for future projection of ART need. Currently estimates can only be obtained using a modelling approach, but its validity is limited by the lack of data.

These data could be collected in ANC clinics, or from VCT services; whoever, there is a problem that individuals cannot be tracked as they may use different clinics,

leading to potential problems of multiple counting, and preventing longitudinal studies of progression rates of individuals being performed.

Causes of loss to follow-up need to be analysed, and cohort studies and treatment programmes should be encouraged to perform and report these analyses. The lack of ability of many health care systems to track patients means that loss-to-follow-up cannot be distinguished from mortality, leading to potential overestimation of death rates. However it was noted that censoring those lost to follow-up may underestimate mortality if many are lost due to ill health preceding death without that death being recorded. Whilst decentralising provision of care may make tracking patients harder, it may improve adherence to treatment regimens, and so reduce mortality, by improving access to care.

There is a need for population-based surveys of HIV-infection stages; routine DHS surveys will typically have too few HIV-positives to provide good data.

4. Impact of changing ART-eligibility criteria on estimated ART-need

Note that changes in guidelines to recommend earlier commencement of ART will substantially increase the estimated ART need, and thus reduce the proportion of need that is currently being met. It is important to make this clear so that undue doubt is not cast on the reliability of estimates in light of their revision. It was recommended that two sets of estimates be produced, indicating demand according to the old and new criteria. Also, countries need estimates of numbers of people eligible for ART according to different criteria so that they can decide which criteria they have the resources to use.

5. Estimation of ART-need in Spectrum

Spectrum calculates the prevalence of HIV by age and sex using incidence inputs from EPP or Workbook, combined with demographic data and data on survival of HIV-positives. The coverage of ART – i.e. the proportion of those needing ART who receive it – can be varied.

Currently, Spectrum estimates ART-need by assuming that individuals who progress to a state two years from death due to AIDS are newly-needing of ART; those who receive ART are then subject to 10% annual mortality. It models the rate of progression from infection to death, and then estimates ART-eligibility by 'working backwards' from the time of death, because the rate of progression to AIDS symptoms was poorly estimated. However, now that there is the need to model ART demand, and data have improved, Spectrum is to be changed to model progression to ART-eligibility and then to death. Furthermore, modelling changing of ART-eligibility criteria and coverage requires a 'forward calculation' approach. Different compartments are needed to capture different stages of infection and treatment, and to distinguish treated and untreated individuals. In the first year of treatment, mortality should be 20%, with 10% annual mortality applied to subsequent years. EPP is also to be modified to incorporate the impact of increasing provision of ART.

The lack of common availability of second-line ART in developing countries means that there is not yet a need to incorporate it into Spectrum, although this is likely to become a requirement in the future.

6. Natural history and mortality of untreated and treated HIV infections

Prediction of the impact of HIV and the effect of ART requires knowledge of the natural history and mortality of both treated and untreated infections. The availability of treatment means that there will be no more studies of untreated infection for ethical reasons.

An analysis of the survival of untreated individuals from CD4 count in the range 200-500 found a median survival time 4-5 years with 95% bounds 2.5-11 years. An important source of variation in survival time is variation in CD4 count within this range at the time of enrolment.

In developed countries, ART can greatly increase the ten-year survival rates of HIV-positives. In developing countries, widespread ART provision is relatively recent and so long-term effects cannot be assessed. There will probably be the same determinants of mortality as in developed countries, plus additional specific determinants, which will need to be investigated.

For analysis of the survival of treated individuals, there are a number collaborations, including ART-CC (www.art-cohort-collaboration.org) and ART-LINC (Sterne *et al.* 2005). Estimated 5-year survival under HAART from CD4 in the range 200-350 was estimated to be 95% (95%CI: 94-96%).

Although the typical prognosis is poorer compared to high-income countries, ART can be highly effective in resource-constrained settings: about 90% of patients survive the first year, despite having low CD4 cell counts at baseline. Factors affecting prognosis are similar to high-income settings – i.e. lower CD4, and advanced age are associated with faster progression of disease.

Limitations of the analysis include a lack of access to individual patient data from resource poor countries, heterogeneity of analysis and reporting in individual studies (e.g. conversion of results to median survival time, or a lack of precision in reported estimates), differences in patient selection and follow-up procedures (e.g. “incident” versus “prevalent” individuals, prospective versus retrospective data collection), and differences in treatment provision (including varying levels of “no treatment” or minimal care).

For improved estimates there is a need for collaborative analyses of individual patient data from several regions with comparable laboratory measurement protocols, definitions of events and outcomes, recording of main treatments, and recording of WHO stage III events/episodes. There is potential in using indirect evidence on patients receiving HAART and formal inclusion of external and expert information via fully probabilistic modelling (i.e. Bayesian approaches).

