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The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review

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Purpose of review
Public health experts are wrestling with how to translate recent scientific findings from pre-exposure prophylaxis (PrEP) effectiveness trials into real-world programmes. This review summarizes clinical trial findings on oral and topical PrEP, discusses how decision-makers can evaluate the place of PrEP within combination prevention and highlights anticipated developments that could be important in future HIV-prevention strategies.

Recent findings
PrEP taken daily as oral tablets to create systemic protection has been found to be effective in the Pre-Exposure Prophylaxis Initiative (iPrEx), Partners’ PrEP and TDF2 trials, but not in Fem-PrEP or the Vaginal and Oral Interventions to Control the Epidemic (VOICE) tenofovir arm. Tenofovir gel for topical protection was effective in CAPRISA 004 when used peri-coitally but not in VOICE with daily use. These findings underscore the importance of adherence to achieve adequate drug levels and the potential additive role of PrEP within combination prevention. Pivotal phase III trials are underway of the dapivirine ring, whereas phase I trials of injectable formulations show promise.

Summary
Antiretroviral-based HIV-prevention programmes should be tailored to those most likely to be adherent, providing them with state-of-the-art counselling and support to achieve high adherence during the time period of use. Long-acting products, if found well tolerated and effective, could be ideal for overcoming adherence challenges.

Keywords
combination HIV prevention, pre-exposure prophylaxis, programme implementation, tenofovir

INTRODUCTION
An estimated 2.2 million individuals acquired HIV infection in 2011 [1], making it paramount to expand HIV-prevention choices for people worldwide. Pre-exposure prophylaxis (PrEP) for HIV is the use of antiretroviral drugs to prevent HIV acquisition [2]. The concept of chemoprophylaxis using the same product for prevention as for treatment is not novel. Travellers to malaria-endemic areas use drugs to prevent malaria and antiretroviral prophylaxis is proven to prevent mother-to-child HIV transmission [3–5]. There is now a growing body of evidence that PrEP, as oral tablets and injections to create systemic protection or gels and rings applied vaginally or rectally for local topical protection, in combination with safer sex measures, is effective in preventing sexual transmission of HIV.

Although early trials of vaginal microbicides [6–8] were not successful, they provided a foundation for subsequent efforts, culminating in proof-of-concept results for a vaginal gel containing the
Biomedical HIV prevention options have expanded recently. Voluntary medical male circumcision (VMMC) reduces HIV transmission from females to males by about 60% [14–16], with scale-up underway in countries with predominantly heterosexual epidemics [17]. Treatment of HIV-positive persons decreases circulating HIV levels, thereby reducing onward transmission [18]. Building on the backbone of behaviour change, male and female condoms, and structural interventions, combination prevention strategies incorporating novel biomedical modalities could bring about an HIV-free generation.

Public health experts are wrestling with how to translate scientific findings from PrEP effectiveness trials into real-world programmes. This review summarizes clinical trial findings on oral and topical PrEP, discusses how decision-makers can evaluate the place of PrEP within combination prevention and highlights anticipated developments that could be important in future prevention strategies.

### TOPICAL AND ORAL PRE-EXPOSURE PROPHYLAXIS: WHAT DO CLINICAL TRIALS REVEAL ABOUT EFFECTIVENESS?

The South African Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial among 889 women reported the first positive PrEP findings in July 2010. Overall effectiveness of 1% tenofovir vaginal gel used before and after sex was 39% [hazard ratio 0.61; 95% confidence interval (CI) 0.40–0.94; P = 0.017], increasing to 54% for women who reported using the product as instructed for more than 80% of their sex acts (P = 0.025) [9]. Threshold tenofovir diphosphate concentrations for protection are unknown, but a case–control analysis revealed that women with cervicovaginal fluid concentrations above 1000 ng/ml had a 74% lower risk of HIV acquisition than women in the placebo arm [19].

In November 2011, the 5000-women Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial’s Data Safety Monitoring Board (DSMB), however, recommended stopping the tenofovir gel arm early for lack of efficacy [20]. Conducted in South Africa, Zambia and Zimbabwe,
VOICE tested 1% tenofovir gel used daily, whether or not sex was anticipated or had occurred. Only after study completion will data analysis indicate whether women used the gel and it provided no protection or they simply did not use it.

