Published in final edited form as:
AIDS. 2012 August 24; 26(13): 1585–1598. doi:10.1097/QAD.0b013e3283543e83.

Antiviral agents and HIV prevention: controversies, conflicts, and consensus

Myron S. Cohen[a,b,c], **Kathryn E. Muessig**[a], **M. Kumi Smith**[b], **Kimberly A. Powers**[a,b], and **Angela D.M. Kashuba**[d]

[a]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA.

[b]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina, USA.

[c]Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, North Carolina, USA.

[d]School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA.

Abstract

Antiviral agents can be used to prevent HIV transmission before exposure as preexpo-sure prophylaxis (PrEP), after exposure as postexposure prophylaxis, and as treatment of infected people for secondary prevention. Considerable research has shed new light on antiviral agents for PrEP and for prevention of secondary HIV transmission. While promising results have emerged from several PrEP trials, the challenges of poor adherence among HIV-negative clients and possible increase in sexual risk behaviors remain a concern. In addition, a broader pipeline of antiviral agents for PrEP that focuses on genital tract pharmacology and safety and resistance issues must be developed. Antiretroviral drugs have also been used to prevent HIV transmission from HIV-infected patients to their HIV-discordant sexual partners. The HIV Prevention Trials Network 052 trial demonstrated nearly complete prevention of HIV transmission by early treatment of infection, but the generalizability of the results to other risk groups – including intravenous drug users and MSM – has not been determined. Most importantly, the best strategy for use of antiretroviral agents to reduce the spread of HIV at either the individual level or the population level has not been developed, and remains the ultimate goal of this area of investigation.

Keywords

antiretroviral agents; HIV prevention; preexposure prophylaxis; treatment as prevention

Introduction

Antiviral agents can be used to prevent HIV transmission in three ways: before exposure as preexposure prophylaxis (PrEP), after exposure as postexposure prophylaxis (PEP), and as treatment of infected people for secondary prevention [1–3]. PEP for HIV prevention has been well established but is not well suited to clinical research investigation. However,

Correspondence to Myron S. Cohen, Institute for Global Health and Infectious Diseases, 2nd Floor, Bioinformatics Building of the University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7030, USA. Tel: +1 919 966 2536; fax: +1 919 966 6714; mscohen@med.unc.edu.

Conflicts of interest
There are no conflicts of interest.

recent research developments in PrEP and secondary prevention provide a unique opportunity to highlight areas of advancement that have galvanized changes in HIV treatment and prevention and to highlight topic areas that remain undecided or controversial.

Assessing the prevention benefits of antiretrovirals: pharmaceutical and observational studies

With the development of antiviral agents in the early 1990s, a confluence of reasoning from two disciplines emerged. Clinical pharmacological studies demonstrated that HIV drugs penetrate the genital tract but with variable success [4–8]. Epidemiologic observational studies suggested that antiretroviral therapy (ART) might play a role in reducing the sexual transmission of HIV.

Intensive investigations of the pharmacology of antiretrovirals in genital secretions have demonstrated that several drugs in different therapeutic classes of antiretrovirals reliably concentrate in the male and female genital tract (Table 1). Drug penetration can be predicted for semen by the degree of antiretroviral protein binding in blood. However, predictors of drug penetration into the female genital tract remain unknown.

The relationship between the penetration of drugs into the genital tract, suppression of genital tract replication with treatment, and the relevance of persistent HIV shedding to HIV transmission remains only partially understood. First, it is clear that persistent intermittent ‘shedding’ of HIV in both male [9–14] and female [15–17] genital secretions can be expected even when treatment has reduced the blood plasma viral load [18].

Several groups have reported detection of HIV in semen resistant to protease inhibitors [19,20], reflecting poor penetration of this class of agents. Conversely, Ghosn *et al.* [21] reported complete suppression of HIV in semen over 48 weeks with the lopinavir–ritonavir combination, even though these agents were only detectable in blood plasma and not in seminal plasma (<30 ng/ml). Inability to completely and consistently suppress replication of HIV in the genital tract in men and women demonstrates that these compartments do not get the full benefit of antiretrovirals. Indeed, quite recently, investigators have argued that the persistent low copy HIV replication might be ascribed to poor penetration or metabolism of ART in lymphoid tissues [22]. After a single dose of tenofovir, we have demonstrated discrepant penetration into cervical, vaginal, and rectal tissues, with cervical and vaginal tissue levels 10–100 times lower for tenofovir and tenofovir diphosphate than those achieved in rectal tissue [23]. Sexually transmitted diseases (STDs) can stimulate shedding of HIV in spite of antiviral therapy [24,25]. However, the results of observational reports and the HIV Prevention Trials Network (HPTN) clinical trial 052 (see below) suggest that HIV shedding (so readily observed in spite of treatment with antiviral agents) may not actually contribute much to HIV transmission.