It was noted that at the start of ART programmes, mortality will be elevated by enrolment of more late-stage infections that will occur subsequently.

7. Variation in CD4 count

There is substantial reported variation in CD4 counts of HIV-negative individuals in different populations (from 670/µl in Wonji, Ethiopia to 1160/µl Kampala), as well as HIV-positive individuals. This means that the thresholds at which ART should ideally commence may be different in different settings. It is important to remember that

within an individual, CD4 counts can vary by up to 200/µl in tests just a few weeks apart.

Williams *et al*. investigated competing models of the decline of CD4 after infection with HIV to determine if the distribution of CD4 among HIV-positive adults in Africa can be accurately predicted from (i) the distribution of CD4 in HIV-negative adults, (ii) time trends in HIV prevalence and (iii) the survival distribution after infection. Prevalence-trend data were used to predict temporal patterns of incidence and mortality and then the distribution of time-since-infection in HIV-positives. It was assumed that survival time post-infection is independent of CD4 at infection – i.e. that those with higher CD4 counts at the time of infection experience proportionately faster declines in CD4 count during infection. Several studies have provided supporting evidence for this assumption. (Mekonnen *et al*. 2005; Lyles *et al*. 1999; Hughes *et al*. 1994 ; Stein *et al*. 1992).

A recent study in South Africa reported that clinical disease stage is a stronger predictor than CD4 of risk of both developing AIDS and dying (*Badri et al*. 2004).

The model can be used in different ways:

- CD4 distribution reflects time trends in the incidence of infection over the preceding twenty years and provides information on the maturity of an epidemic.
- CD4 data among HIV-negative people and projected trends in HIV prevalence can be used to forecast CD4 in HIV-positive people.
- To the extent that CD4 levels determine ART needs we can predict the future demand for antiretrovirals and other drugs, and for health care in general.

Further studies and better data on the factors that determine levels and rates of decline in CD4 among HIV-positive and negative people would help to test and refine the model, with a view to assessing the state of HIV epidemics, future demand for ART and determining the most effective criteria for initiating ART.

8. The effect of ART on sexual risk behaviour

ART-recipients often have increased sexual behaviour, resulting from improvements in their health and feelings of well-being. Whether or not this results in a net increase in rates of HIV transmission depends upon the extent to which increased rates of sexual contact are counteracted by reduced infectivity due to a reduced viral load.

An important potential effect of the widespread provision of ART is *behavioural disinhibition* – an increase in risk behaviour in the population in response to the belief that HIV infection is no longer a serious medical condition, but rather one that can be readily managed. This effect may apply to both HIV-positive and HIV-negative individuals, and generally appears to be particularly apparent in the latter – which may potentially cancel-out the HIV-incidence-reducing effect of ART's reduction in HIV infectivity.

9. The effect of ART on HIV-infectivity

The effect of ART on HIV-infectivity is not currently incorporated into Spectrum. However it is a feature of ASSA2002 model.

10. Treatment failure

Difficult decisions need to be made regarding provision of second-line therapy in cases of treatment failure, since it is much more expensive than first-line therapy and may add relatively few years to the *average* life-expectancy of patients.

The need for second-line therapy cannot be estimated from data collected in developed countries, because decisions to change regimen are made on an individual basis, based on detailed diagnostic investigation of the patient, whilst in developing countries broadly-applicable algorithms to be used in the absence of detailed investigation are required. It will depend upon the locality, including what proportion of the population has received informal treatment with poor adherence resulting in development of resistant infection.

Data are lacking on the survival of those on second-line therapy, and are needed for programme-planning.

11. ART and fertility

It was noted that ART can increase female fertility, resulting in a marked increase in births, sometimes due to 'replacement' of children lost to HIV-mortality.

HIV treatment and prevention in children

1. Prevention of mother-to-child transmission (PMTCT)

(Also see the Reference Group report, *Rates of mother-to-child transmission and the impact of different PMTCT regimens*.)

PMTCT regimens vary in their efficacy. The mother's disease stage affects both the transmission probability in the absence of PMTCT treatment, and the efficacy of treatment.

Provision of PMTCT only at delivery means missing the opportunity to prevent one-third of all preventable mother-to-child-transmission events. Hence there is a need for earlier diagnosis and intervention.

Breast-feeding is an important route of mother-to child- transmission, with a risk of late postnatal transmission of up to ~0.9%/month, which increases the transmission risk (additively) by up to 4-5% if breast-feeding continues to age 6 months. Breast-feeding can account for up to 40% of transmission events in populations where it is the norm, with the highest risk occurring in the first few weeks. However it should be noted that infant mortality and morbidity is typically higher in formula-fed populations, and so early weaning may not be an optimal strategy for some populations. A barrier to promotion of breast-feeding replacement is potential stigmatisation.

