

**UNAIDS/WHO Pre-Exposure Prophylaxis Modelling Meeting
29-30 March 2011
Hotel Royal Plaza
Montreux, Switzerland**

MEETING REPORT

INTRODUCTION

Mathematical modellers and public health professionals at the forefront of research on PrEP—including both CAPRISA 004 and iPrEx trial statisticians—were convened to a UNAIDS/WHO consultation in Montreux, 29-30 March 2011. The modelling teams were in a position to indicate to leading PrEP trialists what additional data would be useful to inform their models while the PrEP trialists were able to comment on the assumptions used by the modelling teams. Discussions about the potential contribution of modelling to decision making were of particular interest to the participants and meeting organisers.

SESSION 1: MODELLING IMPACTS AND COSTS FOR ORAL PrEP

Cost estimates for PrEP service delivery models

To help answer key questions such as “is PrEP cost-effective?”, “can we afford it?” and “will people use it?”, Andy Hastings introduced a cost-effectiveness model tailored to South Africa. To evaluate the price range for PrEP per person per year, this bottom-up costing model uses inputs derived from a value chain of service delivery elements such as antiretroviral drugs, HIV testing costs, human resources, and facility costs. Three delivery scenarios are accommodated—low, moderate, and high—with differing physician involvement (ranging from reduced to significant), clinic visits (1 to 4 per year), HIV testing (2 to 4 per year). Three methods are used to compute the ensuing costs based on a granular approach, the WHO CHOICE database, or activity costing/CEGAA (Centre for Economic Governance and AIDS in Africa). The three methods yield a similar cost, at around US\$150 per person-year on PrEP for the low scenario, rising to US\$180 and US\$250 for the moderate and high scenarios, respectively.

Population-level impact of PrEP in 3 epidemiological contexts in sub-Saharan Africa

Ide Cremin presented three population-level deterministic compartmental models for heterosexual transmission of HIV, analysing the impact of PrEP over the 2012-2022 period. To capture heterogeneity in sexual risk behaviour, populations are sub-divided into three sub-populations (low, medium, high), based on partnership formation rates. PrEP parameters include efficacy of PrEP per sex act, pill-taking behaviour (proportion of sex acts under “poor” or “good” adherence), coverage, and scale-up period. Life-long antiretroviral treatment, condom use, and male circumcision are included in the model.

- In Cotonou, urban Benin, prevalence among the general population was estimated to be 1.7% in 2006. However, prevalence among female sex workers is considerably higher at 30% in 2007. The model considers the risk of HIV transmission between 4 groups: sex workers, their regular clients, other men, and other women. Given an efficacy of 80% and a coverage of 10%, infections averted over 10 years range from 2% to 17% depending on the degree of prioritisation, highlighting the importance of prioritising PrEP to sex workers and

their clients in this concentrated epidemic setting. Under this model's 80% efficacy per sex act assumption, good adherence yields up to 3 times more infections averted than poor pill-taking behaviour.

- In Kisumu, Kenya, where HIV prevalence fell from 30% to 15% between 1999 and 2010, prioritisation to sub-populations at higher risk of HIV exposure amplifies the impact of PrEP. Under assumptions of 80% efficacy, 50% adherence, 20% of the adult population starting on PrEP for 5 years (mean duration), and 5 years to reach this coverage level, infections averted double from 9% to nearly 19% depending on degree of prioritisation. Assuming the cost of maintaining a person on PrEP ranges from US\$453 to US\$157 per year, estimated costs per infection averted range widely: from US\$150,000 with no prioritisation and high cost PrEP (US\$453), down to less than US\$10,000 with maximum prioritisation and low cost PrEP (US\$157).
- In KwaZulu Natal, South Africa, where HIV prevalence reached 22% in 2007 and is slowly decreasing, given the same assumptions regarding coverage and efficacy, the level of adherence has a strong influence on the overall impact. If PrEP is used in 70% of sex acts and population coverage is uniform at 30% (no prioritisation), around 20% of infections are averted over ten years. Prioritising for people at higher risk of HIV exposure leads to less substantial benefits than in Kisumu or, especially, Cotonou. In KwaZulu Natal, with a price for PrEP ranging between US\$150 to 250 per person per year, the cost per infection averted is reduced from US\$10,000-17,000 (with no prioritisation) to US\$6000-10,000 when prioritised for women at higher risk of HIV exposure.

Antiretroviral therapy or PrEP in serodiscordant partnerships

Using an individual-based model focused on serodiscordant couples, Tim Hallett explained that the objective is for the HIV-negative partner to be alive and HIV-free at age 50—an objective based on averting rather than delaying HIV transmission.

- Comparison A: the HIV-negative partner starts PrEP immediately until his or her HIV-positive partner is put on treatment at CD4<200 cells/ μ L *versus* the HIV-positive partner starts treatment at CD4<350 cells/ μ L with no PrEP for the HIV-negative partner.
- Comparison B: the HIV-negative partner is on PrEP until the HIV-positive partner starts treatment at CD4<350 cells/ μ L *versus* starting treatment at CD4<500 cells/ μ L with no PrEP for the HIV-negative partner.

The results show that PrEP can be more cost-effective than initiation of antiretroviral therapy at 350 cells/ μ L, if the cost of PrEP < 40% cost of HIV therapy and PrEP effectiveness > 60%. Two types of couples are considered in the model: low risk (high condom use and few external partners, typical of the Partners in Prevention clinical trial participants) and “more typical couples”, with an HIV transmission risk of 2% and 9% per year, respectively. PrEP is far more cost-effective in couples at higher risk of HIV infection. The difference is particularly strong in the “PrEP until treatment at CD4<350 cells/ μ L” *versus* treatment at CD4<500 cells/ μ L comparison, where a PrEP regimen costing around 50% of a treatment regimen would be more cost-effective than earlier treatment, even if PrEP is only 30% effective.