HIV transmission among HIV-serodiscordant couples has been the subject of several observational studies [26,27]. A subset of these studies with information on index partner ART status (Table 2) allows us to consider the effects of these drugs on transmission risk [28–37]. Reduction of HIV transmission with treatment has been reported in all but one report from China. In the study from China, 1927 infected people in stable HIV-discordant couples were offered free ART [37]. Over 4918 person-years of follow-up time, similar proportions of participants who were taking antiretrovirals and participants who were not taking antiretrovirals infected their susceptible sexual partners (4.8 vs. 3.2%, $P = 0.12$). However, there is no way to judge whether, or how, the infected persons were taking their medications, and genetic tests were not performed to confirm linked transmissions within the pairs.

Attia *et al.* [26] undertook a meta-analysis that emphasized the limited data (five studies total, with a combined 1098 person-years of follow-up) available from observational studies for demonstrating transmission prevention related to ART. Nonetheless, these results, and modeling of transmission probabilities with ART (reviewed in [38]), led to the rather controversial 2007 'Swiss Statement' [39]. In this declaration, the investigators concluded – based on available data – that under particular circumstances, treated, HIV-infected persons could engage in unprotected sex acts with minimal risk of transmission to an HIV-negative partner. The Swiss Statement requirements included informed consent from the HIV-negative partner, HIV-positive partner on ART suppressed to undetectable levels of blood plasma HIV for at least 6 months, and lack of any other STDs. The Swiss people took these recommendations seriously. In an analysis conducted among 7309 HIV-infected persons in the Swiss HIV Cohort Study, after the Swiss Statement was issued, participants were 1.24–2.04 (varied by risk group) times more likely to report unprotected sexual contacts [40].

Clinical trials in stable heterosexual couples and generalizability to other contexts

To determine the magnitude and durability of a prevention effect from ART, a randomized controlled trial was conducted by the HPTN [41]. In the HPTN 052 trial, 1763 sexually active HIV-discordant couples (in a stable relationship over the past 3 months reporting vaginal or anal intercourse at least three times during that period) were recruited from 13 sites in nine countries. At enrollment, the HIV-positive participant was required to be ART-naive and have a CD4 cell count between 350 and 550 cells/μl; individuals with active tuberculosis were excluded. Participants were randomized to start ART at study enrollment (early therapy) or after two consecutive CD4 cell count measures less than or equal to 250 cells/ml and more than 200 cells/μl (delayed therapy). The history of the HPTN 052 trial has been previously reported [42]. The HPTN 052 study is ongoing and scheduled for completion in 2015. However, because of the overwhelming benefits of ART observed in the first 1.7 years of average follow-up, the National Institutes of Health (NIH) Multinational Data Safety Monitoring Board (DSMB) recommended on 28 April 2011 that the sponsor (NIH) make the interim results available. The individuals in the early treatment arm had greater than 96% protection from HIV acquisition from their HIV-infected partner [41]. The single HIV transmission event in the treated group was ascribed to transmission before HIV suppression was possible (Jabara, Ping, Swanstrom, personal communication). Individuals in the early arm had reduced episodes of opportunistic infection, especially extrapulmonary tuberculosis. Further analysis has demonstrated that patients receiving early ART had delayed time to a primary HIV endpoint and significantly reduced secondary clinical endpoints (Grinsztejn, *et al.*, abstract submitted, IAS 2012). Following the DSMB decision, all participants in the delayed treatment arm who had not already initiated treatment (due to CD4 cell count <250 cells/μl) were offered antiretroviral drugs. HPTN 052 is continuing so as to determine the durability of the prevention benefit and to monitor individuals in the delayed arm for adverse clinical events realized even after ART has been initiated; an observational study has suggested that delayed initiation of ART even at higher CD4 cell counts could lead to cardiovascular and other complications [43–45].

A key question from HPTN 052 is the generalizability to other contexts: heterosexual couples with CD4 cell counts lower and higher than those studied in HPTN 052, high-risk heterosexual individuals (e.g., sex workers and their clients), MSM, and intravenous drug users (IDUs). There are no data to address this issue directly. The PEPFAR Scientific Advisory Board concluded that for heterosexual transmission, there is no reason to believe that ART will not suppress HIV transmission regardless of pretreatment viral burden or stage of disease [46]. For MSM, a WHO Expert Committee concluded that there is no reason to presume that treated, HIV-infected MSM will not be rendered less contagious [47].

However, the biology of HIV transmission is sufficiently different in IDUs and MSM as compared with heterosexual transmission, warranting further consideration and study (K.E. Muessig, *et al.*, under review).

For example, the number of HIV variants acquired and the efficiency of transmission are higher in MSM and IDU than in heterosexual transmission [48]. Additionally, whether ART reduces infectivity through anal sex by the same order of magnitude as for vaginal sex remains uncertain (K.E. Muessig, *et al.*, under review). Although such an effect is widely assumed, this is a key missing piece of evidence. Although an individual-level clinical trial among MSM may be unethical in light of the results of HPTN 052, at least two observational studies are underway to assess the effects of ART on HIV transmission among MSM. The Partners of People on ART: A New Evaluation of the Risks (PARTNER) Study [49] and the 'Opposites Attract' study [50] will recruit serodiscordant male–male couples in Europe and Australia/Thailand, respectively. In these studies, serodiscordant couples who are engaging in anal intercourse, and in whom the HIV-infected partner is on ART, will be followed longitudinally to estimate the rate of HIV transmission.