It is not clear whether ART reduces transmission through breast-feeding, although the long half-life of nevirapine – which is commonly used for PMTCT at delivery – may mean that it continues to offer protection for the first few weeks of breast feeding.

It is hypothesised that "safer" breastfeeding, through provision of infant or maternal ART prophylaxis, with early weaning might reduce transmission. There is a need to evaluate safety and efficacy of ART provision as well as the safety of early weaning.

The balance of risks and benefits of maternal HAART prescribed solely for PMTCT in resource-limited settings is unknown. Provision of HAART to mothers who have HIV disease is recommended for their own health and can reduce in utero / intrapartum / early postnatal mother-to-child transmission to 2-3%. Short AZT + SD NVP for women who don't need ART reduces in utero/ intrapartum/early postnatal MTCT to 2-4%.

In HIV-positive children, and potentially-HIV-positive children born to HIV-positive mothers, cotrimoxazole prophylaxis may protect against opportunistic infections.

2. Modelling PMTCT in Spectrum

There are many PMTCT regimens, and modelling in Spectrum requires that their impacts be summarised in a few parameters. (In fact, there are many different ART regimens, and their impacts are also similarly-simplified for modelling.) Currently Spectrum considers three categories of HIV-positive mothers: (i) those not receiving PMTCT treatment; (ii) those receiving PMTCT treatment but not ART; (iii) those receiving ART.

It was recommended that Spectrum provide default parameter estimates for the effectiveness of PMTCT, but that the user be allowed to modify them if required. It should be possible to specify several protocols, with different effectiveness parameters, and the coverage of each one.

Recommendations for modelling of PMTCT regimens in Spectrum were:

- Retain the breastfeeding categories: short, medium, long.
- Retain the programme breast-feeding options: None, replacement feeding, exclusive feeding.
- Provide the following treatment options, and allow specification of the proportion of women receiving them: SD NVP, SD NVP + AZT, other.
- For women receiving HAART, the mother-to-child transmission rates should be 2% in the absence of breastfeeding, and 4-5% with breastfeeding.

3. HIV-diagnosis in infants

Serological diagnosis of HIV infection is not possible in children of HIV-positive mothers who are below the age of 18 months, due to the presence of maternally-derived antibodies. Since virological testing is often not available, those children should be given presumptive cotrimoxazole prophylaxis. However, coverage is currently low.

A four-stage clinical scale has now been defined for children, as follows.

<table>
<tr><th>WHO Paediatric Stage</th><th>Availability of CD4 cell measurement</th><th colspan="2">ART recommendation
≤18 mo > 18 mo</th></tr>
<tr><td rowspan="2">4</td><td>CD4</td><td colspan="2" rowspan="2">Treat all irrespective CD4</td></tr>
<tr><td>No CD4</td></tr>
<tr><td rowspan="2">3</td><td>CD4</td><td rowspan="2">Treat all</td><td>CD4 guided</td></tr>
<tr><td>No CD4</td><td>Treat all</td></tr>
<tr><td rowspan="2">2</td><td>CD4</td><td colspan="2">If close to or below CD4 threshold</td></tr>
<tr><td>No CD4</td><td colspan="2">At or below TLC threshold</td></tr>
<tr><td rowspan="2">1</td><td>CD4</td><td colspan="2">Only if at or below CD4 threshold</td></tr>
<tr><td>No CD4</td><td colspan="2">Do not treat</td></tr>
</table>

Additionally, if CD4-percentage or CD4 count falls below the following age-dependent thresholds then ART should be commenced, regardless of clinical stage, since a drop of CD4 below these levels significantly increase the risk of disease progression and mortality.

Age specific recommendations-severe immunodeficiency				
Age (months)	<11	12-35	36-59	≥60
%CD4	25%	20%	15%	15%
CD4 count	1500	750	350	200
Total lymphocyte count	4000	3000	2500	1500

Measured CD4-percentage is a more reliable indicator of disease stage than simple CD4 count, particularly in children, although the latter is more widely-available. Total lymphocyte count can also be used as an indicator.

The revised guidelines also address management of toxicity and treatment failure.

4. Cotrimoxazole prophylaxis

Cotrimoxazole is highly protective against *Pneumocystis carinii* pneumonia, and may also protect against bacterial infections, toxoplasma, malaria, and diarrhoeal disease, in HIV-positives, both adults and children. A study in Zambia (Chintu *et al*. 2004) – a high-bacterial-resistance setting – found that cotrimoxazole prophylaxis reduced mortality by 43% and hospital admission rates by 23%.

An observational cohort study in Uganda (Mermin *et al*. 2004) reported that mortality was reduced by 46%, and that mean annual decline of CD4-cell count in HIV-positives was lower. However, there was debate over whether prophylaxis against opportunistic infection reduces rates of HIV-disease progression, or merely averts some early deaths, allowing progression to continue for longer (Gilks 1993).