PrEP in South Africa: a window of opportunity

Carel Pretorius presented an age-structured model for South Africa in which the spread of HIV is governed by the rate at which women engage with new partners, a rate which decreases with age. Partner choice is modelled as a function of the age of the woman and of her potential partner, the HIV transmission risk per relationship is higher for susceptible women, and condom use decreases with age. The model assumes that a universal test-and-treat programme starts in 2014, has a 20% per year enrolment rate, and is fully scaled-up by 2019. Prevention effectiveness for antiretroviral therapy and PrEP are both set at 90% and annual drop-out rates for both programmes are 1.5%. Drug resistance and condom substitution are not considered in

the model. Costs for HIV treatment are set at US\$600 per year, against US\$150 for PrEP (US\$134 for medicines, US\$12 for counselling, and US\$4 for tests). Results show that if PrEP is introduced while treatment scale-up is underway, PrEP coverage must be high to achieve additional benefit. If prioritized for 15–35-year-old women and achieving 30%–60% coverage, PrEP would avert 10%–25% of infections in that group (5%–12% of all infections) in the period 2014–2025. Cost per infection averted is in the range of US\$12,500–20,000 but escalates drastically when antiretroviral therapy coverage reaches 3–3.5 times 2010 levels. This reveals the conditions under which the window of opportunity for PrEP will close.

Why targeting strategies may not work

Most HIV prevention models—especially if they include costing—show that prioritizing interventions to the individuals or groups most likely to benefit from them is necessary for success. As David Gerberry explained, this implies being able to describe, identify, and access sub-populations at higher risk and being able to quantify the excess risk attributable to them. Information on sexual behaviour is required for modelling purposes, but sexual behaviour surveys are notoriously unreliable. Defining sub-populations may be easy (e.g. women with more than 7 partners per year for whom <50% of sex acts are covered by condoms) but locating and accessing individuals with these characteristics may prove impossible. A more practical approach would be to use objective criteria such as “women aged 15–30”, although this will include people who do not require the intervention, e.g. because of being sexually inactive. Such issues may be addressed by asking screening questions such as “Have you had sex in the past 30 days?” but it is known that some people are prepared to lie in order to obtain a desirable medication. For all these reasons prioritising, however desirable, may not be feasible—or only at a substantial cost.

Resource allocation for HIV prevention

Globally, there are 2.6 million new HIV infections every year, while 65% of eligible HIV-positive people still do not receive treatment. Margaret Brandeau asked what the appropriate resource allocation should be between prevention and treatment, given that two new infections occur for each person entering treatment. This is the sort of resource allocation question that decision makers must answer. A practical tool would assist them in identifying solutions that will stand up to scientific and public scrutiny. The modelling community should be able and willing to deliver such a tool, while remaining aware of challenges such as epidemic diversity, nonlinear epidemic growth (most HIV prevention models are linear), intervention overlap, and economies/diseconomies of scale. Diseconomies of scale, or diminishing returns, are rarely included in models but may be important. For example, the first people recruited from a sub-population may be relatively easy to recruit, but recruitment becomes harder and more expensive as it progresses.

An interactive planning model

An interactive model to support country-specific programmes has been developed for male circumcision and is now needed for PrEP. The web-based system presented at the meeting by John Stover was developed so that decision makers could use it by themselves, but in practice a technical expert, usually in the Ministry of Health, is needed to help navigate the system. Modellers who are unsure whether they should simplify their models in order to appeal to the end user should be aware that even simple models cannot generally be used by policy makers without skilled assistance. The male circumcision interactive tool (Decision Makers Programme Planning Tool) is designed for 13 priority countries with high HIV prevalence and sub-optimal male circumcision prevalence. It is fitted with the most recent data on local demographics, epidemic dynamics, and facility costs. It permits exploration of diverse options for population prioritising (by age and risk), service delivery, and speed of scale-up, etc.—which it then

projects into the future. John presented an interactive programme planning model which incorporates PrEP into HIV prevention and treatment programmes that are being scaled up. A challenge is to incorporate the diverse roll-out scenarios that PrEP would likely entail.

DISCUSSION TO ROUND UP SESSION 1

Service delivery

Facility costs may be different for roll-out to men or to women, because pre-existing clinics and services for women are usable in certain countries and there are no equivalent services for men. The cost of HIV treatment (including antiretroviral therapy) should be considered as part of the cost of not preventing HIV transmission. However, the total costs of not treating a person with HIV are difficult to measure. One suggestion is to present the cost of PrEP as a relative cost, e.g. percentage of the cost of not preventing HIV infection, as more accessible way of presenting results to decision makers. Comparisons may also be made between PrEP and male circumcision. In a high HIV prevalence setting, male circumcision costs are estimated to be in the range of US\$150-900 per infection averted.

Assumptions and inputs for models

HIV infections linked to acute infection represent a significant minority of HIV infections (around 27% according to some sources). Condom use declines with age, but this is not always included in models. Many models start running in recent years, however the epidemic started long before it became visible; some models should be adjusted to account for that fact. Diseconomies of scale can be linked to the law of diminishing returns: most interventions reach the “easiest” people first, then reaching others becomes increasingly difficult. Specifically, moving interventions from urban into rural areas can imply large increases in costs. A drop-out rate should be modelled for people on PrEP: assuming no drop-out is unrealistic. Even under the drive for universal access, complete coverage for HIV treatment is not likely to ever be achieved, so it is surprising to see 100% treatment coverage in models.

PrEP modelling community

A systematic comparison of models could bring new ideas and insights into the PrEP modelling community. This would include not only models of PrEP, HIV treatment or male circumcision, but also models in other fields. Areas where recent scale-up has taken place would be most interesting. An idea would be to create a group of modellers, similar to the group meeting today, which would exchange views regularly on assumptions and other features of PrEP models. Costs per infection averted vary widely from one model to another, in the range of US\$6000-20,000. Costing for PrEP needs to be more carefully defined (e.g. financial and economic costs are not the same) and the span of results requires further debate in the modelling community.

Service delivery

For delivering PrEP, physicians could be replaced by nurses or other trained personnel. This would have a strong impact on costs, although training and supervision programmes would be needed. Legal constraints in countries such as Botswana, where the use of medical doctors to deliver antiretroviral therapy is compulsory, must be taken into account. Investment in motivational counselling and programme management would increase adherence, but at a significant cost. Service integration is often cited as a cost-saving approach, but PEPFAR recently cut its service delivery costs by doing the opposite, i.e. using specific delivery channels.

