Advancing HIV prevention science: the roads from Cape Town

At the recent HIV Research for Prevention 2014 (HIV R4P) conference in Cape Town, South Africa, almost 1400 researchers from around the world came together to discuss advances in biobehavioural HIV prevention science. The rationale for this first-time meeting was that investigators need to understand the latest research findings from a wide array of disciplines, if the most promising approaches to HIV prevention can be transformed into sustained, cohesive responses that will arrest the pandemic.

In the few years since the HPTN 052 trial showed that earlier initiation of antiretroviral therapy for HIV-infected people decreased HIV transmission to their serodiscordant partners,1 the concept of “treatment as prevention” has been popularised.2 Annualised global HIV incidence has decreased by a third annually since the height of the epidemic from more than 3 million to about 2 million cases per year.3 Four large community-randomised studies are underway in South Africa, Botswana, Zambia, Kenya, and Uganda to understand the population-level impact of earlier antiretroviral treatment combined with other evidence-based prevention services.4 However, initial successes have been followed by subsequent increased HIV spread in some populations. Favourable or stable national trends could mask rising HIV incidence in key populations—i.e., men who have sex with men (MSM), sex workers, people who inject drugs, vulnerable youth—often due to decreased access to services because of stigma and discrimination.5 Despite annual HIV incidence decreasing over the past decade, with several million new infections a year, and with declining mortality among people living with HIV, the epidemic continues to grow.6 Expansion of treatment is an appropriate aspiration, but research to optimise other prevention approaches remains necessary.

During the past 5 years, seven efficacy trials of oral or topical tenofovir-based regimens used for pre-exposure prophylaxis (PrEP) to prevent HIV acquisition have been completed, with five showing efficacy.6-10 Efficacy studies in diverse populations now show that chemoprophylaxis works, but many factors can limit adherence.11-12 Investigators have learned that in trials that did not show PrEP efficacy11-12 some participants who enrolled in PrEP trials were motivated by economic and medical incentives, did not perceive themselves at increased risk for HIV, or did not trust researchers.13 Just before and during HIV R4P, two newer PrEP studies, PROUD4 in the UK and IPERGAY5 in France, announced they were moving MSM participants from the control conditions (waiting list or placebo) to receive tenofovir-emtricitabine because interim analyses showed incontrovertible efficacy of tenofovir/emtricitabine as PrEP, adding new evidence that PrEP can become an important prevention tool. Further research is underway to develop culturally tailored programmes to enhance adherence for those who can most benefit from PrEP. Careful assessment of pharmacological and behavioural patterns will lead to recommendations for optimised use of PrEP, with the possibility of less than daily dosing.16

Other methods of prevention discussed at HIV R4P included topical gels and intravaginal rings, which have been investigated as ways to minimise systemic antiretroviral exposures, and could be co-formulated with hormonal contraception to provide dual protection. In the next few months, the FACTS trial, a new topical tenofovir gel efficacy study, will be completed in South Africa to determine if the findings of CAPRISA 0049 can be replicated; if successful, the results should facilitate the path for licensure of the first vaginal microbicide. This advance would provide additional impetus for efficacy studies of rectal tenofovir gel to protect those who engage in anal intercourse.
Two efficacy studies of intravaginal dapivirine rings, the ASPRIE and RING studies, will be completed within the next 2 years, and, if successful, will offer another method of HIV prevention. Two long-acting partermally administered antiretrovirals, dapivirine and cabotegravir, are in early clinical trials, and could obviate the need for daily adherence. Over the next few years, chemoprophylaxis will provide various options for HIV prevention, analogous to birth control.

A safe and effective vaccine still remains the Holy Grail for an “AIDS-free generation,” and although no breakthroughs were announced at HIV R4P, the presentations reflected increasing optimism that progress is being made. The finding in the Thai RV 144 trial that a combination of a canarypox vector boosted by HIV envelope antigens was associated with a 31% reduction in HIV transmission has led to new insights about the correlates of protection, suggesting that non-neutralising antibodies might play an important part in the prevention of HIV transmission by facilitating cell-associated cytotoxicity, enhancing phagocytosis, or by other mechanisms that need further elucidation. An efficacy trial of a Clade-C optimised combination vaccine regimen is planned to be conducted in South Africa.