5. HIV's impact on child mortality

HIV has had the greatest impact on child mortality in countries where child mortality was previously lowest. Across Africa, HIV causes 10% of child mortality and at least a third of mortality before five years of age.

The types of infections and symptoms exhibited by HIV-negative and positive children are similar, but the latter experience much higher incidence. HIV-positive children exhibit significantly reduced growth rates, in terms of both height and weight, but treatment results in the 'gap' being closed greatly. HAART improved the average weight gain of HIV-infected children from subnormal to normal after 1 year and improved average height growth to nearly normal after 2 years (Nachman *et al*. 2005).

Disease progression is more rapid in those infected pre-partum, and is particularly high in the first year of life. No other prognostic indicators of rapid progression are known. ART greatly reduces progression rates. It was recommended that a 'double Weibull' survival function be used to model progression rates, accounting for the presence of fast- and slow-progressors. For purposes of estimation, it is important that very early deaths are detected, which may often not occur – resulting in underestimation of HIV infections occurring in children and underestimation of progression rates.

In a pooled analysis based on individual data from 7 such RCT in sub-Saharan Africa, 3500 exposed children were included, of which nearly 700 were infected (Newell *et al*. 2004). It was estimated that about 5% of uninfected and 35% of infected children will die before age one year, and 7.5% and 52.5% by two years of age.

ART is effective in prolonging life of HIV-positive children in both developed and developing countries, although data on children under two years in developing countries are scarce.

HIV also causes child mortality through orphanhood. HIV-negative children born to HIV-infected mothers have higher morbidity and mortality than infants born to uninfected mothers. One study found that children (both HIV-negative and -positive) whose mother had died were 2-3.5 times more likely to die than those whose mothers survived (Newell *et al*. 2004).

Survival times post-HIV-infection are longer in children than adults, and modelling needs to account for this. It was recommended that Spectrum be modified to permit HIV-positive children to survive beyond the age of 15 years, and to divide them into two groups: slow- and fast-progressors.

Recommendations for modifications to Spectrum were:
Child mortality

- To examine US and European data using information on time starting treatment and assuming progression to death in about 2 years.
- To examine South African HSRC data and determine what survival pattern reproduces the prevalence pattern.
- Allow HIV-positive children to survive past age 15.
- Since data are currently lacking on survival of HIV-positive children past age 5 years, use young adult survival data.
- For HIV-positive children on ART, assume annual mortality is 5%, which is not reduced by additional provision of cotrimoxazole.
- For HIV-positive children on cotrimoxazole but not ART, assume annual mortality of 10%.

Child ART treatment need

- In the short term, assume treatment is required 2 years before death, as for adults (although this is to be changed).

Estimates and projections, and uncertainty estimation

1. Distribution of HIV by age and sex in Spectrum

Spectrum distributes HIV infections by age and sex, assuming that the force of infection differs by age and sex but remains constant over time, using an 'average' pattern derived from DHS data from multiple countries. Since prevalence varies amongst countries, the pattern is standardised with respect to the prevalence in 35-39-year-olds.

As more and better data become available, the patterns used need to be revised. Unfortunately, the data are noisy, and there is substantial variation amongst even neighbouring countries. There is no discernible pattern in countries with HIV prevalence below 5% and the patterns are unclear even in high-prevalence countries, where larger numbers of infections give a clearer 'signal'. Furthermore, there is substantial variation in the distribution of infection *within* many countries.

Comparison of Spectrum outputs based upon Spectrum's default patterns and DHS data with prevalence measurements from DHS surveys found that prevalence in females was predicted more accurately than in males. Whilst some predictions were close to the observed patterns, some were very different, and some did not seem reasonable epidemiologically.

It was recommended that country-specific age- and sex-distributions from DHS data be used for countries with HIV prevalence >5%. For low-prevalence countries, Spectrum's default patterns should be used since DHS data have insufficient power to estimate prevalence distributions. For low-prevalence countries, pooling data may allow a pattern to be determined, which could be compared with high-prevalence countries to see if it is similar or not, indicating whether a different default pattern may be needed.

The default female/male prevalence ratio for generalised epidemics has been increased from 1.3 to 1.5. It was recommended that this default value be used unless country-specific DHS data indicate a significantly different ratio. Cohort studies should be analysed to discern temporal patterns in the sex-ratio.

It was strongly recommended that *empirically-measured* HIV prevalence in 15-24-year-olds should be the reported indicator, not a model-derived estimate using data for other age-groups, since this is subject to too much uncertainty.

