



## **EATG Community Meeting on R&D priorities in pre-exposure prophylaxis (PrEP) for HIV**

25 September 2010

Brussels, Hotel Radisson



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# **EATG Community Meeting on R&D priorities in pre-exposure prophylaxis (PrEP) for HIV**

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## **Executive Summary**

This meeting was organised by the European AIDS Treatment Group (EATG), as part of its advocacy and dissemination activities as the community partner within Europrise, the European HIV vaccines and microbicides network ([www.europrise.org](http://www.europrise.org)).

The objective of the meeting was to bring together researchers, community advocates, the European regulatory body, a health technology evaluation agency and pharmaceutical companies with a PrEP R&D programme to discuss scientific, policy, regulatory and reimbursement issues related to PrEP.

Six representatives from the field presented on different aspects of PrEP; issues raised were then discussed by two panels, one of community representatives and one of representatives from pharmaceutical companies involved in PrEP research.

- The epidemiologist: **Vicky Jaspers** of the Institute of tropical Medicine in Antwerp introduced the current and recent efficacy trials of oral and topical PrEP.
- The social researcher: **Bruno Spire** of AIDES and ANRS in France introduced a proposed trial of PrEP in gay men in France, using it as an example of research/community collaboration.
- The treatment activist: **François Berdougou-le Blanc** of TRT5 spoke about the community liaison aspect of this trial.
- The clinical researcher: **Sheena McCormack** of the Medical Research Council in the UK spoke about what would be needed before PrEP could be licensed and rolled out.

- The regulator: **Leonor Emes** of the European Medicines Agency spoke about regulatory requirements for prevention methods and the EMA structures researchers could use to help with licensing.
- The evaluator: **Jane Cowl** of the NICE in the UK spoke in general about the process of evaluating health technologies for use by national health systems, and how HIV technologies were likely to be evaluated.
- The prevention advocate: **Kevin Fisher** of AVAC spoke about community reaction to, and understanding of PrEP in the wake of the successful CAPRISA 004 microbicide trial.<sup>1</sup>

### Emerging themes and discussions

The following themes, recommendations and priorities emerged from the meeting.

**1. Involving the community.** It is not surprising that this was a major theme at a community meeting. However what became clear was the necessity of involving the affected and at-risk communities at large, not just involving the HIV-positive community and treatment/prevention activists. The main community experts in HIV prevention are HIV positive, yet it is HIV-negative people who will in the main participate in trials and who will eventually use many of the prevention methods being trialled.

It was agreed that it is necessary to move out beyond the HIV positive community and into the at-risk populations to achieve genuine community 'buy-in' to these approaches. These at-risk populations vary from people in poorer countries who are rarely consulted, to prevention-literate groups in richer countries who may have difficulty changing their paradigm from condoms-and-behaviour-change to broader biomedical ideas - and may even see danger in them. If microbicides and PrEP studies continue to produce positive results, this will be an opportunity to do this kind of proactive outreach and dissemination work.

It also needs to involve better liaison between HIV activists and researchers and campaigners in different but allied fields such as gay activists, women's activists, human rights experts in these fields, and so on.

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<sup>1</sup> Karim QA et al. *Effectiveness of 1% tenofovir vaginal microbicide gel in South African women: results of the CAPRISA 004 trial*. Eighteenth World AIDS Conference, Vienna. Abstract TUSS0502. 2010. See <http://pag.aids2010.org/session.aspx?s=13>

At the same time, HIV-positive treatment and prevention activists are the only people with the scientific literacy and the access to funders and policymakers to really lead in this field. We owe it to our broader communities to continue to advance this field and include them in the discussion.

**2. A rational, comprehensive prevention development programme.** We need a rational and co-ordinated programme that evaluates the contribution of different prevention technologies, selects and moves forward only the most promising candidates, and once methods are licensed makes rational decisions about which ones to fund and for whom.

HIV treatment has been 'owned' by the pharmaceutical industry and commercial competition has been a spur for rational advances in drug development. No one body has 'stewardship' of prevention development in a similar way and as a result we see distortions such as the fact that only two antiretroviral drugs have so far been involved in prevention efficacy trials.

Because public funders support a high proportion of prevention development, decisions may be unduly influenced by government priorities, including decisions to restrict HIV funding and changes in policy priorities.

**3. Licensing requirements.** Given the CAPRISA 004 result, will one more positive result in a topical microbicide trial be enough to 'clinch the deal' on licensing? It took three trials all reporting at least 50% efficacy for circumcision to be accepted as a valid prevention method. Will the same apply to oral PrEP or will higher efficacies be required, given the greater potential for resistance?

**4. Access policy and implementation.** This links to the discussion about general licensing, access and distribution policy. At present the normative agencies still have most of their energy engaged in trial design and other aspects of the development process. But the time to discuss how to persuade states to fund these new prevention technologies is *now*. Policy also involves making decisions about clinical questions such as how often it is feasible to test for HIV people who are taking PrEP and whether to monitor for resistance.

**5. Research gaps.** So far PrEP and microbicide trials have either used continuous dosing or two doses before and after sex. But the way they are most likely to be used is if taken/applied as a single dose. Single-dose studies are planned but there

are few or no comparison studies that directly compare single- versus double-dose strategies and continuous versus single-dose.

Neglected populations include pregnant women, and above all adolescents. The most vulnerable populations of all in terms of HIV incidence is teenage girls in Africa, followed closely by teenage gay men and young IDUs in various countries, and epidemiologists such as Brian Williams<sup>2</sup> are recommending that this would be the most rational group to take PrEP, but so far there have been no studies in under-18s. The other big research gap is the one scientific one of finding correlates of protection. We do not know what tissue concentration in the genitals is protective, or how to time doses so that concentration peaks at the right time to be effective.

**6. Information gaps.** This refers not so much to things that researchers don't know as things the at-risk communities don't know. The facts about biomedical protection need to be spelled out in simple and clear terms to members of the at-risk communities. This includes clear guidance on the influence of ARVs and viral load on infectiousness: it is not satisfactory for normative agencies like WHO to say more research is needed before we can issue clear guidance on infectiousness as there is considerable anxiety, controversy and ignorance of the data we already have amongst people who might benefit from knowing them.

**7. Non-ARV/over-the-counter formulations.** Although we need to be very cautious at the moment to evaluate safety and the potential for ARV-based PrEP and microbicides to generate HIV drug resistance, we should not let go of the long-term goal of a microbicide or oral prevention medicine that could be sold or provided without prescription. This could be ARV- or non-ARV based. Although the willingness of at-risk people to go to clinics for prevention methods has probably been underestimated, ideally these prevention methods, in the long term, should be as accessible as a condom, if not more so.

**8. Behavioural prevention.** Biomedical prevention methods will not – at least not without supreme efficacy – change the need for behavioural prevention methods. Behaviour-change support will be needed to help people evaluate if they are/have been at risk, to empower them to seek PrEP, to educate them in correct use, and to support adherence.

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<sup>2</sup> Pretorius C et al. *Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa*. PLoS ONE 5(11): e13646. doi:10.1371/journal.pone.0013646. 2010.

**9. Ethics/trial design.** At some point equipoise will be reached and it will become unethical to compare a PrEP/microbicide regimen against placebo. This could happen quite soon if current nearly-completed PrEP trials report high efficacy. If PrEP regimens become standard of care, how do we advance technologies and devise trials of better regimens? We also need to continue to advocate for the rights to treatment of seroconverters in trials and of those diagnosed with HIV during screening.