The HIV R4P meeting also highlighted the role that broadly neutralising antibodies (BNAbs) might have in HIV prevention. Several antibodies have been isolated from long-term non-progressors, rare HIV-infected individuals who retain virological control after living with HIV for decades. More recently, researchers have postulated that BNAbs might be administered for immunoprophylaxis. Early studies of parenteral BNA administration have shown safety, and efficacy studies of passive immunoprophylaxis are being planned for African infants born to HIV-infected, treatment-naive mothers and for high-risk HIV-uninfected populations. The current generation of BNAbs may not have sufficient potency, breadth, and duration to merit licensure, but proof that the administration of BNAbs could decrease HIV incidence would be a major advance for the field, since vaccine candidates could be developed using the results as benchmarks, and newer, more potent BNAbs could also be developed for immunoprophylaxis.

As highlighted at HIV R4P, resources for HIV prevention are a major concern. Until each method of prevention has well-established correlates of protection, the optimal way to show efficacy is to undertake randomised, controlled trials. HIV transmission is not efficient, and since counselling trial participants attenuates the risk of HIV acquisition, thousands of volunteers are needed for each efficacy trial. This means that the costs from bench to deployment for each new product are many million dollars. HIV R4P delegates left Cape Town with renewed optimism, along with the hope that funders and the public will understand that much more research needs to be done to optimise HIV prevention.

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KM has received unrestricted research and educational grants from Gilead, Viiv, and Bristol-Myers Squibb.

PROUD study interim analysis finds pre-exposure prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men in the UK

16 October 2014

An interim analysis of the PROUD study data has shown that pre-exposure prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men (MSM) at high risk of infection. On this basis, the PROUD Trial Steering Committee has announced that participants currently on the deferred arm of the study, who have not yet started PrEP, will be offered the opportunity to begin PrEP ahead of schedule.

PrEP involves HIV-negative people taking antiretroviral drugs (that are usually used to treat HIV) to reduce their risk of becoming infected if they are at high risk of exposure to the virus. Placebo controlled trials have already shown that PrEP works to protect against acquiring HIV and that protection is best when the daily tablet is taken consistently. Currently PrEP is only available in England through the PROUD study. There are still a number of outstanding questions about real-life effectiveness and the costs of implementing PrEP in the UK:

- Does PrEP reduce HIV, taking account of changes in risk behaviour and adherence?
- Are most-at-risk UK MSM interested in PrEP as additional protection against HIV?
- Will they take the tablets regularly enough to protect themselves?
- What effect will taking PrEP have on their sexual risk behaviour?
- Will resistance be a big problem in any breakthrough HIV infections?
- Will PrEP be cost-effective in the UK?

The PROUD study was designed as a pilot to find out if it would be feasible to conduct a larger study to answer these questions. The fact that the study has been able to address this question after enrolling only 545 MSM implies that PROUD recruited men at higher risk of HIV than expected, and the level of protection from PrEP was high.

The PROUD study includes HIV-negative gay men, other men who have sex with men, and transgender women, who reported having anal sex without condoms recently. Each participant was randomised to either start PrEP (a daily Truvada tablet) straight away (the immediate arm), or after 12 months in the study (the deferred arm). All participants are offered regular testing for HIV and sexually transmitted infections, condoms and safer sex support.
PrEP approaches for Truvada based regimens in studies:  IperGay & PROUD

The PROUD Study  Examining the impact on gay men of using Pre-Exposure Prophylaxis (PrEP)  PROUD Study Summary  The two-year study will recruit volunteers across England, who will be placed at random into one of two groups. One group will use PrEP from the start of the study, and the other group will receive PrEP after 12 months. Both groups will receive support to remain HIV negative throughout the study. Participants are asked to keep a short daily diary, fill out a monthly questionnaire and attend a clinic appointment every three months. This study is looking at a new way to reduce the risk of getting HIV. It will look at the impact of taking PrEP on how often men have sex; how often they use condoms; and whether they get other sexually transmitted infections.