2. Ante-natal clinic (ANC) data: availability and quality

In the WHO African Region 32 countries (70%) reported ANC surveillance data, of which 90% report urban and rural data. Coverage of ANC surveillance in Africa has increased steadily over time, but there has been a decline in the number of sites from a peak in 2002, possibly due to some countries redirecting efforts towards population-based surveys. There is increasing representation of rural areas. However, many countries report only aggregated data and only around half report trends in the positivity of 15-24-year-olds, which can be used as an indicator of incidence.

While WHO African Region countries have improved in their reporting of the age of pregnant women recruited into the ANC sentinel surveillance systems, less than half

of these countries are providing this information. Of the few countries that do collect data on age, a number of them focus on reporting the age of 15- to 19-year-olds. Prevalence among 15- to 19-year-old ANC attendees is a relatively unstable indicator of trends in HIV incidence and prevalence, and thus prevalence among the ANC attendees 15–24 years of age is a preferred measure. This makes it difficult to monitor the UNGASS indicator, which requires monitoring of HIV prevalence among the young ANC attendees aged 15–24 years.

In discerning trends, there are problems with inconsistent reporting; differences in classification of sites in different countries; changes in the sites used, and in the categorisation (urban, peri-urban, rural) of the sites – which may be due to urbanisation causing changes in the nature of the sites, or merely due to changes in classification. Additionally, patterns of attendance may change – e.g. women attending to obtain contraception. Only a few countries have enough data and consistency of sites and time series to allow a trend in the 15-to-24-years-old age-group to be discerned. The following ANC prevalence trends are apparent: (i) stable: Botswana, Gambia, Ghana, South Africa; (ii) increasing: Swaziland; (ii) declining: Burundi, Burkina Faso, Zimbabwe.

Criteria for assessing the quality of ANC data are:
- frequency and timeliness of data collection;
- appropriateness of populations under surveillance;
- consistency of the sites/locations and groups measured over time; and
- coverage/representativeness of the groups for the adult populations (either groups at highest risk or general adult population).

The reliability of testing procedures was highlighted as an important consideration. It was recommended that weak 'positive' results in rapid tests should be confirmed using a more reliable test, since many are false positives in cases where individuals have been referred to clinics. Fluctuations in positivity rates may indicate unreliable testing procedures with many false positives. Changing to more-specific tests may produce a spurious declining trend in ANC positivity.

Reduction in female fertility due to HIV is most marked in older women, so a change in the age-distribution of HIV prevalence may alter the bias of ANC prevalence estimates. This may occur as an epidemic matures.

For validation, it is desirable to have DHS and ANC data from the same year, to examine the relationship between ANC positivity and population prevalence, but this is rare. Where comparison was possible (Botswana, Ghana, Lesotho, South Africa, Tanzania, Zimbabwe), ANC positivity was higher than population prevalence, with the exception of Zimbabwe, where they were similar.

3. Relationship between HIV prevalence in ante-natal clinic (ANC) attendees and the general population

It is important to understand the relationship between HIV prevalence in ante-natal clinic (ANC) attendees and the general population, and how it may change over time. Validation of trends in ANC HIV-prevalence data using population-based HIV-prevalence surveys is necessary.

Comparison of HIV prevalence in ANC with the general female population in Uganda

In Uganda, HIV prevalence in ANC surveillance is lower than in the general female population.

In Rakai, HIV prevalence was lower in pregnant women aged 15-49-years than in non-pregnant women in the same age-range, with the exception that in 2004 in women aged 40+ years. However, the age-specific differentials change over time, with prevalence in non-pregnant women being greater by half in 1994 (20.2% vs 13.2%) and being almost twice as high in 2004 (15.4% vs 8.5%).

ANC surveillance HIV prevalence is lower than prevalence in women measured by DHS in Uganda. Given the differential prevalence in pregnant and non-pregnant women, DHS prevalence should be broken-down by pregnancy status. The bias in ANC prevalence, and how it changes over time, needs further investigation.

Comparison of HIV prevalence in young people in Manicaland, Zimbabwe from a population-based survey with ANC data

Data from the Manicaland HIV/STD Prevention Project provide the first example of a decline in ANC prevalence being confirmed by a decline in HIV prevalence in the general population.

HIV ANC prevalence declined from around 30% in 2000 to around 22% in 2004. HIV prevalence also declined in surveyed populations between surveys conducted in the periods 1998-2000 and 2001-3, in females from 25.9% to 22.3% and in males from 19.5% to 18.2%. Declines were observed in all age-categories except for the oldest, 35-44-year-olds, in which small increases were seen. This increase may be due to the epidemic maturing.