**10. Social/structural inequity.** Allied closely to this is the broader question of stigma, inequity and social marginalisation. We are in many cases advocating for the rights of women to methods of HIV prevention that they only have to use because so far the broader question of their empowerment in relationship to men has not been solved. On a more practical level, trials of biomedical prevention methods must not let researcher, legislators and governments 'off the hook' in terms of advocating for structural change and addressing inequities. These are the broader drivers of the HIV epidemic, even if it may be difficult to prove scientifically that structural change directly leads to specific health outcomes in the short time of a trial. Finally, and much more practically, none of these biomedical prevention methods will work, including 'Treatment as Prevention', if unaddressed stigma and legal persecution make people reluctant to come forward for HIV testing or to access prevention methods, for fear of being identified as HIV-positive and/or a member of a stigmatised at-risk population.

**11. Funding.** The CAPRISA results were a bright moment in an increasingly darkening climate for the funding of HIV in general. The global economic downturn is combining with policy change against single-disease, 'vertical' treatment programmes to create a situation in which the goal of universal global access to antiretrovirals as treatment is becoming harder to reach and may even be receding. In this situation it is understandable if advocates and affected community members question whether putting more money into biomedical prevention would mean removing money from ARV treatment. They do not need to be competitors, but we need continuing, high-quality economic modelling and forecasting to establish that, funding and providing HIV prevention methods will be cost-effective, and by how much, if only in the long term. At present HIV biomedical research only needs a fraction of the money that global ARV provision needs in order to continue its research programme and it would be tragic if arguments about treatment access were used to starve prevention programmes of what they need to continue. It is ethically both imperative to provide the funding to stop the world's HIV-positive people dying of AIDS, AND to provide the funding to stop more people getting HIV in the first place, so they will never have to depend on taking drugs for a lifetime.

## **MEETING REPORT**

### **Purpose of the meeting**

This meeting was organised by the European AIDS Treatment Group (EATG), as part of its advocacy and dissemination activities as the community partner within Europrise, the European HIV vaccines and microbicides network ([www.europrise.org](http://www.europrise.org)).

The Europrise consortium involves 132 institutions from 22 countries. These partners represent 14 projects funded by the European Commission in the sixth Framework Programme (FP6) as well as one project funded by the Gates Foundation. Europrise is the first organisation, both in Europe and internationally, to bring such groups together in a truly integrated fashion.

The objective of the meeting was to bring together researchers, community advocates, the European regulatory body, a health technology evaluation agency and pharmaceutical companies with a PrEP R&D programme to discuss scientific, policy, regulatory and reimbursement issues related to PrEP. This one-day meeting was part three days concentrating on PrEP run by the European Community Advisory Board (ECAB) as part of its regular series of meetings with industry and researchers.

### **Attendees**

The advocacy bodies represented, as well as EATG, included the AIDS Vaccine Advocacy Coalition (AVAC); the Drug Development Committee of the US Treatment Activist Coalition (DDC); the Global Campaign for Microbicides (GCM); the Global Network of People living with HIV/AIDS (GNP+); and NAM publications ([aidsmap.com](http://aidsmap.com)).

Also attending were representatives from Europrise, the European Medicines Agency (EMA), AIDES, France; the UK National Institute for Health and Clinical Excellence (NICE); Gilead Sciences, Merck Sharp and Dohme, Tibotec (a division of Janssen Pharmaceutica) and ViiV Healthcare.

### **Meeting Objectives**

David Haerry is the representative for EATG in its role as a Europrise partner. David summed up what he saw as desirable the aims for the meeting. It would be good to discuss:

1. To come to an understanding regarding the missing scientific data we still need in order to fully evaluate the efficacy of PrEP.
2. To discuss the use of PrEP strategies in combination with other prevention approaches.
3. To look at the potential impact of PrEP in IDUs (microbicides will not work in this population)

4. To discuss upcoming trial data and how to handle positive results.
5. To initiate a dialogue with the European regulatory bodies regarding the requirements for assessing ARVs for use in PrEP.
6. To initiate a dialogue with an established Health Technology Assessment body (NICE) regarding the conditions under which they would consider recommending ARV reimbursement if used as PrEP
7. To discuss Community concerns related to PrEP research with all stakeholders represented at the meeting
8. To gain a general overview of the agenda of the industry as it relates to prevention research and PrEP in particular.
9. To generate a European advocacy agenda for PrEP.

### **Vicky Jaspers: Update on ongoing pre-exposure prophylaxis clinical research**

Vicky Jaspers is an epidemiologist at the Institute of Tropical Medicine in Antwerp.

She said that new prevention technologies have tended to be treated as two different concepts by prevention advocates, but more recently the two concepts have drawn closer together.

It is better to talk of pre-exposure prophylaxis as the use of antiretroviral (ARV) products, often, though not always, at a lower dose than ARVs for treatment, which can be used orally (PrEP) or topically (microbicide gels and other formulations).

So far, amongst the ARVs, only tenofovir and FTC have been the subject of efficacy trials. Other drugs are the subject of agreements between manufacturing companies and public/private research partnerships. Numerous ARVs and other candidate molecules are being evaluated in preclinical trials as are novel formulations.

#### **Overview of current PrEP studies: efficacy trials and timelines**

There are currently five efficacy trials of oral and topical PrEP underway, two of which will report in early 2011. A total of just over 21,500 volunteers are involved in these trials. Heterosexual women are the most-represented study population, but heterosexual men, men who have sex with men (MSM) and injecting drug users (IDU) are also represented.

PrEP trials have to be conducted in all high-risk populations because efficacy may be very different according to risk group. Populations have to be high-risk because initially PrEP is unlikely to have enough efficacy for trials in low-incidence populations to have the power to demonstrate efficacy.

- **Discussion point:** *It is at present ethical for all trials to be placebo-controlled, as efficacy convincing enough for regulators has yet to be demonstrated. But the question of what to use in the control arm of a trial of a new candidate once a PrEP regimen or microbicide has demonstrated convincing efficacy is*

*one that will need to be addressed, as it will have major implications for trial size and feasibility.*

### **Current efficacy trials**

This report comes in the wake of the first trial of PrEP to demonstrate a statistically significant positive result: the CAPRISA 004 Trial of tenofovir gel as a coitally-dependent (used before and after sex) vaginal microbicide in 889 South African women.<sup>3</sup> This found an overall efficacy of 39%. This proof-of-concept was a landmark in a research endeavour that has already lasted 20 years, but more positive results are needed before licensing PrEP can be considered. There are currently five efficacy trials of PrEP ongoing, all but one only considering oral PrEP.

These are:

**IPrEX:** This compares *Truvada* versus placebo in 2500 men who have sex with men (MSM - 1250 per arm) in six countries in four continents: Brazil, Ecuador, Peru, South Africa, Thailand and the US. Results are expected imminently, in early 2011 at the latest. See <http://clinicaltrials.gov/ct2/show/NCT00458393?term=iPrex&rank=2>

**CDC 4370:** this compares tenofovir-PrEP versus placebo among 2400 HIV-negative Injection Drug Users (1200 per arm) in Bangkok and Rayong Province, Thailand. Results are expected in early 2011.

See <http://clinicaltrials.gov/ct2/show/NCT00119106?term=CDC+4370&rank=1>

- **Discussion point:** *Early results indicate lower than expected HIV incidence in the whole study population,<sup>4</sup> which could affect the trial's ability to produce a significant result. This factor has also affected CDC 4940, a study in heterosexual men and women in Botswana.*

**PartnersPrEP:** a trial comparing both tenofovir and *Truvada* against placebo in 2350 serodiscordant couples (783 HIV negative partners in each arm). Results are expected in 2012. See <http://clinicaltrials.gov/ct2/show/NCT00557245>.