Antiretroviral treatment and population-level benefits

The individual benefits of ART may translate to a population-level effect in some parts of the world; however, the data used to support this conclusion have been controversial in large part because of the limitations of the methods employed (Smith, *et al.*, under review). Eight published ecological studies have examined trends in the HIV epidemic – in some cases using measures of HIV incidence – and concomitant availability of antiretrovirals (Table 3) [51–58]. These studies are interesting and provocative, but they are inevitably subject to considerable confounding and bias. The measurement of antiretroviral use is also problematic, as HIV transmission can only be prevented with reliable and durable suppression of HIV.

Ecological studies have had mixed results. In San Francisco, investigators argue that new diagnoses of HIV have fallen as a result of broader availability of ART and demonstrable reduction in viremia in some members of the 'community', broadly defined as people with recognized HIV who are receiving treatment [52]. In British Columbia, antiretrovirals have been related to reductions in new diagnoses of HIV among IDUs [53], a population that has received many other successful interventions [59,60] and in whom adherence to antiretrovirals may be poor [61]. HIV incidence among other groups such as MSM in the USA, Australia, France and Amsterdam may be rising, in spite of the wide availability of antiretroviral drugs [62–66]. In Canada, the portion of MSM making up the estimated number of incident infections increased between 2005 and 2008 [67]. Conversely, HIV incidence worldwide has been falling dramatically; between 2001 and 2009, HIV incidence decreased by more than 25% in 33 countries, 22 of which were in sub-Saharan Africa [68]. These declines are most readily ascribed to a complex set of interventions including antiretroviral drugs. So, although it is certainly possible that ART is reducing the incidence of HIV in communities with broad access to ART, the methods used in ecological studies, along with a large number of unaddressed issues and incongruent results, preclude a definitive answer to this hypothesis.

Most recently, investigators in South Africa reported results from a study in KwaZulu-Natal in which they compared the densityof ART coverage in different communities with HIV sero-conversion in a longitudinal cohort of 16 667 people. They adjusted their analysis to consider sexual behavior, socio-demographic variables associated with HIV acquisition, and HIV prevalence in the surrounding community (range <10 to >40%). In the adjusted analysis, each percentage point increase in ART coverage of all HIV-positive persons in the

surrounding community resulted in a 1.7% ($P < 0.001$) reduction in risk of HIV acquisition for HIV-negative persons living in that community [69]. These results present the most compelling population-level evidence to date that treatment with ART can reduce incidence of HIV.

Community randomized trials

Given the need to understand the proper balance between antiretrovirals and other modes of HIV prevention, as well as the magnitude of benefit of combination prevention, population-level clinical trials are planned. At least 50 studies are ongoing or planned [70], some of which are quite ambitious. HPTN 065 is a study designed to determine whether people with HIV in New York City and Washington, District of Columbia, can be detected and efficiently linked to care [71]. Three studies are being supported by a variety of agencies including the Office of the Global AIDS Coordinator (PEPFAR), USAID, the Bill and Melinda Gates Foundation, the US Centers for Disease Control (CDC) and the US NIH, and one study by the French National Agency for Research on AIDS and viral hepatitis (ANRS). In a study in Botswana, the investigators intend to find and treat people with the highest viral loads, as they may be most contagious [72]. All of these studies are likely to use molecular phylogeny to better understand the spread of HIV, and new cases introduced from outside the target communities.

Treatment as prevention, though exciting, cannot be guaranteed success at the population level. Can enough people be detected, linked to care, and properly treated to make a difference [73–75]? Also, current HIV detection strategies cannot find people with acute and early HIV disease [74,75], who may or may not contribute greatly to the spread of HIV [76–79]. The biology and epidemiology of acute HIV infection have been extensively reviewed; the relative importance of acute HIV infection to the spread of HIV is the subject of current debate [80].

Preexposure prophylaxis

PrEP is used to prevent many infectious diseases (e.g., endocarditis, malaria). However, usage of PrEP is subject to universal questions: does the agent work (biological plausibility); can the agent be given at the right time to work (pharmacokinetics and dynamics); will at-risk individuals use the agent properly and reliably; will cost and toxicity outweigh the benefit(s) of the intervention; and is usage sufficiently limited? In essence, the right drugs must be used at the right time for the right duration.

Attempts to develop PrEP regimens for HIV have been challenging, and the results confusing. We have summarized the work from seven trials (Table 4) [41,81–86]. To date, a limited number of agents have been used, selected primarily because they are well tolerated and because they provided protection in a macaque model using either rectal or vaginal exposure to SIV [87,88]. However (as discussed below), the relative safety of daily oral tenofovir for HIV-negative people has been questioned [89].