The South African Follow-on AIDS Consortium of Tenofovir Studies (FACTS) 001 trial enrolling 2900 women uses the same peri-coital dosing as CAPRISA 004 [21]. The US FDA considers FACTS 001 the second pivotal trial needed for licensure of coital-use 1% tenofovir gel and has agreed to fast track approval should it confirm a reduction in women’s risk of HIV acquisition [22]. Meanwhile, CAPRISA 008 is exploring the acceptability and feasibility of offering tenofovir gel in family planning clinics to CAPRISA 004 participants.

Trials of oral PrEP for HIV have also had mixed results. The Pre-Exposure Prophylaxis Initiative (iPrEx) trial in Brazil, Ecuador, Peru, South Africa, Thailand and the US evaluated daily oral TDF/FTC in 2499 HIV-negative men or transgender women who have sex with men. Recruited participants were considered at higher risk for HIV exposure because they used condoms inconsistently or not at all during sex with a partner of positive or unknown HIV status, had high numbers of sex partners or exchanged sex for commodities. They were randomized to once-daily TDF/FTC versus placebo. Whereas the overall reduction in risk was 44% (95% CI 15–63), plasma and intracellular drug levels among those in the active arm differed: 8% of seroconverters versus 54% of nonseroconverters had detectable drug [23]. Those who took the pills were almost 13 times less likely to seroconvert than those with no drug detected (OR 12.9; 95% CI 1.7–99.3); a 92% reduction in HIV acquisition risk (CI 40–99%). On the basis of the iPrEx findings, the US Centers for Disease Control released interim clinical guidelines for similar patients [24]. A post-trial implementation study, iPrEx-open label extension (OLE), is gathering ‘real-world’ information on ways to improve adherence while reducing HIV testing frequency to quarterly, rather than monthly, as in the trial. It will determine whether knowledge of PrEP effectiveness stimulates improved adherence, thereby reducing the risk of HIV acquisition, or leads to behavioural risk compensation, that is an altered perception of risk associated with more risky sexual behaviours [25].

In July 2011, the DSMBs of two trials, the Partners’ PrEP trial in Kenya and Uganda among 4758 serodiscordant heterosexual couples (one partner was HIV-positive and one was HIV-negative) and the Botswana TDF2 HIV Prevention Study (TDF2) trial in Botswana among 1219 heterosexual men and women, recommended revealing their results publicly. TDF/FTC taken daily reduced HIV risk by 62% (95% CI 23–83; \( P = 0.03 \)) in TDF2 [26\*] and by 75% (95% CI 55–87; \( P < 0.001 \)) in Partners’ PrEP [27\*]. The TDF-only arm of Partners’ PrEP found a 67% (95% CI 44–81; \( P < 0.001 \)) reduction in risk. Whereas TDF2 is offering TDF/FTC to all participants after the trial, Partners’ PrEP, having found no significant difference between TDF alone and TDF/FTC, has randomized placebo recipients to the two active arms. Of note, the TDF2 trial was underpowered to show differences in PrEP effectiveness between men and women, whereas the Partners’ PrEP trial found no significant difference by sex.

In contrast, the VOICE trial closed its oral TDF arm for futility in September 2011 [28] and the completed Fem-PrEP trial, conducted among 2120 HIV-negative women in Kenya, South Africa and Tanzania, found that TDF/FTC taken daily did not protect women. Although 95% of women in both arms of Fem-PrEP reported that they usually or always took their pills and pill counts suggested that study drug was taken on 88% of days, only 15% of seroconverting women had target plasma drug levels at either end of the infection window. The investigators concluded that the study could not evaluate PrEP effectiveness due to poor adherence [29\*].

KEY ISSUES IDENTIFIED IN THE CLINICAL TRIALS

Among the key issues that clinical trials conducted to date have identified are adherence, drug resistance, behavioural risk compensation and safety.