Social Science Component:  In addition to completing questionnaires and daily diaries, we will ask approximately 50 men enrolled in the PROUD pilot study to take part in one-to-one discussions and around another 80 men to take part in one of approximately ten group-discussions.

From the one-to-one discussions, we want to understand factors that could influence the uptake of PrEP, how men will use PrEP and how using PrEP will influence men’s sexual behaviour and sex lives more generally. From the group discussions, we want to understand factors that could influence other men to join a larger PROUD trial in the future or influence them to leave the PROUD study early, as well as finding ways to improve the study. The discussions will be very interactive and men will be encouraged to talk freely about the PROUD study and their experiences with PrEP. For more detailed information about the one-to-one and group discussions and what is involved in taking part, please read the Supplementary Participant Information Sheet and Supplementary Informed Consent form.

The discussion guides were developed by the social science advisory group (SSAG) which comprises researchers working in HIV prevention research in England, Scotland and France.

10/30/2014 Why the IPERGAY Study Could Substantially Increase Use of PrEP  the IPERGAY study of intermittent pre-exposure prophylaxis (PrEP) was stopped early by the Data Safety Monitoring Board, and for the best reason – the evidence demonstrating that it prevented HIV was overwhelming. here’s the official announcement. (Scroll down for the English.) And for those who can’t believe the name, it stands for “Intervention Prophylactique pour Et avec les Gays”.

Here’s a short English version of the study: IPERGAY was a randomized trial of intermittent, “on demand” PrEP vs placebo done in high risk, HIV negative, men who have sex with men (MSM) in France and Canada. The specific strategy tested was:
• Two tablets of tenofovir/emtricitabine (Truvada) from 2-24 hours before sex
• One tablet 24 hours later
• Another tablet 24 hours after that one

So a total of 4 tablets over 3 days for episodic sexual activity, with an option for daily use for more frequent exposures.

We saw the pharmacokinetic data from IPERGAY in Melbourne, which showed that this strategy generated blood levels of tenofovir highly predictive of protection, and that appears to be borne out in these results. The full study detail are not yet available, but encouragingly they are reported to be better than iPrEx (the first study of PrEP in MSM). These results, along with the PROUD trial done in Britain — also stopped early for efficacy — substantially strengthen the data for PrEP in MSM. So will the results increase the prescribing of PrEP? Even though the FDA has only approved it for daily use for prevention? I say it will, and here’s why:

1. Patients have been asking about intermittent “on demand” dosing since the first day people were even thinking about PrEP.
2. Even though iPrEx was a study of daily PrEP, it appears that many study subjects were taking it intermittently — and still were protected if they got drug levels correlating with 4 or more pills/week.
3. Compared with daily dosing, this IPERGAY strategy will cost less.
4. It will also reduce drug exposure, and hence likely toxicity.
5. No one can say “IPERGAY” without smiling. Said with a French accent, of course.


One Response to “Why the IPERGAY Study Could Substantially Increase Use of PrEP”


While we wait for the actual results, it is also interesting to note that the Melbourne abstract showed a median of 2 sex events per week. That would result in 4 or more doses of Truvada per week. In the iPrEx OLE (daily dosing), 4 or more doses per week is associated with high protection. Ipergay “on demand” dosing may turn out to be very close to daily dosing in the many men frequently having sex. The true test of “on demand” will be to evaluate protection in those men who had infrequent sexual events — those where they are relying on only the 4 doses for protection without carryover drug levels from recent dosing for another sexual event.
Press release

A SIGNIFICANT BREAKTHROUGH IN THE FIGHT AGAINST HIV/AIDS

A drug taken at the time of sexual intercourse effectively reduces the risk of infection

The ANRS IPERGAY trial demonstrates the effectiveness of a preventive treatment (antiretroviral treatment) against HIV/AIDS when taken at the time of sexual intercourse. All trial participants will now benefit from this prophylaxis.