Two trials have used 1% tenofovir gel intravaginally with different results. Although the populations were similar, the dosage schedules were different. In the CAPRISA 004 study [81] heterosexual women at high risk of infection, ages 18–40 years, used the gel in a coitally dependent manner: one dose of gel up to 12 h before sex and one dose of gel up to 12 h after sex, with no more than two doses in 24 h. In one arm of the VOICE trial [86], women ages 18–45 used a dose of gel daily, regardless of sexual activity. The CAPRISA 004 study demonstrated 39% protection against HIV acquisition by tenofovir gel, whereas the tenofovir gel arm of the VOICE trial was stopped for futility. The reasons for the failure

of tenofovir gel in VOICE trial after the success of CAPRISA 004 have not yet been determined.

Five studies of oral PrEP have been undertaken (Table 4) [82–86]. iPrEx is the only study devoted to MSM. In this trial [82], 2499 MSM in South America and the USA were provided a daily fixed-dose combination pill of tenofovir with emtricitabine. The investigators reported a 44% reduction in HIV acquisition compared with placebo controls. Data were also analyzed to consider self-reported pill usage. Incidence was reduced by 73% if self-reported adherence was high (>90% of doses taken), 50% if adherence was intermediate (>50% of doses), and 32% if adherence was low (<50% of doses). Among those who reported good adherence (taking study drug 50% of days), 46% of men who remained HIV-negative and 92% of men who seroconverted had no drug detected in selected blood and cell samples (Grant *et al.*, 2010, Supplemental Table 8). The iPrEx investigators also used a case–control design to measure the association between detectable antiretrovirals in blood plasma and peripheral blood mononuclear cells and incident HIV infection. The majority of incident infections in the study drug arm had pharmacokinetic data available (34/36), and only 9% of these individuals had detectable study drug levels in selected plasma and cell specimens as compared with 51% of those who did not become infected. On the basis of this result, the authors argue that PrEP resulted in a relative risk reduction of 92% [95% confidence interval (CI) 40–99%] comparing patients with detectable study drug levels to those without detectable drug levels. Despite these promising findings, both self-report and pharmacologic markers raise concerns for accurately and reliably measuring drug adherence, an issue we discuss below.

Three studies of oral PrEP have involved women. The TDF2 study [83] enrolled 540 women and 660 men randomized to receive a daily fixed dose combination pill of tenofovir–emtricitabine or placebo. Study participants were predominantly unmarried adults ages 21–29 years living in Botswana. In this study, tenofovir–emtricitabine offered 64% protection against HIV infection. However, the study numbers were too small to draw definitive conclusions about protection in men and women separately, and 30% of those enrolled did not complete the study. In the FEM-PrEP study [85,90], 2120 heterosexual women aged 18–45 years living in high-prevalence areas in Kenya, South Africa, and Tanzania were randomized to receive either daily tenofovir–emtricitabine (FTC/TDF) or placebo. This study was discontinued for futility in April 2011. The investigators recently reported an HIV incidence rate of 4.7/100 person-years among the FTC/TDF group and 5.0/100 person-years in the placebo group for a hazard ratio for infection of 0.94 (95% CI 0.59–1.52, $P = 0.81$) [90]. Adherence may have been a critical contributing factor as less than 50% of infected cases and uninfected matched controls had detectable study drug in their blood plasma. Finally, the VOICE (MTN-003) study [86] enrolled heterosexual women aged 18–45 years in high-prevalence areas of Uganda, South Africa, and Zimbabwe. Women were randomized to daily oral tenofovir or daily oral tenofovir–emtricitabine. In September 2011, the daily oral tenofovir arm was stopped for futility, whereas the daily oral tenofovir–emtricitabine arm continues.

The largest trial, Partners in Prevention, focused on 4758 discordant heterosexual couples in Kenya and Uganda (38% negative women and 62% negative men) who reported intensive condom use and received counseling, in addition to the seronegative partner receiving daily tenofovir or daily tenofovir–emtricitabine. At the 2011 International AIDS Society meeting, the investigators reported that daily tenofovir conferred 62% protection against HIV acquisition and daily tenofovir–emtricitabine conferred 73% protection against HIV acquisition [83]. At the 2012 Conference for Retroviruses and Opportunistic Infections, the authors updated their results reporting 67% protection from daily tenofovir and 75% protection from the combined regimen [91]. Only two individuals who were infected at

randomization and one individual infected after randomization developed resistance (K65R or M184V mutation).

These trials differ in many ways. However, clearly, poor adherence would limit success as reported for FEM-PrEP and iPrEx. It is also possible that the drugs employed are not perfectly suited to PrEP, especially in women. Substantial differences in antiretroviral drug concentrations in mucosal tissues have been reported [23,92], which may help explain these discordant study findings [93]. As noted above, after the first dose of oral FTC/TDF, rectal tissue concentrations are far greater than cervical or vaginal tissue concentrations [23]. This could explain why tenofovir–emtricitabine conferred protective efficacy in iPrEx [82], despite only modest adherence. In the VOICE 003 trial [86], the lack of protection with oral TDF could reflect low tissue concentrations of the drug in the cervix and vagina. Furthermore, differences between study populations in risk behaviors and underlying rate of infection deserve consideration.