Sub-populations at higher risk

These sub-populations evolve over time, with people newly at risk while others may, for example, stop drug injecting or sex work. In models, the success rate of prioritisation (targeting)

needs to be taken into account, because aiming for 80% coverage of a specific sub-population may result in, say, 60% coverage. The specificity and sensitivity of the prioritisation needs to be modelled (type I and type II errors corresponding to people at higher risk not being included and people at lower risk being included, respectively). In generalised epidemic settings, many “higher risk” individuals are likely to already be HIV-positive. This proportion should be discounted in the models (e.g. if 1000 people are prioritised to receive PrEP in a high-prevalence setting, perhaps 200 of them will test HIV-positive at screening so only a maximum of 800 could be offered PrEP). Finally, prioritisation strategies may focus not only on certain categories of the population, but also on certain times or life events that may befall any person such as migration, loss of income, depression/alcohol, deteriorating relationships, and deepening relationships.

Male circumcision

UNAIDS and USAID are supporting costing studies for male circumcision in selected countries in East and Southern Africa. Although carried out for programme planning reasons, this is the kind of exercise that yields useful data for modellers. There are considerable differences between male circumcision service delivery (a single intervention with time-limited follow-up) and PrEP service delivery (more complex and ongoing). They can be modelled respectively as efficacy per act or efficacy over time. Modelling approaches and interactive tools are expected to be more complicated than for male circumcision. Interactions between PrEP and male circumcision also need to be addressed: an HIV-negative man living with an HIV-positive woman may be offered either intervention, or both.

Engaging decision makers

Modellers must spend more time engaging policy makers. For male circumcision, advocacy engaged at country level proved most successful. Decision makers wanted to know both the cost-effectiveness of male circumcision and its absolute cost (for budgetary reasons). They also wanted to see a service delivery model. This has yet to be developed for PrEP. Economic development issues are important and feature prominently in decision makers’ minds: most countries featuring in PrEP models urgently require sustainable economic growth and job creation. The scale-up of PrEP must coincide (and be seen to coincide) with economic development. Resource allocation models often assume that the envelope budget for health is fixed, but political pressure can be applied to move it upwards or downwards. Politicians are likely to compare the potential impact of interventions against HIV with interventions against other diseases or conditions. For advocacy purposes, it may be useful to develop worst-case scenarios for decision makers, i.e. disinvestment in HIV prevention.

SESSION 2: MODELLING IMPACTS FOR TOPICAL PrEP

The CAPRISA 004 clinical trial: Implications for modellers

CAPRISA 004 investigated the use of a 1% tenofovir vaginal gel versus placebo in a rural and an urban site in KwaZulu Natal, South Africa. On behalf of the CAPRISA 004 trial group, Anneke Grobler explained that the women recruited for this phase IIb double-blind randomised clinical trial were not at any higher risk of HIV acquisition than other women living in the same areas. More recruitment occurred at the rural site (Vulindlela, n=611) than at the urban site (Durban, n=278). Among the 2160 women screened for inclusion in the trial, 536 (25%) were found to be HIV-positive, and 132 (6%) were not sexually active. Altogether, 889 women were randomised with the retention rate approximately 95% in both intervention and control arms. In analyzing the results for HIV transmission (38 infections in the tenofovir arm *versus* 60 in the placebo arm), the 39% point estimate for efficacy (p=0.017) can be differentiated according to low adherers (<50% gel adherence, 28% efficacy), intermediate adherers (50-80% gel

adherence, 38% efficacy), and high adherers (80% gel adherence, 54% efficacy). The intervention was also effective against HSV-2 transmission with 29 infections in the tenofovir arm and 58 in the control arm ($p=0.003$) and a point estimate of 51% protection against HSV-2 (CI: 22-70%). Tenofovir cervicovaginal fluid concentrations correlate with HSV-2 infection status. CAPRISA 004 provides proof of concept that tenofovir can prevent both HIV and HSV-2 infection. No tenofovir resistance was observed; there were no substantive safety concerns; and there was no sign of risk compensation. The gel was well accepted by the women in the study, some of whom considered it to be empowering. However, the applicator for the gel is too expensive for effective roll-out, with work underway to develop a cheaper applicator, and confirmatory trial evidence is needed for licensure.

Modelling tenofovir gel in South Africa

Using a modified SI model (S: susceptible; I: infected) derived from previous work on male circumcision, Brian Williams showed that large-scale implementation of tenofovir gel could have a major impact on the HIV epidemic in South Africa. With low or high coverage, respectively, between 0.5 and 1 million new HIV cases could be averted every year over 10 years but the corresponding dip in mortality would take far longer to appear. Using a simple costing function, the cost per HIV infection averted is evaluated at US\$1500. This is to be compared to the cost per HIV infection *not* averted which is approximately US\$8400 (cost of keeping a person on antiretroviral therapy for 23 years, reference Berguet *et al. Sexually Transmitted Infections*, 2010). In conclusion, full-scale roll-out of tenofovir gel could save up to 100,000 women's lives each year in South Africa alone. This intervention is cost effective in settings such as South Africa where the incidence of HIV infection is high. Given these modelling results, as well as the data from CAPRISA 004, engagement with regulators and decision makers should continue pending additional data for licensure from other clinical trials.

Predicting the impact of vaginal microbicides in a generalised HIV epidemic

To evaluate the potential long-term effect of widespread introduction of a microbicide gel on HIV incidence in a generalised heterosexual HIV epidemic, Valentina Cambiano modelled the impact of gel use by sexually active women aged 15-65, undiagnosed with HIV, who constitute around 50% of women in the modelled population. Gel adherence and effectiveness are assumed to be similar to the data from the CAPRISA 004 trial. Further assumptions are a 50% decrease in unprotected long-term sexual partnerships after being diagnosed with HIV, as well as a 15% decrease in the probability of having short-term male sexual partners with whom they have unprotected sex. Three scenarios were compared: no intervention; medical prescription and an HIV test required for topical PrEP; and topical PrEP available over the counter (with no HIV test). The compulsory HIV test prior to PrEP leads to more HIV cases being diagnosed in the population (with a consequent reduction in risk behaviour) and to a higher number of HIV-positive people being placed on antiretroviral treatment. In order to study potential impact, optimistic scenarios were considered in which around 10% of eligible women may be expected to use topical PrEP if the prescription and HIV test are compulsory, rising to around 40% if access is over-the-counter. The corresponding reduction in HIV incidence is predicted to be around 0.5 per 100 person-years for both service delivery mechanisms. For women, results are better if PrEP is distributed over the counter. However, the assumption that HIV diagnosis leads to a reduction in unprotected sex results in the model predicting a more rapid HIV incidence reduction in men if HIV testing is compulsory prior to women starting on PrEP. In conclusion, tenofovir gel could make a major, sustained impact on HIV incidence in men as well as in women, if widely used and adhered to, and if not used as a substitute for condoms.