**FEM-PrEP:** a trial of oral *Truvada* versus placebo in 3900 women (1950 in each arm) in Kenya, Malawi, South Africa, Tanzania and Zimbabwe. Results are expected in 2013.

See <http://clinicaltrials.gov/ct2/show/NCT00625404?term=FEM-PrEP&rank=1>.

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<sup>4</sup> Martin M et al. *Screening, Enrollment, and Follow-up of Injecting Drug Users in an HIV Pre-exposure Prophylaxis Trial in Bangkok*. Fifth IAS Conference on HIV pathogenesis, treatment and prevention, Cape Town. Abstract WEPEC081. 2009.

**VOICE** (Vaginal and Oral Interventions to Control the Epidemic, MTN 003): VOICE is the only current trial to investigate both oral and topical PrEP and the only topical microbicide efficacy trial currently underway. It compares daily oral tenofovir, daily oral *Truvada* and daily topical tenofovir gel, all against placebos. There are 5000 participants (833 in each arm) in Malawi, South Africa, Uganda and Zimbabwe. Results expected in 2013. See <http://www.mtnstopshiv.org/news/studies/mtn003>.

- **Discussion point:** *since CAPRISA, should we be advancing topical-PrEP (microbicide) studies with more urgency?*

### **Other safety/dosing trials (phase II)**

A number of smaller trials are also ongoing or (in one case) have recently finished. These are not powered to detect efficacy but most of them cover areas not researched by the large efficacy trials.

The one that finished was **CDC4243**: tenofovir PrEP versus placebo in 400 US MSM. This produced no safety concerns and, although it was not powered to show efficacy none of the six HIV infections seen during the trial were in men taking tenofovir.<sup>5</sup>

### **Others include:**

**CDC 4940**: this study has compared tenofovir/FTC (*Truvada*) against placebo in 1200 heterosexual men and women (600 per arm) in Francistown, Botswana, one of the world's highest-prevalence locations. It was originally designed as a phase III efficacy trial but incidence in the trial population turned out to be too low to demonstrate efficacy. Results are expected imminently. For more information, see [www.cdc.gov/hiv/prep/resources/factsheets/botswanatdf2.htm](http://www.cdc.gov/hiv/prep/resources/factsheets/botswanatdf2.htm).

**MTN001** compares oral and vaginal tenofovir in women. Also with results expected imminently, this trial compares adherence to, and the pharmacokinetics of, tenofovir microbicide gel versus tenofovir oral PrEP in 144 women (36 per arm) in South Africa.

**(ATN) PCS 082**: this is comparing *Truvada* PrEP with placebo in 99 young MSM (aged 18-22) in the USA, with results expected in March 2011.

**IAVI E001 and IAVI E002** are comparing *Truvada* PrEP taken every day versus intermittently in 77 high-risk women and men in Kenya (trial 001) and in 77 serodiscordant heterosexual couples in Uganda (trial 002). (29 people taking PrEP or

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<sup>5</sup> Grohskopf L et al. *Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 pre-exposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM)*. Eighteenth International AIDS Conference, Vienna, abstract FRLBC102, 2010.

placebo per arm). 'Intermittently' means twice a week plus before/after sex. Results are expected soon.

### **Other noteworthy trials planned**

The International Partnership for Microbicides (IPM) is continuing its programme of research, the most advanced strand of which is the development of a vaginal ring impregnated with the NNRTI drug dapivirine (TMC120) and replaced every four weeks. Adherence, acceptability and drug concentration results were presented at the Microbicides 2010 conference in 2010.<sup>67</sup> Efficacy studies are planned.

One innovative trial would have taken place in Europe, at the St Stephen's HIV Centre at the Chelsea and Westminster Hospital in London, UK. This was a trial of rilpivirine (TMC278), the new NNRTI developed by Janssen, which is due to be licensed in 2011. However instead of daily oral dosing it would be given as a monthly injection of the nanoparticle-suspension formulation currently under development. This trial has been put on hold due to concerns about plasma levels achieved by the formulation. Researchers intend to resume this trial with a new formulation.

A trial of PrEP in gay men is planned in France: see Bruno Spire and François Berdugo's presentations.

- **Discussion point:** *Would PrEP prove to be a footnote – or a breakthrough? Vicky Jaspers asked. If efficacious, would it only be accessed by (or accessible to) a small number of high-risk people or would it have wide applicability?*

### **Post-presentation questions, answers and comments:**

**Why, so far, have there been no trials conducted in Europe?** There have been plenty of preclinical and phase I safety studies of microbicides. This may be partly due to the EU's bias towards funding preclinical research and partly because oral PrEP was initially not included within the remit of research networks.

**Would it be worth the HIV-negative partner in a serodiscordant couple taking PrEP if their partner was on effective treatment?** This question was asked because a study among serodiscordant couples is in early planning stages in Switzerland. Incidence would probably be so low that no efficacy could be demonstrated, but it was still worth studying safety, acceptability and impact on psychological measures.

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<sup>6</sup> Loxley A et al. *Combination ethylene vinyl acetate intravaginal vaginal rings containing dapivirine and maraviroc*. Abstract 185. Microbicides 2010 Conference, Pittsburgh.

<sup>7</sup> Woodson C et al. *Safety and acceptability of vaginal ring as microbicide delivery method in African women*. Abstract LB4. Microbicides 2010 Conference, Pittsburgh.

**To what extent do people think clinicians are already prescribing PrEP on an individual basis?** Panellists thought this was quite a rare practice, possibly a bit of an 'urban myth'. It would have to be paid for privately. US studies have reported very low levels of awareness and use in the gay community.<sup>8</sup>

**Why do the trials all feature the same drugs?** This is partly because when tenofovir was being developed, the researchers had the foresight to do animal-model studies of it as prophylaxis. Also, up till now drugs have been too problematic in terms of toxicity, dosing or resistance.

**What is being done in terms of community preparedness?** WHO is preparing guidance on PrEP, and they held two regional consultations in 2009 on the implementation of PrEP in west Africa and are about to hold one in east Africa. One in Latin America is being held in 2011.

### **Bruno Spire: Pre-exposure prophylaxis in France**

Bruno Spire is President of France's largest HIV NGO, AIDES, and a social scientist conducting research for France's national HIV research organisation, ANRS.

Spire presented the plans for a trial of intermittent PrEP amongst gay men in France and Quebec. He said that men who have sex with men in France were a good study population for PrEP. HIV incidence continues to be high in this group<sup>9</sup> and results from CDC4243 and IPrEX had shown good tolerance of the study drug and lack of risk compensation.

There is, however, as yet no study of PrEP in a European population and no study of intermittent dosing in MSM. Dosing would be coitally-dependent, and the regimen similar to that used in the CAPRISA 004 trial. A dose would be taken at least four hours before sex (or anticipated sex), and again two hours afterwards.

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<sup>8</sup> Liu A et al. *Low levels of pre-exposure prophylaxis awareness and use among HIV-negative/unknown gay/bisexual men: San Francisco Bay Area residents, circuit party attendees, and clients of an urban STD clinic.* Sixteenth International AIDS Conference, Toronto, abstract THLB0101, 2006.

<sup>9</sup> Le Vu S et al. *Population-based HIV incidence in France, 2003 to 2008.* Seventeenth Conference on Retroviruses and Opportunistic Infections, abstract 36LB, San Francisco, 2010.

Animal studies<sup>10</sup> have shown that taking a dose less than four hours before sex has lower efficacy. However one audience member said that data shows that if the dose of *Truvada* is doubled, sufficient drug concentration can be achieved in the rectum only two hours before exposure

To be eligible for enrolment, participants would be high risk men who have sex with men over 18. 'High risk' means having had unprotected anal intercourse more than twice in the last six months, or who have had more than 20 partners regardless of self-reported condom use.