Two new studies (HPTN 067 and HPTN 069) sponsored by the HIV Prevention Trials Network (HPTN), one study sponsored by ANRS (IPERGAY), and an extension of the iPrEx study (iPrEx OLE) are addressing some of the limitations of the previous PrEP studies. Due to the adherence issues with daily PrEP dosing, the behavioral study HPTN 067 (the ADAPT study: Alternative Dosing to Augment PrEP Pill-Taking) is designed to test the hypothesis that recommending intermittent usage of oral tenofovir–emtricitabine, compared with recommending daily usage, will be associated with equivalent coverage of sex events before and after exposure dosing, lower number of pills needed for coverage, and decreased severity and frequency of self-reported side effects [94]. HPTN 067 is enrolling 180 MSM and 180 heterosexual women and aims to identify dosing regimens that foster healthy sexual practices and pill-taking behavior in people at high risk of infection. The study includes a 6-week lead-in period, which includes directly observed therapy at enrollment and weeks 1 through 4, followed by 1 week without dosing to determine individual steady-state pharmacokinetics. Participants are then randomly assigned to one of three dosage groups in a 1 : 1 : 1 ratio: daily dosing, time-driven dosing, and event-driven dosing to be completed over 24 weeks.

iPrEx OLE (open-label extension) is a continuation of the iPrEx study that is enrolling participants in 11 sites in Peru, Ecuador, Brazil, the USA, South Africa, and Thailand [95]. It is hoped that knowing with certainty that one is on the study drug (and not placebo) will lead to higher medication adherence. The 72-week study will also assess the long-term efficacy and safety of PrEP, changes in sexual behavior, drug resistance, changes in bone mineral density and fat distribution, and the impact on hepatitis infection.

The IPERGAY study sponsored by ANRS is a randomized controlled trial among HIV-negative MSM testing the prevention efficacy of Truvada (tenofovir–emtricitabine; Gilead Sciences Inc., Foster City, California, USA) in combination with regular HIV/STD testing, immunization against hepatitis A and B, postexposure treatment as needed, and condom distribution [96]. Enrollment is currently ongoing in France and will also be extended to Canada.

Due to the possible limitations related to efficacy and toxicity (see below) of tenofovir–emtricitabine, HPTN 069 (NEXT-PrEP: Novel Exploration of Therapeutics for PREP) is assessing the safety and tolerability of maraviroc-containing PrEP regimens [97]. HPTN 069 is enrolling 400 MSM and 200 heterosexual women and will compare 48-week safety and tolerability of daily maraviroc, maraviroc–emtricitabine, maraviroc–tenofovir, or tenofovir–emtricitabine. Secondary objectives will include evaluation of electronically monitored

adherence, pharmacokinetics in systemic and genital tract compartments, and efficacy of ex-vivo HIV challenge in tissue biopsy explants.

Alternative drugs and delivery systems more appropriate to PrEP are also being pursued. Vaginal rings for women containing antiretrovirals would be similar in concept to vaginal rings currently used for contraception and hormone replacement therapy [98]. These rings could maintain long-term, sustained antiretroviral release for local efficacy. Due to the long-term drug release, rings can be used in a coitally independent manner and inserted monthly, which could have an adherence benefit over gels or pills.

Dapivirine [TMC120; Janssen R&D Ireland (previously Tibotec)] has been formulated into a ring and is currently undergoing phase III studies [99]. Two phase I studies evaluating dapivirine 25 or 200 mg delivered from a vaginal ring over 7 days in 25 healthy women found the ring to be well tolerated, with adverse effects similar to placebo. Mucosal fluid sampled at up to 7 days after insertion in all women from the introitus, cervix, and ring area had mean drug concentrations 1000 times the 50% effective concentration (EC_{50}) against wild-type HIV-1 [100,101]. A combination dapivirine and maraviroc ring is currently undergoing a phase 1 safety and pharmaco-kinetic study.

An alternate formulation for better adherence is a long-acting injectable product that could be administered every 30–90 days. A rilpivirine (RPV) (TMC278 LA) nanosuspension is in early phase of development for this purpose [102,103]. In an exploratory study among 32 HIV-negative participants, a single intramuscular injection with either 300, 600, or 1200 mg of RPV showed varying, prolonged plasma, genital tract, and male rectum concentrations over 84 days [103]. Optimal dosage, differences in drug concentrations in various biological compartments, and long-term safety of multiple doses all require further study.

Although a potentially strong addition to the biomedical technologies available for HIV prevention, PrEP has given rise to a number of concerns [104]. First, HIV resistance is an important consideration while using oral antiviral agents. Among the 10 individuals enrolled in iPrEx with unrecognized HIV infection at baseline (and therefore subsequent unwitting exposure to ART directed at PrEP rather than treatment), three developed FTC-resistant mutations; this resistant mutation would be expected from the double-drug therapy employed [105]. However, among 36 men who became HIV infected during the trial in the FTC-TDF group, no ART resistance was observed. These results have sometimes been interpreted to indicate that PrEP does not threaten the utility of the ART agents used [106]. However, given the low adherence rates recorded in iPrEx, these results could also suggest that the study individuals used no ART product during the time after HIV was acquired and diagnosed. Detection of ART resistance markers represents a surrogate for failed PrEP usage, and ART resistance might compromise future management of people using PrEP who acquire HIV [105].