More than 6000 people discover their HIV status in France each year. Sexual transmission accounts for 99% of these infections. It is therefore an urgent priority to develop new prevention approaches especially for the most at-risk groups to be infected. Men who have sex with men (MSM) represent 42% of these new cases, and are therefore a key population to target.

Over the last couple of years, several research teams around the world have tried an original approach for prevention seeking to reduce the risk of HIV infection using antiretroviral drugs. The concept of pre-exposure prophylaxis, or PrEP, using daily antiretroviral drugs has so far shown mixed results in the different populations studied.

The IPREX trial among MSM showed that the HIV infection rate was reduced by 42% among those using daily PrEP with two antiretroviral drugs (tenofovir / emtricitabine: Truvada®) as compared to those receiving a placebo. More recently, the PROUD study conducted in MSM in the UK randomized participants to either immediate or deferred PrEP (after one year) using daily Truvada®. The PROUD data safety monitoring board (DSMB) recommended, on October 16 2014, to give daily PrEP to all trial participants in the deferred arm in light of interim results showing that PrEP was "highly protective against HIV." No detailed data were shown in this announcement.

The ANRS IPERGAY trial:
The ANRS (France REcherche Nord&Sud Sida-hiv Hépatites) IPERGAY trial differs from the other two trials by using "on demand" prophylaxis only at the time sexual intercourse. Coordinated by Professor Jean-Michel Molina (University Paris-Diderot Paris 7, and Saint-Louis hospital, Paris), the trial began in February 2012 in MSM at high risk of HIV-infection. As part of a global and combined prevention framework, a package of measures are offered to the participants (personalized and frequent counseling, repeated HIV testing, screening and treatment for other sexually transmitted infections, hepatitis B vaccination, condoms and gel distribution). Participants were randomized in two groups: one group received on demand Truvada®, the other group its placebo. Tablets, provided by Gilead laboratories, are taken at the time of sexual intercourse. This double-blind trial (neither the participants nor the doctors know the treatment received) is being conducted in France with more than 400 volunteers (Paris: Saint-Louis hospital and Tenon hospital. Lyon: Croix-Rousse hospital. Nantes: Hôtel-Dieu
university hospital. Nice: Archet hospital. Tourcoing: Gustave Dron hospital) and Canada (Montreal university hospital). The trial particularity also relies on the active participation of the AIDES community group and close collaboration with a community advisory board comprising several gay community groups.

Following the decision taken by the PROUD team to give daily Truvada® to all participants, the ANRS urgently contacted the IPERGAY trial data safety monitoring board (DSMB).

The recommendation given to the ANRS

The ANRS IPERGAY’ DSMB exchanged with its counterpart of the PROUD trial. The DSMB then examined the "unblinded" data from the ANRS IPERGAY trial, i.e. examined the incidence rate of HIV infection (number of new cases) in the two groups of participants (the group receiving "on demand" Truvada® and the group receiving its placebo).

The DSMB found a significant difference in incidence between the two groups with a very significant reduction in the risk of HIV infection in the on demand PrEP group, much higher than the one observed in the IPREX trial. The DSMB therefore recommended that all trial participants will benefit from "on demand" Truvada®.

The ANRS decision

This recommendation was immediately endorsed by the ANRS and by the trial Scientific Committee. The ANRS decided:

- Truvada® will be made available to all participants of the ANRS IPERGAY trial. Participants will be contacted to make an appointment as soon as possible at their trial site.

- Regulatory and ethical procedures related to this change will be implemented and trial partners and health officials informed.

The full results of the ANRS IPERGAY trial should be available early 2015. The trial will continue for at least a year. It is indeed important to ensure the continued long term benefit of "on demand" PrEP and also assess its long-term safety.

According to Professor Jean-Michel Molina: "The biomedical concept of on demand PrEP at the time of sexual exposure, in a broader prevention framework, is validated. We owe it to all trial volunteers without whom we could never have achieved these results". He adds: " We must not forget that condoms remain the cornerstone of HIV prevention. Combining all prevention tools that have proved to be effective will certainly allow us to better control the HIV/AIDS epidemics ".