Numbers depend on the baseline incidence observed in the trial population, but a rough estimate is 1000-2000 people.

There would be basic safer-sex counselling and information at each visit, but discussion is underway on whether to do more in-depth counselling using motivational interviewing. This could either be done for all participants, or could be done as a substudy. Motivational-interviewing counselling would not be done by specialist psychologists but by peer counsellors from AIDS service organisations. This aspect of the study would be organised by TRT-5, and is the subject of François' talk below. This would mean there was a strong component of social as well as clinical science in the trial, as other prevention studies have shown that there is a strong socio-psychological component to the efficacy of any prevention intervention.

**A feasibility study** was done in 2009 a year ago to estimate the degree of acceptability for an intermittent PrEP trial. Four hundred and forty-three eligible men completed the questionnaire. Forty per cent of respondents said they would be interested in participating in such a trial (10% 'very interested' and 30% 'quite interested'). Those who were interested were on average younger, with more partners, had had more casual unprotected sex, and were less educated.

Even if IPrEX showed 90% efficacy they would still do the study. Intermittent PrEP is likely to be the only feasible type, because health systems would not agree to fund continuous PrEP. Intermittent dosing allows an individual to manage their risk according to their lifestyle as well as reducing cost and potential toxicity. The more PrEP was a matter of choice and taken when desired, the more chance it would be funded.

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<sup>10</sup> Garcia-Lerma G et al. *Prevention of rectal simian HIV transmission in macaques by intermittent pre-exposure prophylaxis with oral Truvada*. Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, abstract 47, 2009.

### **Questions, answers and comments:**

**Had researchers factored in the degree to which incidence is likely to go down due to the safer-sex counselling?** – Yes, though it was difficult to estimate this in advance.

**Would researchers be proactively recruiting hard to reach populations such as migrants, bisexuals, and MSM who inject drugs?** – Researchers will try to ensure the population is representative. Illegal/undocumented immigrants cannot be recruited because trial subjects have to have French social security numbers.

**Should daily PrEP be the control arm if IPrEX reports high efficacy?** No, because for any chance of a significant result, more than 10,000 people would need to be recruited.

**How is it planned to measure adherence?** Self-reports of adherence are not reliable so a non-invasive technique will be used: measuring drug concentrations in hair.

**Will post-exposure prophylaxis (PEP) be provided if requested?** PEP will be available for a high-risk exposure but it has to be reported.

### **François Berdougo-le Blanc: Community participation in a PrEP trial project**

François spoke on behalf of the PrEP task force of TRT-5. TRT-5 stands for Treatments and Therapeutic Research, and is a coalition of ten French HIV/AIDS organisations, i.e. the French Community Advisory Board (CAB).

Why did a treatment advocacy group accept the invitation to participate in a trial of PrEP? TRT-5 wanted firstly to build the right task force to promote the needs of people who will be involved in the trial and to protect the safety of the research participants, and secondly to facilitate unbiased public consultation within the gay community regarding the project.

There needs to be community buy-in; not only should the trial be in the interests of the community, there must be a “community of interests” – a coalition of researchers, activists, trial participants and the broader community who support the trial and want to make it work.

TRT-5 therefore undertook a consultation exercise with the broader lesbian, gay, bisexual and transsexual (LGBT) community. They held twelve meetings in ten main French cities targeting HIV-negative gay individuals and HIV and LGBT (lesbian, gay, bisexual and transgender) associations.

More than 300 people attended at the community consultations and 70 people made comments on the net. However most people were representatives of various organisations: only 50 unaffiliated gay citizens turned up.

There was a general feeling that HIV prevention amongst gay men was no longer effective and it was felt we were facing a turning point. We do not even understand the prevention behaviours of gay men as a community and also need to understand

the way the perception of HIV as a chronic, manageable disease had changed the picture. Gay men were faced with a bewildering variety of choices and strategies: condoms, frequent testing, PEP, and sexual risk reduction strategies like serosorting.

Attendants wondered whether PrEP was really the priority. Would it be better to develop more sophisticated behavioural interventions to encourage condom use – or go down the ‘treatment as prevention’ road and expand testing?

It was acknowledged there was a tension between supporting a condom-focused approach to HIV prevention and a broader ‘combination prevention’ approach. People asked whether, if we concentrated on biomedical interventions, it meant that we gave up altogether on trying to facilitate behaviour change. There was a feeling that it was a potentially expensive and complex prevention tool replacing a cheap and easy one.

Would the availability of PrEP encourage irresponsibility over condom use? Should we be promoting ‘PrEP plus’, i.e. using it as a backup for condom use, or ‘PrEP instead’ of condoms?

Attendees had questions around the subject of “PrEP for whom?” How were people defined as ‘high risk’, and who did the defining? Would the researchers’ definition dictate who got access to PrEP in the future?

If the trial goes ahead, further consultations, including consultations with subcultures within the MSM community, would need to be done.

### **Questions, answers and comments**

**In the case of serodiscordant couples, why treat the HIV-negative partner when you could treat the HIV-positive partner and get the same result?** Couples are not necessarily assured the the HIV-positive partner is uninfected on fully suppressive treatment. The positive person could go into treatment failure or have transient high viral loads. The idea that an undetectable person is non-infectious is still new in France and even if undetectable, people are still regarded as dangerous.

**Was there concern about whether the pharmaceutical companies had a financial interest in this?** A more common question was why we were suggesting this expensive intervention when people in low-income countries were not getting HIV treatment.

**We need the normative agencies such as WHO to produce definitive guidelines on risk, including the effect of ARVs on infectiousness. Yes:** we had no idea before these consultations how the gay community saw the ‘Treatment as Prevention’ debate at all. It is quite a new debate within the community.

**I still have questions around the idea of giving someone *Truvada* now, to stop them getting something that would involve them taking *Truvada* later.** GC: The difference is that if you have HIV you still need to take ARVs now, and for the rest of your life, even if you have long ago ceased to be a ‘high risk’ person.

## **Sheena McCormack: The PrEP Research Agenda**

Sheena McCormack of the UK Medical Research Council outlined the current options we have for HIV prevention and criteria for selection of ARVs as possible PrEP candidates.

Drug safety and resistance patterns need to be well characterised and it needs to reach high and sustained levels in the genital tract. The drug needs to get where it is needed, when it is needed. Drugs also have a short window of opportunity in which to work, which is why dose timing is important: local T-cells are infected within four hours of exposure but drugs can't be given immediately in advance of sexual exposure. This is why sustained-release formulations such as a vaginal ring or depot injection may be ideal. Drug levels must be seen to correspond with protection. We don't know exactly where and in what tissues drug levels need to be high, and at what time point.

At present, tenofovir, 3TC, FTC, *Truvada*, darunavir and maraviroc are being studied as prophylaxis in clinical trials as well as the unlicensed NNRTIs dapivirine (TMC120) and UC-781.

### **Criteria for licensure**

For a drug or procedure to be license for prevention, it would need at least two trials demonstrating reasonable efficacy. For one trial to be regarded as sufficient there would need to be a very high level of efficacy shown – over 60% - and it would have to be very unlikely that the result was due to chance ( $p < 0.001$ ). The first circumcision trial, for instance, demonstrated that it had 60% efficacy but rollout did not start till two other RCTs had confirmed the findings.

There has to be safety data out to at least twelve months and safety needs to have been evaluated in over a thousand people. Safety in pregnancy must have been established.