Insights from microbicide modelling

Charlotte Watts presented a population level deterministic compartmental model of heterosexual HIV transmission, including stages of HIV progression, co-infection with other sexually transmitted diseases, and access to the relevant medical services. Microbicides or topical PrEP are likely to have more impact in settings where condom use is low (<40% of sexual acts) but could increase HIV incidence in settings where condom use is high if condom substitution occurs. In generalized epidemics, high numbers of infections can be averted without a strong impact on incidence, whereas the opposite is true in concentrated epidemics. A historical perspective shows that in low- to middle-income countries the implementation of health interventions is in the range of 12-15 years between launch and peak uptake—and that coverage rarely exceeds 50-60%. So models assuming that a high coverage can be reached within 5-10 years may be overly optimistic. A model of tenofovir introduction in Gauteng, South Africa, investigates a gradual increase to 60% coverage over a ten-year period, followed by a five-year saturation period. The costs of introducing the intervention are: 48% for the product, 42% for HIV testing and counselling, 9% for the facility-based delivery, and 1% for media support (no staff training costs are considered in this model). Costs for antiretroviral therapy are US\$1000 per year. Preliminary results show that programme costs can be significantly offset by treatment costs averted, but that topical PrEP adherence is a key factor for cost effectiveness. Net cost savings per HIV infection averted are US\$276 (US\$16 per DALY saved) if adherence is 50%, moving up to US\$1444 (US\$86 per DALY saved) if adherence is 72%. Next steps would be an increased policy focus on how to maximise uptake and coverage, while reducing costs.

Rectal microbicides for heterosexual populations

Only 2% of the US\$244 million invested in research and development on microbicides in 2008 was devoted to rectal microbicides, although a rectal microbicide is needed not only for men who have sex with men but also for many heterosexuals. Some surveys report that 1-6% of heterosexuals practised anal sex during their most recent sex act. Detailed interviews in South Africa (Cape Town township and STI clinic) indicate that up to 10-15% of heterosexuals engage regularly in anal sex (amounting to 40-50% of their sex acts). In face-to-face interviews in Cotonou, Benin, 3.5% of participants declared practicing anal intercourse; this figure increased to 17.5% in an anonymous survey. The risk of HIV transmission is 4-20 times higher in unprotected receptive anal intercourse than in unprotected vaginal intercourse. Condoms are less used for anal sex than for vaginal sex, and anal sex is more often unplanned. Marie-Claude Boily presented a deterministic model assuming 5-10% anal sex acts among heterosexual sex acts, a relative risk of HIV infection per act of 4 to 20 (compared to vaginal sex) for the female partner and of 2 for the male partner, with no condom substitution. The microbicide intervention is modelled with 100% coverage, 75% adherence, 50% efficacy, and HIV risk reduction only for the female partner. When anal sex is not included in the model, a vaginal microbicide may avert 35% of female infections during the first year, going up to 41% after 25 years. If 5% of sex acts are modelled as anal sex, after 25 years only 17% to 39% of female HIV infections will be averted (using a relative risk for receptive anal sex of 4 and 10, respectively). The model predicts that a rectal microbicide would only be more useful than a vaginal microbicide if a high proportion (>20%) of heterosexual sex acts are anal. The use of dual indication microbicides (both vaginal and rectal) would be more effective in preventing HIV than either single indication in heterosexual populations who practice unprotected anal intercourse. It is important to include anal sex in heterosexual models, although not enough is known about the possible migration of tenofovir between the vagina and rectum.

DISCUSSION TO ROUND UP SESSION 2

Vaginal and rectal microbicides

Marketing one product for both vaginal and rectal uses would be an advantage. Reformulation of the 1% tenofovir product for rectal use may be necessary because the current formulation is hyperosmolar and liable to induce diarrhoea, although an encouraging safety study on rectal use was presented at the CROI 2010 meeting. The anal indication is expected to be submitted for registration soon.

Model complexity and metrics

In the debate between the advantages of complex versus simple models to convince decision makers, it is clear that both levels are needed. To make the results easier to understand inside and outside the modelling community, there is a need for similar metrics such as dollars per infection averted, DALYs or QALYs. It would be useful to ask policy makers what would be most useful for them. Once a common metric is established, it would become possible to set up a validation process for the tools produced by the various modelling groups. If it can be shown that different approaches yield similar results then this will increase believability and impact.

Inputs and outputs

As a group, PrEP modellers should make their voice heard about the data (inputs) that are required for their models; for example there is a lack of behavioural studies that would inform assumptions. There also is a need to make assumptions clearer and more explicit. Among the outputs of the models, decision makers are likely to be interested in are costs saved, investment generated, jobs created, and other economic variables.

Service delivery

Topical PrEP could be distributed over the counter and/or linked to on-site HIV testing in venues such as pharmacies or family planning clinics. A lot of work will be required on product positioning and demand creation for these topical microbicides. A comprehensive business model including PEPFAR and other main players is yet to be developed. As a field, it is felt that microbicides are lagging behind oral PrEP. It takes time for innovations to be applied in populations, for example, measles coverage of 20% in 1980-85 did not expand to 60% coverage until 1995-2000. Experience shows that voluntary processes rarely move beyond a 60-80% uptake.