According to Professor Jean-François Delfraissy, Director of ANRS, "This is a major breakthrough in the fight against HIV. The results of the ANRS IPERGAY trial should change national and international recommendations towards HIV prevention".

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HIV RESEARCH FOR PREVENTION
Shaping the Science of Prevention
Cape Town, South Africa 28-31 October 2014

http://webcasts.hivr4p.org/yi/2014/28?link=nav&linkc=date

Preclinical Evaluation of TMC-278 LA, a Long-acting Formulation of Rilpivirine, Demonstrates Significant Protection from Vaginal HIV Infection
Olivia Snyder......http://webcasts.hivr4p.org/console/player/25019?mediaType=audio& UNC Chapel Hill, Chapel Hill, NC, United States

HIV PrEP Dose Rationale for Cabotegravir (GSK1265744) Long-acting Injectable Nanosuspension
Bill Spreen..........http://webcasts.hivr4p.org/console/player/25020?mediaType=audio& GlaxoSmithKline R&D, Research Triangle Park, NC, United States

ICAAC/2014: GSK Long-Acting ART Integrase inhibitor - Cabotegravir Injected Every 1, 2, or 3 Months Yields Adequate Troughs in Simulation - (09/09/14)


"GSK744 LA has afforded high---level protection against repeated intrarectal SHIV challenges in rhesus macaques......plasma concentrations >3X PAIC90 result in 100% protection.....plasma levels corresponding to protection can be readily achieved in man with quarterly 800mg intramuscular injections......These data support moving GSK744 LA into clinical evaluation as PrEP in high-risk men who have sex with men - Phase 2 safety and tolerability studies commence in Spring 2014....These data support the evaluation of GSK744 LA as PrEP in other challenge models - Low---dose intravaginal (40LB see link to this CROI webcast below) and high---dose intravaginal (941LB)"

Tenofovir Reservoir Intravaginal Rings Provide Superior Pharmacokinetics and Higher Sustained Drug Levels than Tenofovir Matrix Rings
Meredith Clark CONRAD Eastern Virginia Medical School, Arlington, VA, United States

A Combination Vaginal Ring Releasing Dapivirine and Darunavir
Diarmid Murphy......http://webcasts.hivr4p.org/console/player/25022?mediaType=slideVideo& Queen's University Belfast, Belfast, United Kingdom

Rectal Specific Gels Containing Maraviroc and/or Tenofovir Protect against Rectal SHIV Transmission in a Macaque Model
Walid Heneine.......http://webcasts.hivr4p.org/console/player/25024?mediaType=slideVideo& Centers for Disease Control and Prevention, Atlanta, GA, United States
Conclusions

- Successful co-formulation of dapivirine and darunavir in matrix-type silicone elastomer vaginal rings
- Both drugs were released in cynomolgus macaques
- Vaginal fluid levels
  - $2 \times 10^3$ – $2 \times 10^5$ ng/g for both drugs
- Serum levels
  - $2 \times 10^1$ – $3 \times 10^2$ pg/ml for both drugs
- Tissue levels
  - Vagina: $1 \times 10^3$ – $5 \times 10^3$ ng/g
  - Cervix: $1 \times 10^2$ – $4 \times 10^2$ ng/g
- Vaginal fluid levels well above in vitro EC$_{50}$ for both drugs

Ongoing work

- Smaller ring sizes
- Additional PK studies
- Challenge studies
Conclusions

- PK analysis revealed rapid drug absorption and tissue dosing from rectal specific gel formulations
- Demonstrated that both 1% MVC and 1% TFV gel are highly protective (~82%) against rectal SHIV infection
- The protection by MVC gel is likely attributed to the >2 logs MVC concentration in rectal tissues than levels achieved by oral dosing
- 1% MVC gel efficacy similar to 1% TFV despite ~1000 higher potency of MVC