The benefits of the intervention must exceed the risks for the national population (not just a sub-population): this is enshrined in EMA article 58. In other words more morbidity and mortality must be prevented by the measure than created by it, over the long term. This is why taking issues like behaviour change into account are crucial.

### **Criteria for rollout**

Of 14 HIV prevention methods, only seven show evidence of efficacy, only four have been subject to a randomised controlled trial and only two showed really persuasive efficacy in those trials (circumcision and the prevention of mother-to-child transmission).

There have been 40 trials of 33 different interventions and only six have produced a statistically positive result. There are the three circumcision trials, the CAPRISA 004 microbicide trial and the Thai RV144 vaccine trial. The sixth trial, the Mwanza trial of treatment for STIs as an HIV prevention intervention, is a warning for HIV prevention

researchers not to hype up single studies. Its results have never been reproduced anywhere else and may have been due to local conditions.

Within this context, the CAPRISA trial could be seen as a triumph. Its strengths were that it showed greater efficacy in more adherent users. It also showed 51% efficacy against HSV-2. There was a correlation between drug levels in tissues and efficacy; drug levels were lower in women who caught HIV than in ones who did not.

However this study was only conducted in a single population. Furthermore, the result leaves room for the true efficacy to be as low as 6%, or as high as 60%: these are the lower and higher bounds for the 95% confidence interval. In contrast, the lower bound for the 95% confidence interval was 19% to 34% in the three circumcision trials.

### **Missing data: research needs**

CAPRISA used a microbicide dose before and after sex. There has been no research yet into the efficacy of *single* dose coitally-dependent PrEP - oral or topical - which is probably how most people would use it.

We also don't know about rectal safety and efficacy of topical PrEP or how long the intervals can be between HIV tests without unacceptable risk of resistance. How would testing be carried out on people taking nationally rolled-out PrEP?

One particularly grievous omission is efficacy and safety in adolescents: trials have excluded under-18s, despite young people being the most vulnerable to HIV infection.

As immediate next steps, the MDP 302 study plans to test one *or* two doses of tenofovir gel in five centres in five African countries. CAPRISA 008 will provide open-label tenofovir gel for HIV-negative women from CAPRISA 004. CAPRISA 009 will follow HIV positive women from CAPRISA 004 to see if they develop resistance, as will a MTN seroconverter study.

We also need a better understanding of how blood and tissue drug levels affect transmission in sexually active couples and, above all, the safest way to promote correct and consistent use.

Funds for microbicide and PrEP trials are short, and fashions are changing in the world of prevention. We need funding to continue the good work of CAPRISA and establish convincing efficacy for ARV-based prevention strategies for HIV-negative people.

### **Questions, answers and comments:**

**We don't know what the correlate of protection is in terms of drug levels.** Pharmacokinetic data in sexually-abstinent women shows that drug levels in vaginal fluid are a good correlate for the amount of tissue absorption, but tissue absorption peaks four hours after using a microbicide and lasts for 24 hours. There is very little plasma absorption. No planned study, unfortunately, will directly compare single dosing with before-and-after dosing as in CAPRISA.

**Has the epidemic in South Africa reached saturation level? Will it start going down anyway?** The continuing high incidence in KwaZulu Natal defies, so far, any model that's been advanced for behaviour to explain it, including high rates of reported condom use. In the MDP301 *PRO2000* trial, women were reporting 90% rates of condom use in the Durban and Johannesburg centres but still there were seroconversions.

**Will a vaginal ring work better?** I'm not sure if women are going to want to use them all the time, and what the drug levels tell us about how long you have to leave them in after sex.

### **Leonor Emes: Regulatory aspects related to PrEP**

Leonor Emes heads the Anti-infectives and Vaccines Safety and Efficacy Sector at the European Medicines Agency (EMA), which she introduced.

EMA was established in 1995. It acts as a nexus of coordination of national medicine agencies: it does not replace them. It generates scientific opinions for EU Marketing Authorisation Applications. There is a centralised procedure for the authorisation of medicines for some conditions, and HIV is one of them. It also gives scientific opinions for "Article 58" procedures. Article 58 is an agreement with the WHO establishing that the EMA can suggest products are licensed which are not necessarily applicable to Europe. Article 58 products should have the same level of requirements as products approved for the EU.

Prevention of HIV is a public health issue, and the EMA is strongly committed to its development, as PrEP, microbicides and vaccines.

No application has been submitted for a PrEP regimen. The EU's position towards PrEP is under discussion, and work is in progress to define regulatory requirements. The EMA needs more dialogue with research sponsors. It feels it is critical to have properly conducted clinical trials, and there are areas where reassurance is needed, especially on safety, adherence, drug resistance and the effect on risk behaviour.

The EMA can give scientific advice to developers in advance of a licensing application. The Scientific Advice Working Party (SAWP) is a multidisciplinary expert group which can give advice and opinions on the development of specific products and on the preconditions for qualification of novel methodologies for a specific use – of which PrEP would be an example. Any product/procedure that has been reviewed by the SAWP gets a strong commitment from the Committee for the Licensing of Human Medical Products (CHMP) to take its marketing authorisation application seriously.

There is also an EMA multidisciplinary ad-hoc group on HIV prevention strategies, initially concerned solely with HIV vaccines. This acts as a place where informal discussions exploring current scientific thinking can take place. It proposes to the CHMP positions regarding HIV prevention strategies and enables the CHMP to provide scientific assistance during the development of prevention products and

procedures. The composition of the ad-hoc group consists of a core group, a vaccines group and a microbicides group.

**Questions, answers and comments:**

**How would you approve combination products?** That's a position we don't yet have with regard to prevention methods.

**How long would the production of a PrEP guideline take?** There are too many things we don't know in order to produce a guideline yet. We are thinking of providing a reflection paper within the next year. This idea has been endorsed by management but not yet by the CHMP.

**Even the WHO has started discussing this topic and developing consultation papers.** The issue here is that the EMA is driven by applications, but I appreciate that in this case we do need to be proactive.

**Jane Cowl: What if PrEP was considered by NICE?**

Jane Cowl is the Programme Manager for the Public and Patient Involvement Project of the UK's National Institute for Health and Clinical Excellence.

NICE comes in after licensing. It is a Health Technology Assessment body. NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

NICE produces guidance for the National Health Service (NHS) in England and Wales (Scotland has its own assessment body) on what works and on cost-effectiveness. Health professionals are expected to take NICE guidance into account when deciding what treatments to give people. It helps the NHS to ensure not only that the money they spend improves health for their communities but also, just as importantly, that they do not spend money on ineffective care.

NICE looks at health promotion and the prevention of illness too, and indeed does more work on this than on clinical topics.

NICE is independent and aims for objectivity and transparency in its work. Independent advisory groups are commissioned, and make decisions. There is patient, carer & public involvement in all these groups.

There are three types of guidance: health technologies, clinical practice guidance and public health guidance including prevention.

For technology appraisals there is a Department of Health direction to NHS to make funding available for recommended treatments within three months unless advised otherwise. Local government and NHS organisations are expected to take account of NICE public health guidance in taking action to achieve the targets set out in the 2004 White Paper 'Choosing Health'.

Technology appraisals can include prevention, such as the appraisal of statins for cardiovascular disease.

NICE identifies relevant patient and community groups and surveys patient/community views and evaluates involvement activities.

From patient groups, NICE wants to know about the personal impact of the condition, outcomes patients want the technology to help with, the impact of a technology on outcome, symptoms, physical and social functioning, quality of life, the impact on family, friends and employers, ease of use, side effects and costs of the technology.

### **NICE and HIV**

So far, NICE has not issued much guidance on HIV-related matters, largely because professional bodies like BHIVA produce guidelines themselves.