SESSION 3: MODELLING IMPACTS IN MEN WHO HAVE SEX WITH MEN

The iPrEx trial: implications for modellers

The iPrEx study included 2499 men who have sex with men (median age 27 years) on 4 continents. Results published in the *New England Journal of Medicine* were from a May 2010 cut-off. In Montreux, David Glidden presented unpublished data through to November 2010. The number of HIV tests performed rose from 40,000 to 50,000 during that time. While 100 seroconversions were recorded in May, the number reached 131 in November: 48 in the active arm, 83 in the placebo arm. Effectiveness remained constant at around 42% (95% CI 18-60%), $p=0.002$. In a nested case-control study, drug was detected in 9% of seroconverters and 51% of matched controls in the active arm who did not acquire HIV infection. There was no evidence of risk compensation either by self-report of sexual practices or as evidence by declining seroincidence overall during the trial. Unprotected receptive anal intercourse declined from 60% to 30% during the trial, across groups, most of the decline taking place during the first 12 weeks after recruitment. Many trials show safer behaviour patterns than in the general population, due to the counselling activities rolled out to all participants. There was no difference in behaviour by

perceived drug assignment. The iPrEx trial identified over 400 HIV-positive people, of whom 130 were at an early stage of HIV infection and therefore likely to be highly contagious. The number needed to treat to avert one seroconversion (over 1 year) in the iPrEx trial is 60. This could be reduced to 35 by prioritising PrEP for men who engage in unprotected receptive anal intercourse. However, sexual behaviour cannot be considered as a static trait.

Analysis and modelling based on iPrEx trial data

Self-reported adherence in the iPrEx trial was 94%, while biochemical tests showed it to be around 50%. There was an enormous difference between trial participants in the USA (97% verified adherence) and those in the other countries participating in the trial: Ecuador, Peru, Brazil, South Africa, Thailand (50% average adherence over these countries). A possible explanation is that US participants are more accustomed to the clinical trial culture than participants from other countries. Drug efficacy was 92% in those who actually took the drug, corresponding to an odds ratio of 12.9 ($p < 0.001$). Two separate groups are observed in the iPrEx trial: one that takes the drug regularly, with a 92% protective effect, and another that does not take the drug and therefore gets zero protection. Models should be adapted accordingly: instead of one group with 42-43% protection, at least two groups should be modelled: adherers and non-adherers. The rollover trial, termed iPrEx-OLE (Open Label Extension) will enable all trial participants to access PrEP and will supply data on adherence in the absence of placebo. Three cases of emtricitabine resistance (and no cases of tenofovir resistance) were found, one in the placebo group and two among people who were antibody negative at enrolment but were subsequently found to have been acutely infected (enrolment specimen PCR-positive). As soon as seroconversion was detected, these two participants were taken off PrEP. Their resistant strain became undetectable within 15-30 weeks with progressive reversion to wild-type). It may be useful to express this result in terms of a cases prevented-to-resistance ratio.

Oral PrEP for men who have sex with men

In Asia and Australia around 82% of HIV-positive people are men who have sex with men. Although no extrapolation of iPrEx results is needed before rolling out oral PrEP for these populations, it is important to involve stakeholders and conduct needed social research and modelling. David Wilson presented an individual-based model of 60,000 men who have sex with men, aged 15-85 years, with sexual behaviours modelled on variables observed in New South Wales, Australia. Around 50% of the men have a regular partner, 17% engage in group sex, and 7% have >50 partners over a 6-month period. Only around 30% of HIV-positive men who have sex with men “always disclose” and a further 60% “sometimes disclose” their serostatus to sexual partners. Insertive/receptive behaviour varies according to the serostatus of the sexual partners, with men favouring the insertive role if the partner is known to be HIV-positive. Prioritising PrEP only to men who have more than 50 partners would not be efficacious because this is a relatively small group. The most efficacious approach would be to prioritise PrEP to regular serodiscordant couples. Because of so-called “disco-dosing” of PrEP, the frontier between PrEP and PEP is becoming increasingly blurred. An on-line survey and focus groups were used to evaluate the acceptability of PrEP/PEP among men who have sex with men. Around 75% of HIV-negative men reporting unprotected anal intercourse said it was unlikely or very unlikely that they would take a daily pill to avert HIV infection. This figure fell to around 58% for taking PEP every time that unprotected anal sex with a casual partner is anticipated. If “disco-dosing” is efficacious, it would be a highly cost-effective strategy, but no data are available to support such a dosing regimen.

DISCUSSION TO ROUND UP SESSION 3

Using PrEP to encourage HIV testing

An advantage of PrEP is that it may motivate HIV testing among those hoping to be HIV-negative. Clinics specialising in sexually transmitted infections would be good places for recruiting people for such HIV testing.

“Disco dosing”

The scientific community needs to find out if "disco dosing" will work for PrEP. Whether disco-dosing is every week-end, or more often, or less often, is likely to make a difference because tenofovir has a half-life of 21 days. Pharmacokinetic/pharmacodynamic (PK/PD) studies to determine how long it takes for tenofovir (and emtricitabine) to reach a satisfactory level in the relevant tissues are key. Data from the MTN003 trial seems to indicate that a single dose is not sufficient to reach adequate tissue levels to prevent rectal acquisition.

The price for PrEP

The price of PrEP to users needs to be discussed, because very different figures are circulating among different modelling groups. Some participants believe that 40 US cents per day is realistic for individuals in high-income countries but even this level would require subsidisation at current prices.

SESSION 4: MODELLING RESISTANCE

Review of evidence on drug resistance

Drug resistance is a critical issue for the use of PrEP. David van de Vijver presented a literature review on the risk of resistance following implementation of PrEP, for tenofovir alone or in combination with emtricitabine. Few studies have addressed this issue. Studies in HIV-infected humans found that short-term use of PrEP drugs is not associated with drug resistance. Similarly, studies in macaques using simian immunodeficiency virus (SIV) found that resistance emerged in only a few monkeys continued on tenofovir/emtricitabine after being infected by SIV. However, results from studies in macaques may not be easily extrapolated to humans because SIV infection has an attenuated course and dosages given to macaques exceed dosages used in humans. Mathematical modelling predicts that the benefits of PrEP outweigh the risks associated with drug resistance. Because tenofovir and emtricitabine are used in first-line treatment regimens, detailed surveillance of drug resistance is required. In particular, patients who became infected while on PrEP must be carefully monitored. In conclusion, the benefits of PrEP outweigh the risks associated with drug resistance.