Second, the long-term biological impacts of FTC-TDF taken for PrEP purposes (as compared with HIV treatment purposes) will require additional study. Specifically, tenofovir has been linked with renal injury [89,107] and loss of bone mineral density (BMD) [108] when used for HIV treatment. Individuals with preexisting renal conditions have been excluded from PrEP studies [109,110]. In the iPrEx study, a nonsignificant trend toward elevated creatinine levels was found among the intervention arm [81], and a substudy showed a small but significant (up to 1%) loss in BMD [111].

An additional concern is that the use of ART as PrEP could affect sexual behavior [112]. In the iPrEx study, the investigators reported no increase in sexual risk behaviors. However, an individual's behavior within an unproven medical trial as compared with behavior of an individual under the belief of effective PrEP in a real-world setting must also be considered.

'Risk compensation', wherein individuals alter their behaviors in response to perceptions of risk, has been documented in relation to the availability of antiretroviral drugs and other biomedical HIV-prevention approaches [113–115]. Furthermore, even within a controlled trial setting such as the iPrEx study, self-reported adherence to ART was less than perfect, and other STDs were detected in both groups, challenging the veracity of the behavioral data collected. Finally, PrEP has generated discussions about resource distribution and how to balance the current HIV treatment coverage gap with expansion of preexposure prevention measures [116].

Taking antiretroviral treatment to scale: modeling, observation, and empirical data

Although investigators have been evaluating the potential utility of antiviral agents for prevention, a virtual parallel universe of researchers have been making the case that the benefits of ART are both inevitable, and already visible. This work has been conducted through evaluation of observational and ecologic data and mathematical modeling.

Mathematical modelers take the best available data and make assumptions about biology and behaviors to provide predictions of the future that are often provocative. A large number of models have focused on the usage of ART by HIV-infected persons to reduce the spread of HIV (Table 5) [117–125], as described in numerous review articles [2,126–128]. The results of several such modeling studies have suggested that expanded ART use could result in substantial reductions in HIV incidence under certain, optimistic conditions [120,129]. However, modeling studies have also shown that the population-level transmission prevention benefits of ART could be severely compromised by such factors as increased risk behavior [130–132], ongoing transmission during acute and early HIV infection [133], antiretroviral drug resistance [124], concentration of risk in population subgroups [122], and sub-optimal ART coverage, effectiveness, or adherence [125,134] (Table 5). Considerable uncertainty surrounds the fundamental assumptions and parameter values used in these models; more empirical data about risk behavior patterns, STD co-transmission, ART uptake and adherence, and effects of ART on infectivity (especially for anal contact and parenteral transmission) will facilitate more reliable model projections.

One area of special interest is the potential balance between PrEP and treatment, as well as the targeted use of antiretroviral-based prevention strategies within discordant couples. Using available data to look at management of HIV-discordant couples, Hallett *et al.* [135] reported that use of PrEP by the uninfected partner could be at least as cost-effective as earlier ART initiation by the infected partner, provided that the annual cost of PrEP is less than 40% the cost of ART and the effectiveness of PrEP exceeds 70%. At the population level, Pretorius *et al.* [136] used a mathematical model to examine the impact and cost-effectiveness of PrEP relative to ART in South Africa. These investigators concluded that PrEP use would be most cost-effective if utilized before ART reaches 65% of HIV-positive persons; as ART coverage increased beyond this level, the cost-effectiveness of PrEP was predicted to decrease rapidly. El-Sadr *et al.* [137] evaluated treatment of HIV-infected partners within serodiscordant couples as a strategy for reducing HIV incidence at the population level and found that the predicted effectiveness in a given setting depended on HIV prevalence and the degree of HIV discordancy. In general, these results do not support a focus on HIV-discordant couples for public health purposes. As with the modeling studies of treatment as prevention described above, these studies indicate that PrEP effectiveness will depend on many factors and that the choice of intervention must take into account the epidemiological context in a given setting.

Combination prevention: the way forward

Implementation of ART as prevention faces substantial challenges, including logistic limitations [73,75], potential changes in risk-taking behaviors, and cost. Indeed, ART usage will need to be part of a combination strategy [138]. In a remarkable 2011 speech at the NIH, Secretary of State Hillary Clinton expressed hope for an 'AIDS Free Generation' [139]. On World AIDS Day 2011, President Barack Obama pledged an additional US$ 35 million for state AIDS drug assistance programs based on the HPTN 052 findings [140]. PEPFAR and the WHO have recommended the use of ART to prevent HIV transmission among heterosexual partners [46,141], and UNAIDS is looking into similar guidelines [68]. But attention to broader use of ART cannot ignore other parts of a prevention package [138]. Secretary Clinton concluded that broader prevention of mother-to-child transmission, more circumcision, and optimal and broader use of ART will point us in the right direction [139]. Additionally, combination prevention strategies [142] will need the continued efforts of behavioral interventions to increase condom use, reduce high-risk behaviors, and address suboptimal antiretroviral adherence and risk compensation. The community-based clinical trials described in this article, though focused on ART, all embrace a similar combination prevention strategy. And all of these trials and advances must also recognize the important discoveries in the field of HIV vaccine [143,144]. It seems reasonable to expect that – after 30 years of work – the tools now available in the HIV prevention toolbox and those that will become available from ongoing research can be expected to control the spread of HIV.

Acknowledgments

The authors wish to thank David Burns, MD, of the National Institute of Allergies and Infectious Diseases and Ward Cates, MD, of FHI360 for their reviews of this manuscript.

K.E.M. and M.K.S. are supported by an NIH institutional training grant (5T32AI007001-35). K.A.P. is supported by the NIH (R01 AI083059, R01 DA025885). M.S.C. is supported by the Center for AIDS Research (CFAR) and the NIH HIV Prevention Trials Network (HPTN-052).

References

1. Cohen MS, Gay C, Kashuba AD, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. Ann Intern Med. 2007; 146:591–601. [PubMed: 17438318]
2. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. Clin Infect Dis. 2010; 50:S85–S95. [PubMed: 20397961]
3. Mayer KH, Venkatesh KK. Antiretroviral therapy as HIV prevention: status and prospects. Am J Public Health. 2010; 100:1867–1876. [PubMed: 20724682]
4. Dumond JB, Yeh RF, Patterson KB, Corbett AH, Jung BH, Rezk NL, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre and postexposure prophylaxis. AIDS. 2007; 21:1899–1907. [PubMed: 17721097]
5. Nicol MR, Kashuba AD. Pharmacologic opportunities for HIV prevention. Clin Pharmacol Ther. 2010; 88:598–609. [PubMed: 20881955]
6. Pereira AS, Kashuba AD, Fiscus SA, Hall JE, Tidwell RR, Troiani L, et al. Nucleoside analogues achieve high concentrations in seminal plasma: relationship between drug concentration and virus burden. J Infect Dis. 1999; 180:2039–2043. [PubMed: 10558966]
7. Kashuba AD, Dyer JR, Kramer LM, Raasch RH, Eron JJ, Cohen MS. Antiretroviral-drug concentrations in semen: implications for sexual transmission of human immunodeficiency virus type 1. Antimicrob Agents Chemother. 1999; 43:1817–1826. [PubMed: 10428898]
8. Ghosn J, Chaix ML, Peytavin G, Rey E, Bresson JL, Goujard C, et al. Penetration of enfuvirtide, tenofovir, efavirenz, and protease inhibitors in the genital tract of HIV-1-infected men. AIDS. 2004; 18:1958–1961. [PubMed: 15353984]

9. Barroso PF, Schechter M, Gupta P, Bressan C, Bomfim A, Harrison LH. Adherence to antiretroviral therapy and persistence of HIV RNA in semen. J Acquir Immune Defic Syndr. 2003; 32:435–440. [PubMed: 12640203]
10. Bujan L, Daudin M, Matsuda T, Righi L, Thauvin L, Berges L, et al. Factors of intermittent HIV-1 excretion in semen and efficiency of sperm processing in obtaining spermatozoa without HIV-1 genomes. AIDS. 2004; 18:757–766. [PubMed: 15075510]
11. Eron JJ, Smeaton LM, Fiscus SA, Gulick RM, Currier JS, Lennox JL, et al. The effects of protease inhibitor therapy on human immunodeficiency virus type 1 levels in semen (AIDS clinical trials group protocol 850). J Infect Dis. 2000; 181:1622–1628. [PubMed: 10783117]
12. Leruez-Ville M, Dulioust E, Costabliola D, Salmon D, Tachet A, Finkielsztejn L, et al. Decrease in HIV-1 seminal shedding in men receiving highly active antiretroviral therapy: an 18 month longitudinal study (ANRS EP012). AIDS. 2002; 16:486–488. [PubMed: 11834963]
13. Sheth PM, Kovacs C, Kemal KS, Jones RB, Raboud JM, Pilon R, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. AIDS. 2009; 23:2050–2054. [PubMed: 19710596]
14. Krieger JN, Coombs RW, Collier AC, Ho DD, Ross SO, Zeh JE, et al. Intermittent shedding of human immunodeficiency virus in semen: implications for sexual transmission. J Urol. 1995; 154:1035–1040. [PubMed: 7637049]
15. Cu-Uvin S, DeLong AK, Venkatesh KK, Hogan JW, Ingersoll J, Kurpewski J, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS. 2010; 24:2489–2497. [PubMed: 20736815]
16. Neely MN, Benning L, Xu J, Strickler HD, Greenblatt RM, Minkoff H, et al. Cervical shedding of HIV-1 RNA among women with low levels of viremia while receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2007; 44:38–42. [PubMed: 17106279]
17. Launay O, Tod M, Tschope I, Si-Mohamed A, Belarbi L, Charpentier C, et al. Residual HIV-1 RNA and HIV-1 DNA production in the genital tract reservoir of women treated with HAART: the prospective ANRS EP24 GYNODYN study. Antivir Ther. 2011; 16:843–852. [PubMed: 21900716]
18. Marcelin AG, Tubiana R, Lambert-Niclot S, Lefebvre G, Dominguez S, Bonmarchand M, et al. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma. AIDS. 2008; 22:1677–1679. [PubMed: 18670231]
19. Mayer KH, Boswell S, Goldstein R, Lo W, Xu C, Tucker L, et al. Persistence of human immunodeficiency virus in semen after adding indinavir to combination antiretroviral therapy. Clin Infect Dis. 1999; 28:1252–1259. [PubMed: 10451162]
20. Eron JJ, Vernazza PL, Johnston DM, Seillier-Moiseiwitsch F, Alcorn TM, Fiscus SA, et al. Resistance of HIV-1 to antiretroviral agents in blood and seminal plasma: implications for transmission. AIDS. 1998; 12:F181–F189. [PubMed: 9814860]
21. Ghosn J, Chaix ML, Peytavin G, Bresson JL, Galimand J, Girard PM, et al. Absence of HIV-1 shedding in male genital tract after 1 year of first-line lopinavir/ritonavir alone or in combination with zidovudine/lamivudine. J Antimicrob Chemother. 2008; 61:1344–1347. [PubMed: 18343806]
22. Cohen J. HIV/AIDS research. Tissue says blood is misleading, confusing HIV cure efforts. Science. 2011; 334:1614. [PubMed: 22194536]
23. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011; 3:112re4.
24. Taylor S, Sadiq ST, Weller I, Kaye S, Workman J, Cane PA, et al. Drug-resistant HIV-1 in the semen of men receiving antiretroviral therapy with acute sexually transmitted infections. Antivir Ther. 2003; 8:479–483. [PubMed: 14640396]
25. Ouedraogo A, Nagot N, Vergne L, Konate I, Weiss HA, Defer MC, et al. Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: a randomized controlled trial. AIDS. 2006; 20:2305–2313. [PubMed: 17117016]
26. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009; 23:1397–1404. [PubMed: 19381076]

27. Guthrie BL, de Bruyn G, Farquhar C. HIV-1-discordant couples in sub-Saharan Africa: explanations and implications for high rates of discordancy. Curr HIV Res. 2007; 5:416–429. [PubMed: 17627505]
28. Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr. 2005; 40:96–101. [PubMed: 16123689]
29. Del Romero J, Castilla J, Hernando V, Rodriguez C, Garcia S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. BMJ. 2010; 340:c2205. [PubMed: 20472675]
30. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010; 375:2092–2098. [PubMed: 20537376]
31. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. AIDS. 2006; 20:85–92. [PubMed: 16327323]
32. Hernando V, del Romero J, Garcia S, Rodriguez C, del Amo J, Castilla J. Reducing sexual risk behavior among steady heterosexual serodiscordant couples in a testing and counseling program. Sex Transm Dis. 2009; 36:621–628. [PubMed: 19955873]
33. Melo MG, Santos BR, De Cassia Lira R, Varella IS, Turella ML, Rocha TM, et al. Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil. Sex Transm Dis. 2008; 35:912–915. [PubMed: 18607309]
34. Musicco M, Lazzarin A, Nicolosi A, Gasparini M, Costigliola P, Arici C, et al. Antiretroviral treatment of men infected with human immunodeficiency virus type 1 reduces the incidence of heterosexual transmission. Italian Study Group on HIV Heterosexual Transmission. Arch Intern Med. 1994; 154:1971–1976. [PubMed: 8074601]
35. Reynolds SJ, Makumbi F, Nakigozi G, Kagaayi J, Gray RH, Wawer M, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. AIDS. 2011; 25:473–477. [PubMed: 21160416]
36. Sullivan P, Kayitenkore K, Chomba E, Karita E, Mwananyanda L, Vwalika C. Reduction of HIV transmission risk while prescribed antiretroviral therapy (ARVT): Misclassification of ARVT status as a methodological issue. AIDS Res Hum Retro-viruses. 2010; 26:A1–A184.
37. Wang L, Ge Z, Luo J, Shan D, Gao X, Ding GW, et al. HIV transmission risk among serodiscordant couples: a retrospective study of former plasma donors in Henan, China. J Acquir Immune Defic Syndr. 2010; 55:232–238. [PubMed: 21423851]
38. Chakraborty H, Sen PK, Helms RW, Vernazza PL, Fiscus SA, Eron JJ, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. AIDS. 2001; 15:621–627. [PubMed: 11317000]
39. Vernazza PL, Hirschelb B. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement anti-rétroviral efficace ne transmettent pas le VIH par voie sexuelle. [HIV-infected patients under HAART without any other sexually transmitted infection do not transmit HIV by sexual intercourse.]. Bull Med Suisse. 2008; 89:165–169.
40. Hasse B, Ledergerber B, Hirschel B, Vernazza P, Glass TR, Jeannin A, et al. Frequency and determinants of unprotected sex among HIV-infected persons: the Swiss HIV Cohort Study. Clin Infect Dis. 2010; 51:1314–1322. [PubMed: 21034200]
41. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493–505. [PubMed: 21767103]
42. