

The HIV Modelling Consortium
The Potential for the Spread of Drug Resistance Due to PrEP

Seattle, Washington
29-30 September 2011

Meeting Report¹

Background

Pre-Exposure Prophylaxis (PrEP) is the use of anti-retroviral (ARV) drugs in men and women uninfected with HIV to prevent HIV infection. If PrEP is to be used in HIV prevention programs on a large scale, an important concern is that this intervention could generate drug-resistant virus. This is important because the drugs used for PrEP could include some of the same drugs currently used in first line regimens of anti-retroviral therapy (ART) and therefore resistance due to PrEP could compromise the effectiveness of treatment. Results of recent trials among men who have sex with men² and heterosexual men and women³ have shown that PrEP can be highly effective at preventing infection, especially for individuals that were found to have detectable concentrations of the drugs in their blood. However, in the last year, one trial testing the effect of oral daily emtricitabine tenofovir PrEP in heterosexual women⁴, and the arm of a large trial testing the effect of oral daily tenofovir in women⁵ have been stopped after interim reviews found that it was unlikely these studies would demonstrate efficacy. Investigations into the likely causes of these outcomes are underway. Therefore, it has become especially important to now investigate the potential for negative outcomes from PrEP interventions.

A meeting of the HIV Modelling Consortium was proposed by the Bill & Melinda Gates Foundation and organized by the consortium secretariat based at Imperial College London at the request of the steering committee of the HIV Modelling Consortium.

¹Available online at www.hivmodelling.org

²Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *N Engl J Med*. 2010 Nov 23.

³University of Washington. Pivotal Study Finds That HIV Medications Are Highly Effective As Prophylaxis Against HIV Infection In Men And Women In Africa [http://depts.washington.edu/astda/resources/PrEP_PressRelease-UW_13Jul2011.pdf]. 2011.; Centers for Disease Control and Prevention. CDC Trial and Another Major Study Find PrEP Can Reduce Risk of HIV Infection among Heterosexuals [<http://www.cdc.gov/nchhstp/newsroom/PrEPHeterosexuals.html>]. 2011.

⁴Family Health International (2011) FHI to Initiate Orderly Closure of FEM-PrEP (<http://www.fhi.org/en/Research/Projects/FEM-PrEP.htm>).

⁵The Microbicide Trials Network (2011) MTN Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women (<http://www.mtnstopshiv.org/node/3619>).

The HIV Modelling Consortium

The HIV Modelling Consortium, funded by the Bill & Melinda Gates Foundation via a grant to Imperial College London, aims to help improve scientific support for decision making by co-coordinating a wide range of research activities in mathematical modelling of the HIV epidemic. This involves:

- Identifying questions that demand mathematical modelling input and identifying new modelling results that may require further validation.
- Facilitating sharing of information, modelling techniques, data and expertise between research groups.
- Providing a forum for rigorous review of new mathematical modelling research and tools.
- Providing funding through sub-contracts to commission research to address those needs.

A steering committee of leaders in HIV programme and policy directs the focus of the work of the consortium. Further information on the HIV Modelling Consortium is available in a standard [briefing document](#) and information about other work packages undertaken by the HIV Modelling Consortium is available at the website www.hivmodelling.org .

Focus of The Meeting

Although the emergence of drug resistance during randomised controlled trials of PrEP has been minimal, the generation of resistant virus remains a legitimate concern for potential scale up of PrEP based prevention programmes. Trials generally follow individuals for two or three years, which is not enough time for the full scale of potential resistance to emerge, and trial participants are much more likely to receive regular HIV tests, be rapidly removed from PrEP after HIV infection occurs, to take their medication as directed, and to refrain from sharing their medication with others who might unknowingly be HIV positive, all of which limit the risk of generating resistance compared to a wider roll-out of PrEP. One way to investigate the potential impact of resistance is through the use of mathematical models. Moreover, through the use of models it should be possible to make recommendations for how future programs could minimize the risk of resistance for maximum health benefit in both resource rich and resource constrained settings.

Several mathematical models have now been developed to estimate the potential for the generation and spread of drug-resistant virus due to PrEP. However, so far there has been a lack of consensus among the models in the projections formed. For models to reliably inform policy, it is vital that we understand where the models agree, where they disagree, and why.