Modelling resistance transmission with oral PrEP

A model to evaluate the potential impact of use of daily oral PrEP (tenofovir and emtricitabine) in serodiscordant long-term heterosexual couples was presented by Andrew Philipps. The probability of having an infected partner (or several) in a 3 month period is modelled, together with the transmission rate per unprotected partner over this period, based on viral load, sex of the partner, and whether a sexually transmitted infection is present. The probability of resistance transmission (and survival of the mutant) when the source partner carries a resistance mutation is modelled in a mutation-specific way. For example, virus with M184V has a 0.2 chance of transmission and survival, given that it was present in the source partner, while K65R has a 0.7 chance. Resistant virus is assumed to be as transmissible as a non-resistant virus, for a given viral load, and it is assumed that those resistance mutations that survive transmission to the new host will persist indefinitely. Under these assumptions, overall incidence of infection with resistant virus is predicted to be very low, however, PrEP acquired resistance, particularly

M184V, is predicted to occur at appreciable levels in people who become infected despite being on PrEP. The extent of this will depend on the frequency of testing in people on PrEP. If the assumption that M184V is infrequently transmitted is correct, the impact of oral PrEP use on transmitted resistance may be small. If PrEP use leads to more HIV testing and counselling and if HIV diagnosis leads to reductions in sexual risk, then introduction of PrEP could stimulate reductions in incidence through this mechanism, as well as through direct drug effects.

Comparing and contrasting resistance implications for oral and topical PrEP

The number of drug-resistant cases appearing in a clinical trial can be modelled as a function of the frequency of testing. A vaginal microbicide model (Wilson et al. PNAS 2008) has suggested that vaginal microbicides may benefit men more than women. Bradley Wagner explained that, although microbicides will be used by women, more infections in men than in women could be prevented if there is a high probability that antiretroviral drugs are systemically absorbed, microbicides are less than 50% effective, and/or adherence is less than 60%. Men will benefit more than women in terms of infections prevented per resistant case, but this advantage decreases as the relative fitness of drug-resistant strains increases. The model assumes that drugs are taken daily, with an HIV test every 3 months, and that the virus reverts to wild type if the HIV-positive subject stops PrEP. Systemic absorption is assumed for both topical and oral PrEP. In another model focussing on men who have sex with men in the San Francisco area (Supervie et al. PNAS 2010), nonlinear response hypersurfaces are used to predict that PrEP could reduce HIV transmission while increasing the proportion of new infections caused by resistant strains. If risk behaviour increases, PrEP could significantly increase transmitted resistance. However, if risk behaviour remains stable, PrEP interventions are likely to decrease transmitted resistance.

Predicting the impact of antiretroviral treatment and PrEP with overlapping regimens on HIV transmission and drug resistance in South Africa

Tenofovir and emtricitabine are used for first-line antiretroviral therapy in South Africa as well as being considered for PrEP, so their joint effects on resistance should be considered. Ume Abbas presented a model using coupled non-linear differential equations, where antiretroviral therapy coverage progresses to 80% in 2012, while PrEP moves to 50% coverage starting in 2012 and taking 2-3 years (with 50-80% adherence and 50-70% efficacy). If both interventions are used together, cumulative HIV infections prevented could reach 28% by 2022. Antiretroviral therapy scale-up combined with PrEP is likely to have a bigger HIV prevention impact than either strategy alone, so either/or arguments should be avoided. The model shows that the prevalence of drug resistance in 2022 could be as high as 9.2%. Treatment is predicted to contribute more than PrEP to the prevalence of drug resistance, although inadvertent PrEP use by HIV-positive people may increase resistance (regular HIV testing is essential). One solution for reducing resistance is to improve the effectiveness of both interventions: if no viruses are replicating, no resistance can emerge. Furthermore, it is necessary to develop non-overlapping antiretroviral drugs for treatment and for preventive indications.

DISCUSSION TO ROUND UP SESSION 4

Model assumptions

Modelling PrEP alone is akin to assuming that no HIV treatment is present, with ramifications for what models estimate about resistance. Given Universal Access commitments made by countries, models should include treatment from its year of introduction and its scale-up rates. When modelling adherence and efficacy, it is important to realise that the 42-44% efficacy of oral PrEP observed in the iPrEx trial already includes a 50% adherence rate. Those adhering to PrEP and those not adhering to PrEP tend to be distinct groups. Adherence patterns are likely

to have an effect on drug resistance. A key assumption is that 80% of people experiencing treatment failure while on PrEP have resistant strains of HIV.

Resistance modelling

In the scientific literature, there are many studies on treatment failure while drug resistance has attracted limited attention. Resistance is likely to increase as more people are placed on antiretroviral therapy, with very little likely to be due to PrEP. Moving tenofovir in or out of first line treatment changes both assumptions and results concerning resistant strains arising under PrEP. Condom use may diminish or even increase while people are on PrEP, leading to an over- or under-estimation of the direct effects of PrEP. An increase in the frequency of testing should decrease the likelihood of resistance, the key driver of resistance being the time on PrEP with HIV.

Epidemic-level considerations

In Southern Africa where there are many serodiscordant couples, there are proportionally fewer acute infections than in concentrated epidemics. It is necessary to expand HIV testing but in resource-constrained settings with hyperendemic epidemics poorly performing tests (including those sold illegally) may lead to a loss of accuracy. The frequency of testing may also diminish coverage. Second-line drugs are more expensive than first-line drugs, so a shift would have considerable financial implications. Many epidemic-level considerations affect cost-effectiveness.

SESSION 5: COMBINATION PREVENTION MODELLING (PANEL DISCUSSION)

Behaviour change and impact of PrEP

For a country such as Peru, where it seems reasonable to assume 80% antiretroviral treatment coverage by 2015, then PrEP can be added to the model to see its effect on costs. Geoff Garnett presented such a 10-year PrEP programme for Lima, under the assumption that high levels of condom use (the case at present) would lead to consistent use of PrEP. Some people might even combine condoms and PrEP, which would further reduce risk of HIV transmission. Despite synergies for interventions, such as rolling out different programmes in the same clinics, it is possible that PrEP will turn out to be too expensive.