ANC prevalence was approximately two-fold higher than in the surveyed general population. It is important to note that 'urban' ANC facilities often serve 'rural' women who travel there, blurring classification. The consequence is that the ratio of crude prevalence (in women) in ANC settings to prevalence in the local community (in both sexes) is much lower in urban areas than rural ones, because HIV prevalence is lower in rural areas so rural women travelling to urban ANC facilities reduce the estimated urban ANC prevalence. However, if ANC data are classified according to the residential location of the women then this difference is eliminated. Therefore it is important to record the location of residence of the individual women who are tested in urban ANC facilities, rather than simply recording the location of the clinic. When data are analysed in this manner, the ratio of ANC prevalence to general population prevalence is the same across residential settings, with estimates in the range 2.3-2.7. It is important to continue population-based studies in parallel with ANC surveys so that any trends in the relationship between ANC- and population-based prevalence estimates can be elucidated.

Declining prevalence is probably due in part to declining incidence, with reported declines in risk behaviour, with an increase in age at sexual debut, and declines in numbers of sexual partners and concurrent sexual partners, and in incidence of casual sex. It may also be due to increasing mortality, although data are not yet available.

Recommendation

In light of the findings above, it was recommended that more comparisons of the ratio of prevalence in pregnant and non-pregnant women be made to assess to what extent this may explain any discrepancies between ANC- and DHS-based prevalence estimates.

4. Estimation of plausibility bounds: generalized epidemics

The quality of data used for national HIV estimates is variable and there is a need for improved methods to estimate plausibility bounds, cognisant of data quality. The existing approach (Grassly *et al*. 2004) was to categorise countries according to HIV prevalence (high, low), epidemic pattern (rising, steady, declining) and data quality (good, average) and to determine patterns of uncertainty that could then be applied to other similar countries. Building on that work, the impact of uncertainty in different data sources on the uncertainty of output estimates is being examined in more detail.

A Monte Carlo approach is being used – i.e. performing multiple (typically 1000) numerical simulations, using parameter values varied within their ranges of uncertainty by statistical sampling from appropriate distributions. Curves that do not fall within a set of plausibility criteria (e.g. if the epidemic is declining but the curve is increasing) are rejected. Urban and rural areas within a country treated separately. EPP is used to produce a set of prevalence curves for each country, and the Spectrum is used to generate a range of outputs for each of these inputs. This is highly demanding computationally.

A key question to be addressed is whether the scaling factor should be assumed to be fixed, or to have its own uncertainty. The number of runs required to achieve convergence to produce robust estimates of plausibility bounds is not yet known.

It was commented that adult AIDS-mortality curves currently used in Spectrum may need to be revised. Additionally, uncertainty in the sex-ratio and age-distribution of HIV prevalence needs to be included in analyses.

A key concern is how to reflect *temporally-changing* patterns of uncertainty in the data, e.g. due to changes in ANC surveillance patterns.

Variation in the assumed start time of the epidemic need not be considered when estimating prevalence of mature epidemics because it makes little difference when they are close to equilibrium.

Calibration to DHS or ANC data should take account of the bias in ANC data.

5. Estimation of plausibility bounds: concentrated epidemics

Estimation of HIV prevalence in concentrated epidemics uses Workbook. Often data are obtained using highly-biased sampling strategies such as convenience samples, and data on the lower-risk groups are often lacking. Estimates of sizes of risk groups are often highly uncertain. Commonly, country-specific data are lacking and so estimates from other countries that are thought to be similar have to be used.

For prevalence estimates in children, regional estimates combining data from several countries have been calculated.

It is intended to use a Monte Carlo approach to generate a range of plausible curves for estimation of uncertainty.

It is important that uncertainty ranges do not obscure perception of genuine trends – e.g. uncertainty in the numerical relationship between ANC prevalence and population prevalence may lead to an uncertainty range that obscures a genuine trend in ANC prevalence which is likely to be indicative of a genuine trend in population prevalence. There is a need to ensure that there is clear reporting of

trends (i.e. % change and uncertainty in this measure) as well as point-estimates of prevalence.

6. Estimation of plausibility bounds: the effect of model structure

It was noted that, in addition to uncertainty in parameter estimates, an important source of uncertainty in model-derived prevalence estimates is model structure, and sensitivity of prevalence estimates to this needs to be investigated by applying different models to common data-sets.

References

Badri M, Bekker LG, Orrell C, Pitt J, Cilliers F, Wood R. Initiating highly active antiretroviral therapy in sub-Saharan Africa: an assessment of the revised World Health Organization scaling-up guidelines. *Aids* 2004;**18**:1159-1168.

Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 2004;**364**:1865-1871.

Gilks CF. The clinical challenge of the HIV epidemic in the developing world. *Lancet* 1993;**342**:1037-1039.

Grassly NC, Morgan M, Walker N, Garnett G, Stanecki KA, Stover J, Brown T, Ghys PD. Uncertainty in estimates of HIV/AIDS: the estimation and application of plausibility bounds. *Sexually Transmitted Infections* 2004;**80**(suppl 1):i31-i38.