The models require a large number of detailed assumptions about the virology,

immunology and epidemiology of susceptible and resistant virus, for which there are substantial uncertainties. There is also a need for this research to feed insights into other models examining the overall cost-effectiveness of HIV prevention programs. Furthermore, new data about patterns of pill taking behaviour, the interaction between adherence, degree of protection and the performance of diagnostics (for patient screening) and propensity for pill sharing behaviour now pose important new questions for existing models.

The meeting brought together mathematical modellers, virologists, immunologists, clinicians, epidemiologists, and clinical trialists to review existing modelling of potential resistance to PrEP, agree on areas of consensus, and identify key uncertainties. Prior to the meeting, five key aims were outlined for the two day meeting. The discussion and outcomes of the meeting are documented below against the original aims of the meeting.

Meeting Discussion and Outcomes

Aim 1: Establish if there is overall agreement in the potential “threat” posed by the generation and spread of drug-resistant HIV due to PrEP across biologists, clinicians, and modellers. If not, identify reasons for this.

All of the models agree that PrEP is likely, at some level, to generate resistance, but the nature and extent of this increase varies between different scenarios considered by the same models, and among models. There appeared to be tentative agreement that ART is likely to be a substantially bigger driver of the emergence and spread of resistance, but further work is required to confirm this conclusion.

Currently, a major problem is that the model output produced by different groups cannot be properly compared since different metrics are used to measure rates of resistance. For example, are we interested in incidence or prevalence? Are we interested in the proportion of new and existing infections that are drug-resistant, or the absolute numbers of each? How do we define emergence of drug-resistance within a host (>1%, >25%, >99% of resistant virus)? How do we define low frequency of resistant virus due to the withdrawal of drugs or their intermittent use (<1%, <25%)?

Before considering other reasons behind the discrepancies between models, it is important to represent the output of the models in a way that makes them directly comparable and which highlights important information. This required decisions about common metrics to be calculated by all of the models, and several were proposed that focussed on levels of prevalence or incidence of resistant infections relative to the number of resistant infection compared with an ‘ART only’ alternative simulation. There was general agreement that the absolute number of resistant infections or population prevalence of resistant infections was a more useful metric for determining the risk of resistance due to PrEP than the prevalence of resistance amongst HIV positive individuals because while PrEP is likely to increase the

latter, it may do so while reducing the overall number of resistant infections in the population if overall HIV incidence is reduced compensatorily, which should not be considered an adverse outcome of PrEP. All agreed that undertaking a model comparison exercise using common output metrics would be a first step towards understanding differences between model results, and which could also highlight areas of agreement not currently apparent.

In this discussion, other general points were also raised about the structure and evaluation of the models themselves:

- What is the role of host heterogeneity in these models? Particularly from work done in the ecological sciences, we know that the inclusion of environmental heterogeneity can have a surprisingly large influence on model results. What impact does (or could) host heterogeneity, such as differences in host behaviour, genotype and/or concurrent infections, have in these models?
- Can the models be simplified? To model as accurately as possible the populations in question, the models developed to date are relatively complicated. An inevitable drawback of complicated models is that it can be difficult to fully understand the dynamics generated. It was suggested that it might be productive to simplify the existing models, eliminating those elements that have little impact on the overall dynamics.
- In interpreting model results, what level of resistance should be deemed 'acceptable' as collateral for a particular prevention benefit? In resource poor settings in particular, infection with resistant virus is likely to drastically worsen an individual's prognosis if regular diagnostics and second and third line ARV therapy are not available. However, this needs to be balanced against the potential benefits of PrEP in terms of reduced overall transmission of the virus.

Action point 1: Agree upon a common set of metrics

Leaders: David van de Vijver and the consortium secretariat

Timeline: 7th October, 2011

Action point 2: Each modeling group output common metrics for headline model results

It should be noted that due to the nature of the different models, it is unlikely that all groups will be able to represent their results in an identical manner.

Leader: David van de Vijver and the consortium secretariat

Timeline: 7th November 2011

Aim 2: Agree on major sources of uncertainty in model results and consider ways to gather suitable data.

Even if the models represent their output in a similar way, it is still likely discrepancies will remain due to the structures of the models, populations modeled,

and the parameters used. It was agreed that the next important step will be to evaluate which parameters can be estimated with some accuracy, which parameters are less certain, and which parameters are likely to have the most influence on model results. These parameters can be partitioned into those relating to the within-host dynamics of the virus, those relating to the transmission of the virus, and those relating to population level dynamics.

Within-host dynamics:

- i. What are the fitnesses of resistant strains within hosts (non-drug taking hosts, hosts on PrEP, hosts on ARV)? How do mutations interact (e.g. epistasis, cross-resistance, multi-class resistance)?
- ii. What is the risk of resistance emerging in an HIV infected individual who is on PrEP? How does adherence affect this risk (e.g. different patterns of pill taking behavior)?
- iii. What is the probability of reversion given different drug regimes, and a what frequency does the resistant virus revert to?
- iv. How does reversion affect future treatment?
- v. How does viral genotype affect viral load and disease progression?
- vi. What are the consequences of different drug combinations and drug pharmacokinetics?

Transmission:

- vii. What is the transmissibility of resistant and susceptible virus between hosts given the drug status of donor and recipient? (E.g. What is the efficacy of PrEP when users are exposed to drug resistant HIV?)
- viii. Is transmissibility of resistant virus reduced only because viral load in the donor is lower, or because it is inherently less transmissible?

Population-level dynamics

- ix. How frequent is HIV testing likely to be, and how reliable will the results be?
- x. What are real patterns of adherence likely to be?
- xi. How will pill sharing affect outcomes?

It was agreed that it would be useful to formalise and make publicly accessible the expert opinions available in the meeting to refine parametrisation of models. The parameter ranges suggested should then be explored in the context of existing models, allowing modellers to identify which of the parameters that have uncertain values are also those to which the system is highly sensitive. This will help to guide priorities for future experimental work.

Action point 3: Compile a list of parameters that are likely to be important. This will be circulated among the modellers to discuss, and then sent to virologists to give indication of parameters value.

Leader: Dobromir Dimitrov, Deenan Pillay & John Mellors

Timeline: 14th October 2011

Aim 3: To explore implications of new data for model development and new analyses.

The aim of this session was to include new data that could be particularly useful in refining the models, especially the processes that lead to the generation of acquired HIV resistance due to PrEP. Three sets of emerging data were described:

i. Partners in Prevention trial

Note, details were presented from a forthcoming paper (Baeten et al., NEJM 2011) on the emergence of resistance in the Partners in PrEP trial, but details are not provided in this report.

- The trial had 3 arms, TDF, FTC/TDF, and Placebo.
- Follow up was for 36 months (although most individuals on PrEP were followed up for about 24 months)
- Some individuals on PrEP were subsequently excluded from study as they were found to be HIV positive before initiating PrEP.
- The TDF and the FTC/TDF arms gave similar levels of protection (>65%).
- Drug-level testing data will enable a calculation of the efficacy of protection for those that were subsequently found to have taken the study drug.
- The active arms are continuing and individuals in the placebo arm are entering the other two arms in equal numbers.
- Data will be available on patterns of adherence based on the records of electronic pill bottles.

ii. Sensitivity/specificity of HIV testing in the real world

- Many HIV rapid tests are available (32 on USAID waiver list)
- Many are cheap (less than a dollar)
- They are easy to use and sensitivity/specificity is >99%. However, in Kenya a half of tests failed procedure, and 15% of these got the wrong answer. In South Africa, only 17% passed procedure. Trained staff and quality assurance is therefore a big issue.
- Imperfectly sensitive tests (especially during the early phases of infection but also at chronic stages) could lead to HIV-infected individuals being initiated on PrEP, increasing the potential for the generation of resistance due to PrEP.

iii. Findings from pre-marketing research

- Surveys were conducted among groups that were anticipated to be among the potential users of PrEP in a number of countries on several continents with the aim of recording their attitudes and acceptance of oral and parenteral PrEP interventions.
- Encouragingly, the surveys indicated that most people would definitely or probably be willing to use PrEP.
- Worryingly for the potential for the spread of drug resistance, many people also said they would be willing to share PrEP.

- Among potential users, the three most important attributes of PrEP were (most important first): route of administration (preferring infrequent injections), dispensing site (preferring local sites, not ART facility), frequency of testing (preferring less frequent HIV testing).
- A paper has been submitted with these findings to PLoS One (Eisingerich et al.).

Aim 4: Discussion of plans for modeling of next generation products (e.g. TMC278 and DPV ring).

A common theme of the meeting is that imperfect adherence is likely to drastically reduce the overall effectiveness of PrEP, and is likely to increase the rate at which resistant virus is generated and spreads. However, it is not known what drug concentrations and combinations are needed to prevent infection while on PrEP, and whether intermittent or episodic dosing is sufficient to prevent infection. For example, animal data suggests that a combination of two drugs is better than one, but new data from the Partners in Prevention trial did not suggest that TDF alone is less effective than a combination of FTC and TDF.

Several products are currently in the 'development pipeline' that have been designed to be less reliant on individual adherence behaviours.

- i. DPV Vaginal ring
 - The ring is located at the vagina and provides a continuous supply of a new form of ARV, DPV.
 - This is going into phase 3 trials starting in Q2 next year (2012).
 - It seems to be well tolerated, but there are few pharmacodynamics measures.
- ii. TMC 278
 - This has been formulated in nanosuspension.
 - To be given by a 2ml injection into the buttocks.
 - Half life of 30-50 days.
 - Likely to be given every 1-3 months.
 - Few pharmacodynamics measures.
 - Seems to have a high concentration in the vagina.
 - Needs refrigeration, otherwise shelf life is very short. NB. If the concentration of drug can be reduced by half, the problem of refrigeration will be avoided.

As with daily oral PrEP, these products are likely to have different levels of acceptance and adherence in different communities. Eventually, there could be a suite of products that individuals can choose from (as with modern contraception). It is hoped that as a consequence adherence will be higher.

There is a need to understand what the relative advantages of these products might be compared to daily-oral TDF-based PrEP, and the potential issues that might arise surrounding the spread of HIV resistance due to the roll-out of these new products, in particular the potential for cross-class NNRTI resistance, compared to TDF resistance that has been the focus of existing PrEP modelling studies. Ideally, these questions will be tackled in a timely manner through the use of mathematical modelling so that key results can help inform which data should be collected during early phases of product development or during subsequent clinical trials. To facilitate this, it was agreed that the HIV modelling consortium will work with the BMGF to produce a document detailing these products and providing guidance on parameter values that might best be used in models based on preliminary indications from on-going work.

Action point 4: Generation of a public “living document” on the consortium website (www.hivmodelling.org) to provide modellers with target product profile and guideline characteristics and parameter values for investigation of new products.

Leaders: BMGF HIV Team and the consortium secretariat.

Aim 5: To discuss how to promote interface between groups modelling the spread of resistance and cost-effectiveness studies.

Conventional wisdom maintained that PrEP will only be rolled out if it is cost-effective and affordable, and that costs associated with PrEP related resistance needs to be included in cost estimates of PrEP interventions. Therefore, there is a need for the group modelling the spread of HIV resistance to interface with groups aiming to estimate the cost-effectiveness of different forms of delivery of PrEP, and vice versa. A set of results that had been presented at a recent PrEP stakeholders meeting was presented. Three main points were made:

1. The relatively high cost of PrEP (and incomplete effectiveness) means that it is unlikely that high coverage population-wide PrEP intervention will ever be implemented. This is in contradiction to many of the assumptions made in existing modelling work examining the spread of resistance. Assumptions about high coverage of PrEP will lead to exaggeration of the spread of resistance due to PrEP.
2. Current coverage levels of treatment for those in immediate clinical need in most of the worst-affected countries is incomplete. As a consequence, scaling-up treatment, over PrEP-based intervention, will be a priority for AIDS programs. Further, in terms of spending resources on ARV-based prevention approaches, analyses tend to suggest, at current costs, an argument for spending on increased access to treatment (for all HIV-infected persons irrespective of their CD4 cell count) before spending on PrEP interventions (delivered either to groups at highest risk, such as young women, or population-wide). Thus, any PrEP intervention will be operating in the context of substantially expanded use of ART. This contradicts existing model assumptions, and assumptions that under-estimate ART coverage

when PrEP is scaled-up will over-estimate the relative contribution of PrEP to the total level of circulating resistant virus.

3. Given the evidence for effectiveness of PrEP in couples, and considering the epidemiology of transmission within, to and from these couples, one of the more cost-effective options for delivering PrEP might be to give it to uninfected individuals who are in stable partnerships with infected individuals. If any of these individuals on PrEP has a breakthrough infection and acquires resistant infection, the individual they are most likely to infect will be their already-infected partner. The dynamics of super-infection, not substantially explored in existing models, would therefore become a key determinant of the spread of resistance.

Given these considerations, it was suggested that future modeling work examining the spread of resistance should aim to represent PrEP interventions that may be more realistic if and when rolled out (lower scale, provided in the context of scaled-up ART, and prioritised to those in stable sero-discordant partnerships).

The HIV Modelling Consortium
The Potential for the Spread of Drug Resistance Due to PrEP

29th & 30th September, 2011
The Bill & Melinda Gates Foundation, Seattle
500 Fifth Ave N, Seattle, WA 98109

FINAL AGENDA

Aims for the meeting:

- 1) Establish if there is overall agreement in the potential “threat” posed by the generation and spread of drug-resistant HIV due to PrEP, across biologists, clinicians and modellers. If not, identify reasons for this.
- 2) Agree on major sources of uncertainty in model results and consider ways to gather suitable data.
- 3) To explore implications of new data for model development and new analyses.
- 4) Discussion of plans for modelling of next generation products (e.g., TMC278 and DPV ring).
- 5) To agree on best use of these emerging insights and results for cost-effectiveness modelling done by other groups.

Outputs:

- Non-technical briefing document, summarising main findings and remaining questions. [Could become co-authored paper.]
- Modelling Consortium meeting report, including review of existing work, findings of model comparison discussion, areas identified for future work.
- (Potentially) Follow-up work within Modelling Consortium’s work package.

Day One:

Introduction

9.00-9.15: Welcome and Introductory Remarks. Geoff Garnett, Stephen Becker
9.15-9.30: Introductory Remarks about The HIV Modelling Consortium and motivation for the meeting. Tim Hallett
9.30-10.00: Principles of Antiretroviral Drug Resistance: Mutation, Selection, Transmission and Persistence. John Mellors
10.00-10.20: Overview of key modelling assumptions and their influence. Dobromir Dimitrov
10.20-10.30: Discussion

10.30-10.45: Coffee

Modelling Talks: 20 mins presentation + 10 mins for questions

Presentations should respond to “What is the message that program makers need to know about resistance; what are the most pivotal assumptions (incl. model structure or specific parameter values) underlying that conclusion; what key items of data

would most strengthen this analysis”

10.45-11.15: Ume Abbas

11.15-11.45: Valentina Cambiano

11.45-12.15: Anna Bershteyn

12.15 - 13.15 --- Lunch ---

13.15-13.45 David Wilson

13.45-14.15: Virginie Supervie

14.15-14.45: David van de Vijver

14.45-15.00: Coffee

Discussion about model results, assumption and interpretation

15.00-16.00: Reactions to existing modelling work and assumptions of (5 mins each):

(i) Clinicians / Epidemiologists: Jared Baeten, Connie Celum, Stephen Becker, Geoff Garnett. [20 mins]

(ii) Virologists/Immunologists: Deenan Pillay, David van de Vijver, John Mellors. [15 min]

(iii) Modellers: Marie-Claude Boily, Jonathon Carlson, Alex Welte [15 mins]

Building Consensus Statements

16.00-17.00: Understanding any difference between models and building consensus about the key messages for current program planning and future data collection. [Aims 1 & 2]

Day Two:

9.00-10.00: New Data That May Be Used in New Modelling

Data from Partners trial (available now or in future)-- behaviours, efficacy estimates, patterns of dosing. Jared Baeten (20 mins)

Sensitivity/specificity of HIV testing in the real world. Christine Rousseau (10 mins)

Findings from pre-marketing research. Geoff Garnett (10 mins)

Discussion re. agreement of key areas for modelling to focus on in the future [Aim 3] (20 mins)

10.00-10.45: Anticipating Future Questions

New products in the pipeline and stages of development (TMC 278, DMV ring, etc.). Stephen Becker: (20 mins)

Discussion re. how to plan for future modelling, data collection needs, etc. [Aim 4] (25 mins)

10.45am: Coffee

11.00 – 12.00am: Interfacing With Other Models and Analyses

Emerging results about cost-effectiveness of PrEP in different settings/
circumstances. Tim Hallett (20 mins)

Building a draft estimate of cost for PrEP delivery (and how this should respond to
model results). Wilson Mok (20 mins)

Discussion re. recommendations from the group about how results from these
models should be interfacing with other exercises/models. [Aim 5] (20 mins)

12.00 - 13.00 -- Lunch ---

13.00 - 14.00: *Wrapping-up Discussion and Next Steps*

Review of outcomes of meeting.

Review of plans for future work.

14.00 Close.

List of Participants

Ume Abbas	abbasu@ccf.org	Cleveland Clinic
Jared Baeten	jbaeten@u.washington.edu	University of Washington
Stephen Becker	Stephen.Becker@gatesfoundation.org	BMGF
Anna Bershteyn	abershteyn@intven.com	Intellectual Ventures
Marie-Claude Boily	mc.boily@imperial.ac.uk	Imperial College London
Charles Boucher	c.boucher@erasmusmc.nl	Erasmus Medical Centre
Valentina Cambiano	v.cambiano@ucl.ac.uk	University College London
Jonathan M. Carlson	carlson@microsoft.com	Microsoft Research
Connie Celum	ccelum@u.washington.edu	University of Washington
Dobromir Dimitrov	ddimitro@scharp.org	University of Washington
Jeff Eaton	jeffrey.eaton08@imperial.ac.uk	Imperial College London
Phillip Eckhoff	peckhoff@intven.com	Intellectual Ventures
Geoff Garnett	geoff.garnett@gatesfoundation.org	BMGF
Tim Hallett	tbhallett@gmail.com	Imperial College London
Catharine Hankins	hankinsc@unaids.org	UNAIDS
Britta Jewell	b.jewell@imperial.ac.uk	Imperial College London
Katrina Lythgoe	k.lythgoe@imperial.ac.uk	Imperial College London
John Mellors	mellors@dom.pitt.edu	Pittsburgh
Wilson Mok	wilmok@gmail.com	BMGF
Alan Perelson	asp@lanl.gov	Los Alamos National Laboratory
Deenan Pillay	d.pillay@ucl.ac.uk	UCL
Christine Rousseau	Christine.Rousseau@gatesfoundation.org	BMGF
Virginie Supervie	v.supervie@gmail.com	UCLA
David van de Vijver	d.vandevijver@erasmusmc.nl	Erasmus Medical Centre
Alex Welte	alexwelte@sun.ac.za	SACEMA
David Wilson	Dwilson@kirby.unsw.edu.au	UNSW

Document Packet Distributed to Meeting Participants

- >> [Supervie et al., HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. PNAS 2010](#)
- >> [Wilson et al., The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics PNAS 2008](#)
- >> [Abbas et al., Potential Impact of Antiretroviral Chemoprophylaxis on HIV-1 Transmission in Resource-Limited Settings PLoS One 2007](#)
- >> [Abbas et al., Factors Influencing the Emergence and Spread of HIV Drug Resistance Arising from Rollout of Antiretroviral Pre-Exposure Prophylaxis \(PrEP\). PLoS One 2011](#)
- >> [UNAIDS Modelling meeting \(Montreux, April 2011\) Meeting Report.](#)
- >> [Baggaley, Powers, Boily. What do mathematical models tell us about the emergence and spread of drug-resistant HIV.](#)
- >> [Shire/Welte. 2011. Modelling the impact of acute infection dynamics on the accumulation of HIV-1 mutations](#)
- >> [Sampah et al. PNAS 2011. Dose–response curve slope is a missing dimension in the analysis of HIV-1 drug resistance \(+ Suppl.\)](#)
- >> [Chou. 2006. Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies](#)