HIV vaccine modelling consensus group

After a meeting with the Ministry of Health of Thailand in March 2010, a vaccine modelling consensus group was formed under the leadership of CDC and UNAIDS. Ky Andersson and John Stover pointed out that 5 of the 6 modelling teams in that group were represented in the Montreux meeting. The group was able to reach an agreement on a standardized reference case and outcome measures for all the articles in a special section issue of *Vaccine* that is to be published for the AIDS Vaccine conference in September 2011. The models all assume a 2020 introduction for the vaccine, reaching maximum coverage in 2025. The standardized reference case used includes vaccine efficacy, rate of exponential decay, population coverage, timing of the vaccination campaign, as well as a common outcome measure (percentage of infections averted), and time horizon for measurement of impact (10 years). Modelling teams included other analyses beyond the reference case in their analyses. The Futures Institute examined a 2020 introduction for an RV144-like vaccine in South Africa, reaching target coverage in 2025. Maintaining 20-80% coverage until 2030 results in 1.0-3.9 million infections averted if current prevention programme activity remains constant and 0.3-1.0 million infections averted if other prevention programme activities are scaled up to Universal Access targets by 2015.

Cost-effectiveness of a partially effective HIV vaccine (RV144)

In line with the reference case of the HIV vaccine modelling consensus group, Elisa Long presented a cost-effectiveness analysis for the USA, using an exponentially declining vaccine efficacy. One-time, 3-year booster, 5-year booster and hybrid delivery schemes were considered at a price of US\$250-500 per person, reaching 60% coverage in 10 years. Cost-effectiveness, expressed as US\$/QALY, varies considerably from US\$21,000 (hybrid regimen, low price) to US\$155,000 (5-year booster, high price). A one-time vaccination is cost-effective for a vaccine with modest efficacy. Augmenting this with a booster every 3 years for key populations would be more economically efficient, if feasible.

DISCUSSION TO ROUND UP SESSION 5

Back to basics

The only real question is “how to stop the epidemic?” There is good reason to believe that PrEP is 90% effective when taken properly, so it is clearly a prevention strategy that can be used at least by men who have sex with men. As with all partially protective prevention modalities in the combination prevention toolbox, people should be encouraged to combine it with other strategies for better protection. In particular, PrEP must not displace other strategies or interventions in the way that the Thai treatment campaign may have crowded out consistent condom use.

Relations with other groups

Information must circulate more effectively between modellers and other scientists, especially between the medical/modelling community and groups working on cost-effectiveness. Modellers bring together scientific data found in clinical trials and other studies, to create models that are relevant to decision-making. There are questions around the type and quality of data that go into the models, and questions on where and how the models should be presented to decision makers. To effectively engage decision makers, it is important to learn to speak their language. It has been said that US\$100,000 per QALY is considered a threshold for some decision makers but this will vary by economic context.

Looking at vaccine modelling

Both the HIV vaccine modelling field and the male circumcision modelling field show that it is possible to bring modellers together on a common platform. It is worth investigating whether consensus could be reached in PrEP modelling for certain assumptions and outcome measures. If the results are convergent, despite the heterogeneity of the modelling approaches, this would inform policy making and programme planning. The idea of a journal supplement to be worked on together, based on a standardized reference case shared by all groups, should be discussed further.

CONCLUSION: KEY POINTS FROM THE MEETING

General issues:

- What are the limitations of current models? Need both simple and complex models – how to link them – what does the ideal resource allocation tool look like? Linking to broader health outcomes.
- How to overcome difficulties in simulating the dynamics of a complex and evolving epidemic from isolated surveys and clinical trials
- If different models/approaches yield similar results, this increases believability of the conclusions.

Data needs

- As a group, modellers need to define what new data are needed and determine potential sources. Among the data needs for modellers are:
 - functional relationships between consistency of use and susceptibility
 - within-person variability in pill-taking behaviour over time
 - oral and topical PK/PD data
 - potential delivery scenarios (task shifting, task sharing, method and frequency of monitoring HIV breakthrough and resistance, drug and testing costs, delivery venues, etc.)
 - life course estimations of patterns of use
 - estimates of risk compensation, including scenarios in both directions, type of risk compensation, break even points for crossing cost-effectiveness lines.

Questions

- Both for communicating between modelling groups and for communicating with the outside, what terminology and metrics can be agreed on (e.g. DALYs, QALYs, infections averted, or infections postponed)?
- Practical country specific roll-out models for PrEP would need what modelling input for policy decision, design, evaluation? Which are the potential ‘innovator’ and ‘early adopter’ countries?
- How would service delivery models vary by context?
- Positive impacts of PrEP on treatment uptake: what are the synergies for topical and oral PrEP for individuals, within dyads, within sub-populations?
- What are the long term economic impacts of PrEP use initiated in the window of opportunity before wide treatment scale-up?
- What is the impact of topical PrEP on stage-specific risk of HIV infection and onward vertical transmission (conception, pregnancy, delivery, lactation)
- What are the prospects for PrEP as a packaged intervention delivered in various forms (topical, oral, patch, injection)?

Considerations

- Link modellers with experts in implementation science/programme science, both at the design stage and for understanding results
- Increase modellers understanding of policy maker concerns and capacity to present modelling results in the context of economic arguments, e.g. productivity, youth employment, security of communities, etc., by facilitating discussions with health economists, and experts in public policy
- Link modelling to health systems strengthening and to a unified health model addressing issues of resource allocation and choice of interventions for scale-up
- Focus on ‘innovator’ or ‘early adopter’ countries with demonstration projects

Knowledge translation

- Policymakers require country-specific information on the potential impact and cost of each intervention on the epidemic, the number of cases averted, and costs
- What metrics communicate best with policy makers? – cases averted, cost per infection averted, life years lived, DALYs, QALYs gained, number needed to treat, cases postponed, ratio of infections averted to resistance created, etc.
- Politicians need to be able to explain to others why they have chosen to do certain things
- Increase modellers' knowledge of the language of policymakers, including about productivity, employment (especially of youth), security of the State, of communities, of citizens

OPEN QUESTIONS

- What are the next steps to proceed to determine whether a degree of consensus can be reached within this PrEP modelling group in order to inform a complex but user-friendly decision makers' programme planning tool?
- How to support further the topical PrEP modelling groups, both to model and to collect data, e.g. PK/PD data to look at rectal concentrations of vaginally applied product?
- How will the PrEP Modelling Group engage with the Modelling Consortium that is being convened by Imperial College?

LIST OF PARTICIPANTS

Abbas Ume	Cleveland Clinic Foundation	ABBASU@ccf.org
Alistar Sabina	Stanford University	ssabina@stanford.edu
Andersson Ky	Futures Institute	kAndersson@futuresinstitute.org
Beke-Wilson Sylvia	UNAIDS	bekewilsons@unaids.org
Boily Marie-Claude	Imperial College	marieclaud.boily@gmail.com
Brandeau Margaret	UNAIDS Consultant	brandeau@stanford.edu
Cambiano Valentina	University College London	v.cambiano@ucl.ac.uk
Christie Derek	UNAIDS	christied@unaids.org
Cremin Ide	Imperial College	ide.cremin05@imperial.ac.uk
Farley Tim	WHO	farleyt@who.int
Gerberry David	UCLA	dgerberry@mednet.ucla.edu
Glidden Dave	Protocol Statistician iPrEx trial	dave@biostat.ucsf.edu
Grant Robert	IPREX PI	rgrant@gladstone.ucsf.edu
Grobler Anneke	CAPRISA, UKZN	grobler@ukzn.ac.za
Hallett Timothy	Imperial College	tbhallett@gmail.com
Hankins Catherine	UNAIDS	hankinsc@unaids.org
Hastings Andrew	Gates Foundation	Andrew.Hastings@gatesfoundation.org
Johnson Leigh	University of Cape Town	Leigh.Johnson@uct.ac.za
Long Elisa	Yale School of Management	elisa.long@yale.edu
Njeuhmeli Emmanuel	USAID	enjeuhmeli@usaid.gov
O'Reilly Kevin	WHO	oreillyk@who.int
Smith Dawn	CDC	dks0@cdc.gov
Stover John	Futures Institute	JStover@FuturesInstitute.org
Van de Vijver David	Erasmus Medical Center	d.vandevijver@erasmusmc.nl
Wagner Brad	UCLA	bwagner@mednet.ucla.edu
Watts Charlotte	London School of Hygiene and Tropical Medicine	Charlotte.Watts@lshtm.ac.uk
Williams Brian	Consultant	williamsbg@me.com
Wilson David	Univ. New South Wales	dwilson@nchecr.unsw.edu.au

**Pre-Exposure Prophylaxis Modelling Meeting
29-30 March 2011
Hotel Royal Plaza
Montreux, Switzerland
AGENDA**

DAY 1 – TUESDAY 29 MARCH

09:00 – 09:15 **Welcome and Meeting Objectives and Conduct: Catherine Hankins**

09:15 – 09:30 **Participant Introductions**

SESSION 1: MODELLING IMPACTS AND COSTS FOR ORAL PrEP

Session Chairperson: Kevin O'Reilly

09:30 – 11:00 Andy Hastings: Cost estimates for PrEP delivery (service delivery model and methodology)

- Ide Cremin: Population-level impact of PrEP in 3 different epidemiological contexts in sub-Saharan Africa
- Tim Hallett: Modelling PrEP in discordant couples
- Carel Pretorius: Window of opportunity for PrEP in South Africa

Questions and discussion: 30 minutes

11:00 – 11:30 **Refreshment break**

1130-1245 David Gerberry: Why targeting strategies may not work

Margaret Brandeau: Resource allocation for HIV prevention

John Stover: Interactive planning model

Questions and discussion: 30 minutes

12:45 – 13:45 **Lunch break (buffet)**

SESSION 2: MODELLING IMPACTS FOR TOPICAL PrEP

Session Chairperson: Catherine Hankins

13:45 – 15:00 Anneke Grobler: CAPRISA 004 for modellers

- Discussion/questions about tenofovir gel data: 10 minutes
- Brian Williams: Modelling tenofovir gel in South Africa
- Valentina Cambiano: Predicted impact of vaginal microbicide introduction in a generalised heterosexual epidemic
- Discussion: 20 minutes

15.00 to 15.30 Refreshment break

1540 to 1630

Charlotte Watts: Modelling topical PrEP introduction, insights from microbicide modelling

- Marie-Claude Boily: What is the role of rectal microbicides to prevent HIV in heterosexual populations?
- Questions and discussion 20 minutes

1630 to 1730

Brian Williams: Similarities and differences in modelling oral versus topical PrEP

- General discussion

DAY 2

0900 to 0930 Summary of Day 1 and discussion

Derek Christie

Session 3: MODELLING IMPACTS IN MEN WHO HAVE SEX WITH MEN

Session Chairperson: John Stover

0930 to 1045

David Glidden: iPrEX for Modellers

- Questions and discussion about iPrEX data: 10 minutes
- Bob Grant: plans for analyses and modelling using iPrEX trial data
- David Wilson (Australia): oral PrEP for men who have sex with men?
- Questions and discussion: 20 minutes

1045 to 1115: Refreshment break

Session 4: MODELLING RESISTANCE

Session Chairperson: Tim Farley

1115 to 1245

David van de Vijver: Review of the risk of HIV drug resistance following implementation of pre-exposure prophylaxis

- Andrew Philipps: Modelling resistance transmission with oral PrEP
- Bradley Wagner: Comparing and contrasting resistance implications for oral and topical PrEP
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- Ume Abbas: Predicting the Impact of Antiretroviral Treatment (ART) and Pre-exposure Prophylaxis (PrEP) with Overlapping Regimens on HIV Transmission and Drug Resistance in South Africa
- Questions and discussion: 30 minutes

1245 to 1400 Lunch break (buffet)

Session 5: COMBINATION PREVENTION MODELLING

Session chairperson: Tim Hallett

1400 to 1500: Panel discussion

- Ky Andersson, Elisa Long, Geoff Garnett, John Stover, Brian Williams (5 minutes each, 2 slides if using them)
- Discussion

1500-1530: Refreshment Break

1530 to 1700

Session 6: General discussion and main conclusions of the meeting

Session chair: Brian Williams

Concluding remarks: Catherine Hankins

Note: All presentations are 12-15 min long to allow time for questions and discussion