Gray RH, Kiwanuka N, Quinn TC, Sewankambo NK, Serwadda D, Mangen FW, Lutalo T, Nalugoda F, Kelly Robert, Meehan M, Chen, MZ, Li C, Wawer MJ. Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. *Aids* 2000;**14**:2371-2381.

Hughes MD, Stein DS, Gundacker HM, Valentine FT, Phair JP and Volberding PA. Within-subject variation in CD4 lymphocyte count in asymptomatic human immunodeficiency virus infection: implications for patient monitoring. *Journal of Infectious Diseases* 1994;**169**:28-36.

Lyles CM, Dorrucci M, Vlahov D, et al. Longitudinal human immunodeficiency virus type 1 load in the Italian seroconversion study: correlates and temporal trends of virus load. *Journal of Infectious Diseases* 1999;**180**:1018-1024.

Mekonnen Y, Geskus RB, Hendriks JC, et al. Low CD4 T Cell Counts before HIV-1 Seroconversion Do Not Affect Disease Progression in Ethiopian Factory Workers. *Journal of Infectious Diseases* 2005;**192**:739-748.

Mermin J, Lule J, Ekwaru JP et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet* 2004;**364**:1428-1434.

Nachman SA, Lindsey JC, Moye J, Stanley KE, Johnson GM, Krogstad PA, Wiznia AA. Growth of Human Immunodeficiency Virus-Infected Children Receiving Highly Active Antiretroviral Therapy. *Pediatric Infectious Disease Journal* 2005;**24**:352-357.

Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 2004;**364**:1236-46.

Stein DS, Korvick JA and Vermund SH. CD4+ lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease: a review. *Journal of Infectious Diseases* 1992;**165**:352-363.

Sterne JA, Hernán MA, Ledergerber B, Tilling K, Weber R, Sendi P, Rickenbach M, Robins JM, Egger M. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005;**366**:378-384.

UNAIDS Reference Group for Estimates, Modelling and Projections. Rates of mother-to-child transmission and the impact of different PMTCT regimens*. Report of a consultation, February-March 2005*.

Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *Aids* 2000;**14**:2361-2370.

Appendix I: Meeting Agenda

TUESDAY 13TH DECEMBER		
Introduction to meeting		
Time	*Speaker*	*Subject*
0900 (15)	Geoff Garnett	Introduction to meeting
BED & incidence estimation; Chair: Stephen Moses		
Time	*Speaker*	*Subject*
0915 (20)	Theresa Diaz	Progress toward use of BED assay for HIV surveillance
0935 (15)	Meade Morgan, Bharat Parekh & Robert Byers	Formulas for Using a Less-Sensitive Assay to Estimate HIV Incidence
0950 (15)	Matthew Price	Prevalent HIV and Seroconverter Panel Specimens from Africa Tested by the BED Incidence Assay
1005 (10)	Wolfgang Hladik	BED and Spectrum-based HIV Incidence Estimates in ANC Clients Addis Ababa, 1995 – 2002
1015 (10)	Andrea Kim	Implementing the BED HIV-1 enzyme immunoassay in HIV antenatal clinic surveillance, Cote d'Ivoire, 1998 – 2004
1025 (10)	Discussion	Brief discussion of whole group
1035 (25)	*Break*	
1100 (15)	Adrian Puren & Thomas Rehle	HIV prevalence and BED HIV incidence: Results from the second national HIV survey in South Africa 2005
1115 (15)	Andrea Kim	Applying the BED HIV-1 incidence enzyme immunoassay in the Kenya Demographic Health Survey, 2003
1130 (5)	Kumnuan Ungchusak	HIV Incidence Estimation in Thailand: Comparing BED Estimates with the Asian Epidemic Model
1135 (15)	Ron Gray	HIV incidence in pregnant, lactating and non-pregnant/non-lactating women
1150 (15)	Basia Zaba, Raphael Isingo & Milly Marston	HIV incidence and pregnancy in the Kisesa cohort study
1205 (15)	Discussion	Brief discussion of whole group
1220 (10)	*Break*	
1230 (30)	Group discussions (first part)	BED discussions (first part) **Group 1**. What should the uses of an ideal incidence test be? e.g. which groups, samples sizes, analyses **Group 2**. What research is required to allow for the use and interpretation of BED results? **Group 3**. What should be the current policy on BED use and interpretation? Can it be used for trends? How should the current policy be communicated? *10 minutes to introduce questions then 20 minutes of discussion*
1300 (60)	*Lunch*	