Adherence

Although differences in the populations studied, sexual behaviours, genital mucosa integrity and other co-factors for HIV acquisition plausibly contributed to the divergent trial results; low levels of actual use leading to inadequate drug concentrations in the genital tract was clearly a key factor [30\*,31\*,32\*]. Whereas self-reported medication use and pill counts were generally unreliable across the trials, there was a clear relationship between detectable drug levels as a marker of adherence and outcome. In Partners’ PrEP, a medication event monitoring system (MEMS) and unannounced household visits, along with partner support, achieved the highest adherence levels. Drug was detected in 82% of 902 samples from a random sub-group of 198 active-arm participants who did not acquire HIV. Relative risk reductions were 86% with detectable TDF and 90% with detectable
TDF/FTC in Partners’ PrEP [27**] and 92% with detectable TDF/FTC in iPrEx [23].

It remains to be seen which of the adherence support measures used in the clinical trials can be effective in PrEP roll-out, but iPrEx found both next-step counselling and neutral assessment to be feasible, acceptable low-intensity approaches [33*]. In next-step counselling, patients are experts, with providers assisting patients to identify adherence-related needs and solutions for incorporating PrEP within the context of their lives. Evaluation is underway in iPrEx-OLE to determine whether this brief adherence-support discussion approach correlates with drug detection levels [34].

The frequency of dosing could impact adherence. However, a study using MEMS in African men who have sex with men and sex workers found lower adherence to intermittent (twice a week) and post-coital dosing than to daily PrEP [35*].

Drug resistance
No case of drug resistance was seen in trial participants who became infected after being placed on tenofovir-containing PrEP [23,26**,27**]. All five cases of resistance found in the iPrEx, Partners’ PrEP and TDF2 started PrEP with unrecognized acute infection, highlighting the critical importance of ensuring that people starting PrEP are not in the HIV-negative window period before HIV antibodies appear. These five cases occurred against a backdrop of a total of 118 infections averted in these trials. It is predicted that drug resistance from treatment scale-up will far exceed that from PrEP [36].

Behavioural risk compensation
As seen in other biomedical HIV prevention trials, reported risky sexual behaviours declined in all arms of the PrEP trials and remained lower through the trials than at baseline. However, participants received monthly counselling, HIV testing and access to condoms. Interestingly, in iPrEx, efficacy was highest in those least likely to report condom use for receptive anal sex at baseline [23], suggesting individual selection preferences for different prevention methods. Whether expectation of known benefit will lead to risk compensation remains to be seen in follow-up studies.

Safety
Adverse events among thousands of healthy, HIV-negative trial participants were not severe and generally declined after the first month [23,26**,27**]. Decreases in bone mineral density scores were seen in TDF2 [26*] and iPrEx [37], but were not measured in Partners’ PrEP or Fem-PrEP, and periods of observation were short (1–2 years). Further monitoring of the effects of TDF and TDF/FTC on bone mineral density over longer periods of use is warranted. Likewise, monitoring liver and kidney (proximal tubular) function, after establishing initial normal hepatic and renal function, will be important in longer-term demonstration projects. Although safety studies of tenofovir use in pregnancy have been generally reassuring [38–40], ongoing assessment of exposed infants to rule out longer-term effects remains important.

Next steps
As conditions of US FDA approval, Truvada’s manufacturer, Gilead Sciences, Inc., will develop an adherence questionnaire to assist prescribers in identifying individuals at risk for low adherence, evaluate viral isolates from individuals who acquire HIV while taking TDF/FTC for drug resistance and collect data on pregnancy outcomes for women who become pregnant while taking TDF/FTC for PrEP.

PRE-EXPOSURE PROPHYLAXIS AS A COMPONENT OF COMBINATION PREVENTION

The challenge for policy makers is to decide what role PrEP should play in strengthening country combination prevention programmes to meet Universal Access Targets [41] and Millennium Development Goals [42]. Combination prevention combines behavioural, biomedical and structural interventions to address both the immediate risks and underlying causes of vulnerability to HIV infection and the pathways that link them [43]. It is evidence-informed, human rights-based and context-specific. Effective prevention programmes are tailored to local epidemics, with relevant components delivered at an intensity, quality and scale necessary to achieve intended effects. The added value of systemic or topical PrEP within combination prevention will depend on its efficacy, cost–effectiveness, acceptability and the availability of resources.

In terms of population-level impact, mathematical modelling predicts that tenofovir gel used by South African women in 80% or more of sexual encounters would avert up to 2 million new infections and 1 million AIDS deaths over 20 years, with gel use as low as 25% being cost effective [44]. Studies of oral PrEP cost–effectiveness have estimated cost per HIV infection averted [45,46*,47], cost per quality-adjusted life year (QALY) gained [46*,48–52], cost per disability-adjusted life year
counts between 350 and 550 cells/ mm^3 and the positive partner began HIV treatment at CD4 cell counts by 96% among serodiscordant couples when the HIV Prevention Trials Network (HPTN 052) trial, a novel antiretroviral-based prevention strategy that also requires knowledge of HIV status. In trials of novel strategies, PrEP may be useful for the seronegative partner for the 6 months until the partner achieves undetectable viral loads on treatment. PrEP may reduce the risk of HIV acquisition per-conceptually when serodiscordant couples desire pregnancy.

Pre-exposure prophylaxis prevents acute HIV infection and its high viraemia fuelling HIV transmission, constituting primary prevention and providing partial protection, as do VMMC and consistent male and female condom use. PrEP can be complementary to early treatment for prevention (T4P), another novel antiretroviral-based strategy that also requires knowledge of HIV status. In the HIV Prevention Trials Network (HPTN 052) trial, T4P reduced genotypically linked HIV transmission by 96% among serodiscordant couples when the HIV-positive partner began HIV treatment at CD4 cell counts between 350 and 550 cells/μl. Some couples may prefer PrEP for the seronegative person to early treatment for the seropositive person. Regardless of whether treatment is initiated early or according to local treatment eligibility criteria, PrEP may be useful for the seronegative partner for the 6 months until the partner achieves undetectable viral loads on treatment. PrEP may reduce the risk of HIV acquisition per-conceptually when serodiscordant couples desire pregnancy.

The acceptability of PrEP has been assessed in populations as diverse as men who have sex with men in China, Thailand, Peru, France, Canada, the USA, and Australia; serodiscordant couples in Kenya; female sex workers in China and truck drivers in India. A study among 1790 sex workers, men who have sex with men, people who inject drugs, serodiscordant couples and young women in Peru, Ukraine, India, Kenya, Botswana, Uganda and South Africa found that respondents generally perceived that PrEP would give them further HIV prevention choices and 61% reported they definitely would use PrEP. Policy makers, healthcare workers and representatives of nongovernment organizations involved in HIV prevention in the same countries expressed appreciation of the potential benefits of PrEP in prioritizing and empowering key populations. Perceived challenges and programmatic considerations resulted in about half indicating that they would wait to see PrEP implemented in other countries before introducing it in their own. Healthcare providers interviewed in California during the year after the iPrEx results acknowledged implementation challenges, but most expressed optimism that they could prescribe and monitor PrEP in their practice.

A key consideration will be provider capacity to assist confirmed HIV-negative people in deciding whether they could adhere and when and for how long PrEP might be a good choice for them to complement condom use and other safer sex measures. As with contraceptive choices, rather than being a continuous prevention strategy, PrEP might be selected by people as circumstances in their lives change or in the context of certain sexual partnerships.

Equity and justice are key ethical issues for decision-makers wishing to avoid exacerbating existing healthcare inequalities. Universal access to antiretroviral treatment has not been achieved in many countries under existing national guidelines. Difficult decisions are required to make PrEP available for those at highest risk of HIV exposure, particularly those who are marginalized and stigmatized. At the population level, prioritization of PrEP for those at highest risk of HIV exposure will require addressing structural barriers such as stigma and discrimination, criminalization and lack of tailored healthcare delivery into which PrEP programming can be integrated. Although PrEP is not approved by national authorities other than the FDA, debate is underway on whether it should be part of the prevention package offered to all HIV prevention trial participants or as a comparator arm in trials of novel strategies.

**FUTURE DEVELOPMENTS**

The PrEP research pipeline is diversifying, in terms of candidate drugs, dosing strategies and delivery mechanisms.
Local prophylaxis
Over 70 microbicide candidates are in the preclinical development pipeline, including 35 attachment, fusion and entry inhibitors [85**,86]. The hyperosmolar properties of vaginal tenofovir gel have been modified for rectal use, with a safety and adherence phase II trial planned for USA, Peru, South Africa and Thailand [87].

Long-term controlled release dosage forms for intravaginal delivery of antiretroviral prophylaxis are the subject of intense interest among engineers and pharmaceutical scientists [88**]. Both the Microbicide Trial Network’s ASPIRE trial [89] and the International Partnership for Microbicides Ring Study [90] are pivotal phase III trials evaluating a vaginal ring that slowly releases the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine to bind to and disable HIV’s reverse transcriptase enzyme. These vaginal rings, inserted and removed by the women themselves, are flexible products that fit comfortably high up inside the vagina, are seldom felt by either partner during sex and are already widely used to deliver hormonal contraception.

Systemic prophylaxis
Findings are awaited from the phase III Bangkok Tenofovir Study, following 2413 people who inject drugs [91]. Phase II trials of intermittent PrEP with TDF/FTC are enrolling in France [92] and the USA [93] to determine whether intermittent pre- and post-exposure dosing provides comparable effectiveness with decreased pill requirements and decreased symptoms. HPTN 069 is testing the entry inhibitor maraviroc against TDF/FTC, alone or in combination [94].

Animal studies of integrase strand inhibitors [95,96] show promise and phase I trials of long-acting injectables, such as the NNRTI rilpivirine (TMC 278) [97] and the HIV integrase inhibitor S/GSK1265744 [98], have reported safety and tolerability.

Multiuse technologies
Work is proceeding to develop multipurpose technologies such as vaginal rings that avert unintended pregnancies and prevent sexually transmitted infections, including HIV [99]. In addition, considerable thought is being given to designing innovative trials to assess potentially beneficial combinations of prevention tools, such as oral PrEP provided concomitantly with an HIV vaccine. Such a combination might prevent HIV acquisition during the course of immunizations before full development of vaccine-induced immunity or might influence immune responses sufficiently during HIV exposure to increase the likelihood of vaccine protection [100*].

CONCLUSION
The incorporation of PrEP into combination HIV-prevention programming is in its formative stage [101]. Thirty years into the HIV epidemic, the current HIV-prevention armamentarium is failing to stop HIV transmission. Clearly, people need HIV prevention options for different periods in their lives as their own circumstances change. PrEP-based discreet, user-controlled protection against HIV transmitted through sex will potentially range from pills and coital gel to rings and long-lasting injectable formulations.

Tailored communication strategies accompanying PrEP introduction need to emphasize the importance of correct and consistent usage, along with the partial protection it affords, and that PrEP is additional to other safer sex strategies, including the correct and consistent use of male and female condoms. As HIV testing and counselling is scaled up, people will increasingly be able to adopt HIV-prevention strategies based on knowledge of serostatus, including the use of antiretroviral-based strategies such as PrEP and T4P. Programme planners and healthcare personnel prescribing any antiretroviral-based prevention strategy should tailor such programmes to those most likely to be adherent, providing them with state-of-the-art counselling and ensuring effective support to achieve high adherence during the period of time they use it. Long-acting products formulated as rings or injectables, if found well tolerated and effective, could be ideal for overcoming PrEP adherence challenges.

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Conflicts of interest
Catherine Hankins: no conflicts of interest.
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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 80).


This review of the pharmacodynamics and pharmacokinetics of tenofovir gel and tablets in women provides the history of the drug’s development, data on its safety, tolerability and efficacy, and a perspective on drug concentrations at sites of exposure, related to adherence, dosage and other factors, as possible explanations for divergent trial results.


FACTS001 http://www.facts-consortium.co.za/.


This randomized controlled trial conducted in Botswana demonstrated a 62% reduction in risk among 1219 heterosexual men and women at risk of HIV exposure who took daily tenofovir/emtricitabine tablets.


This randomized controlled trial conducted in Kenya and Uganda among 4758 serocordant couples had the highest adherence and the highest effectiveness levels of all PEP trials to date, demonstrating risk reductions of 67% for oral tenofovir and 79% for tenofovir/emtricitabine, rising when tenofovir was detected to 86 and 90%, respectively.


This fast track article reviews the discrepant results between topical and oral PEP trials showing efficacy and those stopped due to futility. Famvir (oral tenofovir emtricitabine) and VOICE (oral and vaginal tenofovir). Adherence is a key factor but variable drug concentration at sites of exposure, the role of acute infection and vaginal mucosal integrity for the prevention of HIV infection. Expert Opin Investig Drugs 2012; 21:695–715.

This commentary presents the pharmacodynamic and pharmacokinetic data supporting the use of antiretroviral drugs for HIV prevention, discusses possible causes of divergent PEP trial results and considers the best strategies for antiretroviral drug use to reduce HIV spread at the individual and the population level.


Neutral assessment and neat-step counselling became hallmarks of the late phase of the successful study of tenofovir/emtricitabine pre-exposure prophylaxis among men and transwomen who have sex with men in the iPrEx trial. This article presents the feasibility and acceptability of this adherence support approach that is now being employed in the open label trial iPrEx OLE.

iPrExOLEx iPrEx Open Label Expansion. (http://www.iexolex.com/iPrExOlx/index.html).

This trial randomized 67 men who have sex with men and 5 female sex workers in Kenya to daily oral PEP or intermittent PEP (Friday, Monday and within 2 h of sex) with tenofovir/emtricitabine versus daily or intermittent placebo, finding that safety was similar across all groups and acceptability was high, regardless of dosing regimen.


change among those not adhering to PrEP would counteract the cost-effectiveness.

- This 9-country trial that enrolled 1763 serodiscordant couples, randomized to have
  - viral load and CD4 count, between 350 and 550 cells/mm³, to determine the impact of PrEP and early antiretroviral therapy on HIV transmission.
  - This model of the impact of PrEP and early antiretroviral therapy assumes a 90% reduction in HIV transmission among serodiscordant couples in South Africa estimates that PrEP provided to the sero-negative partner was at least as cost-effective as early antiretroviral treatment in keeping couples alive and without a new HIV infection, if the annual cost of PrEP is less than 40% the cost of ART and PrEP is more than 70% effective.

- In an 1861 assessment of PrEP for HIV prevention for HIV-serodiscordant heterosexual couples in South Africa estimates that PrEP provided to the sero-negative partner was at least as cost-effective as early antiretroviral treatment in keeping couples alive and without a new HIV infection, if the annual cost of PrEP is less than 40% the cost of ART and PrEP is more than 70% effective.


- This model testing the population-level impact, cost, and cost-effectiveness of a PrEP programme offered to men and transwomen who have sex with men in Peru. This study showed that PrEP would not achieve a cost-effective impact of a programme tailored to those most vulnerable to HIV exposure.


- This model testing the population-level impact, cost, and cost-effectiveness of a PrEP programme offered to men and transwomen who have sex with men in Lima, Peru. This study showed that PrEP would not achieve a cost-effective impact of a programme tailored to those most vulnerable to HIV exposure.


- This model testing the population-level impact, cost, and cost-effectiveness of a PrEP programme offered to men and transwomen who have sex with men in Peru. This study showed that PrEP would not achieve a cost-effective impact of a programme tailored to those most vulnerable to HIV exposure.


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15 million on ART by 2015: a realistic target or just a dream?

92. ANRS Intervention Preventive de l’Exposition aux Risques avec et pour les GAYS. http://wwwipergayfr/.
94. HPTN 069. Phase II randomized, double-blind, study of safety and tolerability of maraviroc, maraviroc + emtricitabine, maraviroc + tenofovir or tenofovir + emtricitabine for preexposure prophylaxis to prevent HIV transmission in at-risk men who have sex with men. http://wwwhptnorg/research_studies/hptn069.asp.
This policy forum presents the rationale for conducting trials that combine HIV vaccine candidates with novel biomedical prevention technologies, including PrEP, and introduces concepts of combination implementation to create additive or synergistic effects, stimulating incremental reductions in HIV incidence.