NICE has issued guidance on the prevention of sexually transmitted infections and is currently going through the process of developing guidance for increasing the uptake of HIV testing among at-risk groups.

If PrEP was referred to NICE, it is difficult to say in advance what would be looked at, but they would want to know about whether the PrEP research design provided appropriate evidence for NICE; the views and experiences of key groups which may benefit from PrEP; issues of acceptability, adherence and adverse or unintended effects; and the benefits and costs of PrEP compared with other biomedical and behavioural interventions for HIV prevention.

### **Questions, answers and comments:**

**Are you independent from the government given that you are entirely funded by the Department of Health?** I'm not aware of a situation where government pressure has changed a NICE guidance. Governments don't want to give up NICE, because we take the decisions they don't want to. We sometimes come out with recommendations governments don't like, for instance a minimum pricing policy on alcohol – and the government can ignore us.

**Do you do special consultation with stakeholder groups?** Yes, on occasion, for instance on topics for young people.

**What counts as evidence?** If a health technology, then primarily clinical trials. But we also take patient opinion into account, especially where it contradicts RCT evidence.

### **Kevin Fisher: High hopes, hard questions and high-quality problems**

Kevin Fisher, Policy Director of AVAC, discussed community preparedness for ARV-based prevention trial results.

The history of community engagement in prevention began with protest and stoppages of the PrEP trials in Cambodia and Cameroon. This was the spur to greater community participation in prevention. Greater consensus since then has grown

around how we provide treatment to those who seroconvert and greater community engagement in PrEP and the PrEP trials.

Another outgrowth of this process has been the development of the UNAIDS/AVAC collaboration of developing Good Participatory Practice Guidelines for HIV prevention trials. These set standards of care. The second version out since the Vienna Conference in 2010. See [www.avac.org/gppdocuments](http://www.avac.org/gppdocuments).

AVAC holds consultations on PrEP in collaboration with, and usually requested or initiated by, in-country partners. They involve multiple partners, present the same information in many venues and languages, and allow communities to meet researchers on their own terms and ask for the information they need.

### **Community feedback post-CAPRISA**

After CAPRISA, we found that communities across Africa were excited about the results. People thought access would be immediate or soon. Questions were posed about how PrEP works, and there were consistent questions on side effects. People asked if the gel protected pregnant and adolescent women, what the effect might be on HIV positive men and whether protection was bi-directional. Others asked whether a man could apply it to the penis and whether it could be used to treat as well as prevent herpes. Fear of fake products hitting the market was also brought up.

Others asked about how we could talk about ARVs as prevention when adequate ARV treatment is still not available.

AVAC has also held consultations in the USA, where cost-effectiveness and who pays was a major theme. People also asked about the potential for viral resistance, whether PrEP would be sold over the counter, and whether it meant one still had to use a condom.

There are also high-level questions we need to ask researchers, industry and regulators. How should the research be shaped and informed by public consultations as new data emerge? Would a positive signal from iPrEx plus the CAPRISA 004 results close the deal on effectiveness of tenofovir as an ARV-based prevention strategy?

Who is driving a comprehensive agenda looking at research questions across formulations (oral, topical), towards a broader pipeline, and at manufacturing and regulatory issues? Who has stewardship over prevention technologies, given that so far the pharmaceutical companies have not been in charge of developing them?

Will the funding for PrEP sustain itself? Funding in 2009 totalled \$52.5 million, of which only \$1.25 million was from industry, with the rest split evenly between public and philanthropic sources.

## Community Roundtable

Panel: Yasmin Halima (GCM), Gus Cairns (NAM/EATG), Kevin Fisher (AVAC).  
Facilitator: Wim Vandavelde (EATG)

Audience question: **Do you think that what we usually call community in the HIV field is the correct social body to involve in the discussions about the new prevention tools? Traditional HIV work is organised around our organisations. Are these the only relevant bodies to organise around these issues and if not, who are?**

**GC:** We need to involve the HIV-negative affected community a lot more than we do. HIV positive people are not confronted by the constant need to avoid HIV. But how you do this is problematic because most at-risk people don't want to be involved in advocacy for new approaches to prevention. However it can be done. IPreX did a series of community consultations which took at least two years before they even started the study. They did not just assume there would be community leaders; they studied the communities in which they were to do the research, identifying different constituencies within MSM who would have different needs and expectations of PrEP. If you don't have such resources, then at least make links with human rights and community organisations that represent the group in which you want to do the trial but have nothing to do with HIV. We mustn't just talk to the usual suspects.

**YH:** Who is the community, and when should they be consulted? Most people who are at high risk of HIV in Africa aren't advocates for HIV and don't belong to organisations. As potential end users, they only usually get consulted when people are preparing the ground for research, but rarely on the broader issues.

HIV activists in bodies like EATG have history, expertise, and influence. They *can* bring companies to the table. It is still the case, unfortunately, that we as western advocates can get the attention of industry and researchers better than local advocates. So we have a responsibility to those people, whether we are living with HIV or not.

Community liaison is still given lip service. I was at an intensive two-day consensus meeting at the WHO recently when in two long days ten minutes was devoted to the community.

Almost all of the two days was taken up with the next trial; there was much less time spent on regulatory issues, partly because the regulators have never had to deal with this question before; and there was almost no time dedicated to policy and implementation.

Policy and implementation means answering questions like; once we've had a confirmatory result, what are we going to do with it? What evidence do funders/leaders need for rollout? How will it be financed? What policies and guidelines will they adhere to? How will we distribute microbicides or PrEP to the people in need? Very little of those two days were devoted to practicalities like how often to test people if we roll out microbicides or PrEP or issues like whether to test for hepatitis at baseline.

**KF:** I agree that we haven't got near to how we bring the people most at risk into the discussion and that's what worries me the most. We need to broaden the discussion so there is a greater consideration of what HIV risk is, almost on a national level. That way you might be able to build support for these programmes and develop an understanding of risk amongst individuals. If you are going to make sure that governments are going to fund and support programmes I think you need to do that too.

Audience comment: **A lot of community organisations, at least in the US, have had a really difficult time in coming around to accept PrEP as part of their work. But they have good programmes, they have good outreach, and they're the way you get understanding of this issue into the MSM population.**

Audience comment: **We need questions answered as to whether PrEP works more or less efficiently against vaginal or rectal transmission, and for people injecting drugs. we need a consensually-agreed agenda that is agreed between the different stakeholders, not just follow the researchers' agenda. It would ask questions like: could be do this intervention in a more cost-effective way? Which evidence-based prevention methodologies are the most efficient? Which would be appropriate for public funding?**

**YH:** My previous point applies to the developed world too. We do have to work closely with the existing prevention community, though we have to include treatment activists because there is no other constituency in any other medical discipline, including in HIV outside of treatment activism, where the advocate community is as literate. We bring a certain level of perspective, of knowledge and of engagement that prevention advocates, unless they do biomedical prevention, don't do. I think we should use their networks, and I think we should bring some of our capacity and competency.

The whole point of trying to develop newer technologies is because traditional prevention is not working. We're not doing this because we want to keep inventing novelties but because if you look at it from the perspective of an African woman or anyone who hasn't had the capacity, autonomy or discretion to be able to make choices, it's very hard to say, "Well, condoms work".

***Quote (YH):** We asked women in KwaZulu Natal: "What distance would you travel to get a microbicide? And a condom?" They said they'd travel further for a microbicide, adding: "Even if you came to my door with a free condom I could not use it, but a microbicide is mine, and I don't have to negotiate it."*

We should have and must come up with a prevention agenda based rationally on the scientific and community needs. A rational development process for biomedical prevention. A lot of people came to the table with their own different ideas and it did not necessarily settle down in the most rational way.

**KF:** Even in the developed world people don't fully understand their own risk and vulnerability. On a rational level you can say "Why doesn't everyone wear condoms? It would be a lot simpler," but even here, some individuals don't feel they have a choice I think if people have PrEP and condoms...they may find something that works for them.

**GC:** Getting people involved in the treatment-as-prevention and PrEP paradigm when they've been used to condoms is very difficult. People are wedded to a particular vision of HIV prevention which is quite difficult to change. A recent UK draft strategy on HIV prevention for gay men included no mention of the role of viral load and treatment until this was pointed out.

Prevention becomes tangled up in moral issues and matters of conflicting human rights and becomes a matter of what you should do if you're 'good'.

People also fear being medicalised, it will all be about doctors doling out more pills to more people. But we will still need behavioural interventions if we have PrEP; we'll have behavioural interventions to persuade and inform people that it might be a good idea if they went along to their doctor and sought out PrEP. We'll have workshops in "How to recognise if you are at high risk", we'll have adherence support. People may find PrEP difficult in the same way they find condoms, or maybe different people will.

I agree that researchers and the community need to work out a common prevention strategy. Researchers get very excited about their individual approaches and tend to get into 'silos'; exactly the role prevention advocates have to play is to get them talking to each other.

I don't agree on funding some approaches and not others if it means dividing the affected communities into the deserving and the non-deserving. Haven't we learned not to do that?

One reason we don't have PrEP already, in my opinion, is because we didn't trial it in gay men in the developed world a high-incidence, literate group, instead of going into Cambodia and trying to do it with highly vulnerable sex workers. We would have probably got proof of concept some years ago. When it came to treatment, people accepted that it was an emergency and that it was kind of OK to provide treatment to gay men in rich countries first and it would kind of trickle down to people in lower-income countries; it did, sooner than many expected, thanks to huge collective effort and the courage of treatment activists in the poorer countries.

In prevention, there seems to be a different idea: everyone's got to have it at once, and unless there are huge national rollout programmes being done, PrEP or microbicides or circumcision are not worth doing at all. PrEP will happen in all sorts of different ways. It will happen as a big national rollout programme, maybe, but it will also happen as PEP has done.

**Audience question: We are dealing with the social and structural inequities that put people at risk and keep them at risk. We are doing so much to get this product out but what are we doing to also deal with the inequities that make their development necessary? I am a social scientist as well as an activist: where is the way for social science to feed into this discussion?**

**Audience comment: Prevention does involve dialogue with the negative and the untested. We need to normalise discussions about HIV in our communities, and the PrEP discussion may be an opportunity to do that. One of the ways forward is to talk about stigma in general with community members. It is a reason people don't want to test, and are still challenged by having tested.**

**With regard to PrEP and Africa, I don't think it's a question of either treatment or prevention. With the treatments we are living longer and I think one of the mistakes we made in the first place in the urgency for treatment was not to emphasise that prevention continued to be important too.**

Audience question: **We've been looking at how you get the product into people's hands in a really accessible way – the same kind of way as a condom. Have we given up on non-ARV-based microbicides?**

Audience question: **Do you think that if there is increased demand for tenofovir and *Truvada* it will drive down the prices so that we can use them for the benefit of both treatment and prevention programmes? Is there an opportunity there?**

**GC:** We all want to address social and structural inequities and we're all aware that they are an extremely important part of what drives the epidemic. The problem is not the political one of whether social inequities should be addressed, but the scientific one of whether you can prove that addressing them makes a difference to health outcomes. Can you generate data to isolate and prove that addressing a specific social inequity improves a specific desired outcome? We, of course, wish to address the social inequity anyway, but HIV prevention funders want outcomes. For similar reasons, behavioural interventions find it difficult to come out with really crystal clear results because it is so difficult to control for the multiplicity of other variables that crowd in.

How do you get the product into people's hands as you would a condom? Over-the-counter availability for ARV-based products may be impossible but we must not at this point *assume* it's impossible. I still think we should have a desire to make PrEP available OTC. This may be a very long-term aim; some drugs get licensed for OTC sale decades after they are licensed for prescription. Equally, as in the case of antibiotics, we have learned that some drugs should *never* be available over the counter.

In terms of oral PrEP, it may turn out that OTC availability is inappropriate because of resistance. The possibilities for over-the-counter availability are somewhat better for topical products: I am yet to be convinced that it is likely or even possible for HIV to develop resistance to a topical agent.

Regarding cost and cost-effectiveness, I'm not sure how much more at present we can drive down drug prices, though there is still some mileage to perhaps halve the price of tenofovir. We need much more sophisticated cost-effectiveness analyses so we can prove to funders that they could save money by using ARVs as prevention. These are going to be very hard to do and they'll need to be iterative; some interventions will have to be put into practice before we can start proving some cost-effectiveness, because you can't do it all with mathematical models.

**YH:** All of this happens within the context of racism, sexism and gender oppression. Sometimes I am personally challenged by trying to reconcile my treatment agenda and my feminist agenda. They're not mutually exclusive but they don't always sit comfortably together. If you consider the rationale for a vaginal microbicide for women it's because there is a confounding factor, and that is men. Men won't do certain things or it puts women at risk of violence if they try to protect themselves.

Therefore we have to give them technologies that allow them to circumvent that instead of really dealing with men: let's not get men to change their behaviours. Having said that, every intervention we as the Global Campaign support is an opportunity. I've never known that we go into a forum to talk about microbicides and talk about nothing else.

Have we given up on non-ARV-based microbicides? The Population Council still has a non-ARV pipeline and is doing preclinical work but for me the issue right now is, let's get a microbicide proven effective. We've had so many years of investment that hadn't shown any result before CAPRISA; we don't want the donors to go home and we don't want the advocate community to give up. We want to bring people in with something that works; then we can improve upon that.

**KF:** Regarding over-the-counter PrEP, I think the question is not, will PrEP cause resistance but, if PrEP causes some resistance, how much resistance would it be worth? That's something we all need to think about.

**Audience comment:** **One example of changing the prevention paradigm is breastfeeding. When new WHO guidelines came out saying that if women were on treatment, it was now better to breastfeed, all of the doctors and nurses in the audience were saying, how can we go home now and tell all these women we've been telling for years not to breastfeed that it is now safe to do it? People turn very conservative when confronted with new guidance.**

**Audience question:** **Regarding community involvement. The Global Campaign has been doing a lot of good work with women who were HIV negative and not already involved in HIV. How did you manage it?**

**Audience comment:** **Regarding non-ARV-based microbicides, I think we'd need one close to the potency of ARV-based microbicides, and I think that is a long way off. We haven't given up but it will be a long time coming. Regarding the question of the broader pipeline and a more comprehensive, broader prevention research strategy : to get a broader pipeline traditionally you need competition; that's how it's worked in industry in drug and disease areas. So I'd like to ask the panel if they think competition would ensure a broader agenda.**

**Audience comment:** **I come from Ukraine, where only 30% of those who need it are on treatment. When we as a community promote PrEP does it mean that we as a community take the drugs away from those who need them? I think we as a community need to promote and present PrEP better because the double stigma against their risk behaviour and against HIV is going to make it very difficult to promote.**

**YH:** how did the Global Campaign do it? We established a presence wherever the clinical trials were happening. We engaged the constituency likely to be directly affected or impacted by the trials. We did a lot of research literacy and HIV prevention literacy training, working very closely with the clinical trials sites. Most of our concerns at the time were about standards of care in those trials. We were able to be an interface between researchers and the community. We do try and go into natural communities as much as possible instead of creating ones. Our primary constituency was always women, but you can't always access women. Sometimes

we first have to talk to men, to traditional leaders, and get permission for meeting to women.

Regarding competition, what I hear from funders is “we don’t dictate research, the researchers come to us with proposals and we fund that,” but I think other things come into it such as government agendas. If industry had got involved in developing microbicides, I wonder if we would have one now. Certainly if companies had been involved we would be testing lots of drugs.

Audience question: How about post-exposure prophylaxis (PEP)? We don’t have data on how long you need to take it for or on what the dosage should be. It should be included as part of comprehensive prevention but we need to know how to use it best.

**GC:** We do know PEP works, it’s about 80% effective, and we do have the evidence, from carefully-conducted prospective cohort trials. They’re not RCTs because you cannot ethically give someone a placebo if a high-risk exposure to HIV has already happened. The best study found about 80% reduced incidence in people with a high risk exposure who had taken PEP, compared to what you would expect if they had not taken PEP. But it also found no overall reduction in HIV incidence amongst the trial participants. This is because people may take PEP once for, say, every ten times they expose themselves to HIV. That’s because PEP is hard to get, you have to go to a clinic, and it’s inconvenient, you have to take it for a month. But it’s also because people don’t think they’ve been at risk. That’s why we need PrEP, because PrEP would just kind of be *there*, ready to be taken.

One comment on the treatment versus prevention debate. Yes, resource limitations are going to be the big thing in HIV in the next few years and yes, we are going to have to keep on campaigning as hard as we can for treatment provision. But in terms of what’s being spent at the moment, what’s being spent on prevention trials is a little dribble compared to the drug treatment budget: \$100 million compared with several tens of billions.

## Industry roundtable

The Panellists for the industry roundtable were Peter Williams (PW), Janssen, Compound Development team leader, rilpivirine; Jim Rooney (JR), Gilead, Medical Affairs department, clinical trials in the developing world; Alex Rinehart (AR), ViiV, Global Strategy Group for maraviroc; and Emilio Fumero (EF), MSD, European Medical Manager for HIV.

### Statements:

#### EF

The only commercial drug MSD has is raltegravir. We have not set a specific scientific plan to address PrEP till now; but are fully committed in this area. We have candidates but have not as yet put any forward for PrEP. We have just held a meeting with scientific leaders and the community to get an idea of clinical needs and gaps. The company fully needs to understand clinical basic research data.

#### PW

Tibotec is involved in dapivirine (TMC120 - DPV) and the IPM programme. The long acting formulation of rilpivirine is in early clinical development. Darunavir (DRV) is available for combination with DPV to the CHAARM programme, who are looking at a RPV and DPV gel.

#### AR

We are working with IPM on maraviroc (MVC), both as a gel and in a ring. We have received quite a few proposals for the use of MVC as an oral agent for PrEP and are engaged with one of the trial networks in the US looking at MVC for oral PrEP.

#### JR

We are of course working with current trials supplying tenofovir (TDF) and *Truvada* (TDF/FTC). If efficacy is proved, the next step will be comparing the efficacy of daily versus single versus two-dose strategies. How will we translate a strategy that's been proven in a clinical trial into the field? You can't test for HIV every month, for instance. What will regulators require? One, two additional studies? Research dollars may fall far short of what will be necessary.

Audience question: **Why don't you pay for microbicide/PrEP trials?**

**JR:** Gilead has supported prevention studies containing about 20,000 patients. We have provided drugs worth about \$10m at cost and \$100m at market value. There's a plan in most of these studies to carry on with a follow-on study if they prove efficacious. I think that's our key role and will be if the strategy is approved.

Audience question: **Let's say hypothetically that IPrEX finds PrEP 75% effective. What then?**

**PW:** We'd have a general commitment to making compounds available to researchers who have a question to answer.

**EF:** We'd still need to understand more about pharmacokinetics, about the development of resistance, and so on.

**AR:** We have 3-4 drugs with different mechanisms of action. Just because one comes to market does not mean we stop researching others.

**JR:** When the first studies of AZT came out we thought great, we have something that has an effect, but it became obvious that the survival benefit was not as good as we'd hoped for. It took about nine years more till we came up with HAART – and we needed to invent viral load testing in the process. The same will apply to PrEP. The first question people will ask is: how can we make it better?

Audience question: **Are you willing to give your compound free to my trial? Even if it's not your compound that ends up being tested?**

**Scott Purdon, ViiV:** On a case-by-case approach we'd be prepared to deliver just our drug, or the drug plus delivery technology in principle.

Audience question: **It seems to me that Pharma doesn't have a business model for PrEP. What happens if an out-licensed drug is successful and you still hold the patent for treatment? Such a situation may well come up in next few years.**

**Jens van Roey, Janssen:** With Tibotec/Janssen and IPM we have been very clear. In principle IPM has all the rights in the territory, the territory being the developing world. In non-territory, namely the USA, Europe, Japan, Australia, Tibotec will license it back and pay IPM a royalty. IPM must use the royalty for ongoing research. We will also pay the costs of development. We don't have to buy back royalty.

**AR:** The agreement for maraviroc is similar.

**JR:** There is already an agreement to provide TDF/FTC at the lowest price possible. That's because there are funders like the Global Fund and PEPFAR to pay for this. In case of TDF gel, it's their responsibility to carry it forward. The challenge will be to show someone else it's a viable business model and that they will be willing to make and sell a gel. Whoever manufactures it also has to do the regulatory work. Then you have to find qualified distributors.

Audience question: **I didn't hear a commitment on treatment for seroconverters. 'Refer to programme' is not good enough, researchers have a responsibility to them.**

**AR:** Industry so far has not taken responsibility for trials and for seroconverters.

**EF:** In the STEP vaccine trial, MSD did work with our partners to follow-up seroconverters and arrange treatment as and when needed.

Audience question: **Is Gilead going to seek an indication for prevention? And are the other companies going to seek an indication?**

**JR:** With respect to registration as preventative drug, yes we will seek it. But labelling for prevention is complex. Oral TDF is already used for the prevention of mother-to-child transmission: guidelines have traditionally been set by the normative agencies (e.g. WHO) rather than being put on a label. In the case of PrEP we are in ongoing discussions with regulators. Many countries may not feel it's necessary.

**AR:** If oral maraviroc turned out to be efficacious then yes, we'd be very interested in seeking an indication for that. But working with regulatory agencies is a multi-year process. We can't go in blindly without guidance from the regulator.

**Leonor, EMA:** Gilead and all companies are welcome to come to us for advice and we are already in discussions about labelling for prevention.

Audience question: **Is there any possible knock-on effect on pricing if ARVs are used for prevention?**

**JR:** We have and are establishing partnerships with generics manufacturers to bring down price as low as possible.

Audience question: **Are you going to pursue tenofovir for HSV-2 prevention?**

**JR:** We're digesting the data...probably by the first part of next year we'll have made a decision on a continuing research programme for HSV-2.

### **David Haerry: Final summary**

Have the meeting goals been answered? I have noted down a few issues I think need to be rolled forward as advocacy points, but I've no doubt there will be more issues arising out of this meeting.

1. We need an efficacy trial of intermittent PrEP, especially of single-dosing.
2. Different dosing/formulations/regimens need to be researched.
4. We hope to be certain how to handle and interpret data from trials and need to collaborate with AVAC. We need to be able to cope with demands for marketing if we get good efficacy.
- 5: Yes, we have started dialogue with EMA.
- 6: We don't have a health technology assessment body in Switzerland but I liked the presentation on NICE and I am glad to hear they are interested in getting modelling on the economic feasibility and efficacy of prevention methods.