TUESDAY 13TH DECEMBER (CONTINUED)		
Time	*Speaker*	*Subject*
1400 (60)	Group discussions (second part)	BED discussions (second part) *30 minutes of group discussion then 3 minutes to report back (10 per group)*
1500 (25)	*Break*	
Circumcision; Chair: Meade Morgan		
Time	*Speaker*	*Subject*
1525 (15)	Bertran Auvert	The impact of male circumcision on the female-to-male transmission of HIV: Results of the intervention trial: ANRS 1265
1540 (15)	Ron Gray	Male Circumcision for HIV Prevention in Men and Women: Observational studies and Randomized trials in Rakai, Uganda
1555 (15)	Stephen Moses	A Randomized Controlled Trial of Male Circumcision to Reduce HIV Incidence in Kisumu, Kenya
1610 (15)	Ann Way	Male Circumcision: DHS Findings
1625 (15)	Stephen Moses & Nico Nagelkerke	Modelling the Effect of Male Circumcision on the HIV epidemic in Africa
1640 (15)	Bertran Auvert & Brian Williams	Impact of male circumcision on the HIV/AIDS pandemic in sub-Saharan Africa
1655 (15)	Cate Hankins	UNAIDS/WHO/SACEMA Consultation: Modelling the Impact of Male Circumcision on HIV Transmission
1710 (35)	Discussion	Recommendations for future modelling: data needs and modelling methods
1745	*Close*	
1930	*Dinner at St George Lycabettus hotel*	

WEDNESDAY 14TH DECEMBER (CONTINUED)		
ART in adults; Chair: Ties Boerma		
Time	*Speaker*	*Subject*
0900 (15)	John Stover	Estimating ART Needs in Spectrum
0915 (15)	Charlie Gilks	When should ART be started?
0930 (15)	Marcel Zwahlen	Natural history and mortality of untreated HIV infection in adults
0945 (15)	Eleanor Gouws	HIV infection, anti-retroviral therapy and CD4+ cell count distributions in African populations
1000 (15)	Francois Dabis	Evidence of effect of ART, modified survival in adults: a synthesis of all available studies including characteristics of patients as they go on treatment
1015 (25)	Discussion	Brief discussion of whole group
1040 (25)	*Break*	
HIV treatment and prevention in children; Chair: Ties Boerma		
Time	*Speaker*	*Subject*
1105 (30)	Lynne Mofenson	Effectiveness of PMTCT and Impact of Adult Therapy on MTCT
1135 (10)	Kirsty Little	Evidence on disease progression and survival in HIV infected children, in the absence of ARV and other supportive treatment
1145 (15)	Milly Marston & Basia Zaba	Child mortality: development of a functional representation for net mortality due to HIV
1200 (15)	Philippe Msellati	Cotrimoxazole prophylaxis Survival and HAART in developed countries
1215 (10)	John Stover	Estimating Child Treatment Needs in Spectrum
1225 (35)	Discussion	Discussion of whole group
1300 (60)	*Lunch*	

WEDNESDAY 14TH DECEMBER		
Group discussions on ART; Chairs: Geoff Garnett & Neff Walker		
Time	*Speaker*	*Subject*
1400 (120)	Group discussions	**Group 1**. ART in adults **Group 2**. ART in children
1600 (60)	Discussion	ART and estimation in EPP/Spectrum
1700 (30)	BED discussion	
1730	*Close*	

THURSDAY 15TH DECEMBER		
Estimates & projections, young people estimates; Chair: Peter Way		
Time	*Speaker*	*Subject*
0900 (15)	John Stover	HIV Prevalence by Age and Sex: Patterns from National Surveys
0915 (15)	Txema Calleja	ANC 15-24-years-old data availability and quality
0930 (15)	Karen Stanecki	Comparison of Spectrum outputs with standard pattern vs country specific DHS results on young people estimates
0945 (15)	Ron Gray	HIV prevalence in pregnant and non-pregnant women in Rakai and Uganda
1000 (15)	Simon Gregson	Levels & Trends in HIV Prevalence in Young People: Comparison of ANC & Community-Based Data in Manicaland, Zimbabwe
1015 (15)	Basia Zaba	ANC and community-based HIV prevalence in age group 15-24
1030 (25)	*Break*	
1055 (15)	Meade Morgan	Plausibility Bounds 2006 for Generalized Epidemics
1110 (15)	John Stover	Plausibility Bounds Around Spectrum-based Indicators
1125 (15)	Neff Walker & Eleanor Gouws	Estimating prevalence in low-level and concentrated epidemics
1140 (15)	*Break*	
1155 (65)	Discussion	Uncertainty estimation, and use of ANC surveillance data
1300 (60)	*Lunch*	
Discussions; Chair: Geoff Garnett		
1400 (10)	Karen Stanecki	HIV Estimates Projections 2005
1410 (50)	Discussion	Projection methods Group 1. Age and sex distributions Group 2. Uncertainty
1500 (25)	*Break*	
Discussions		
1525 (80)	Discussions	Continuation of discussions
1650 (10)	Geoff Garnett	Closing remarks
1700	*Close*	

Appendix II: List of Participants

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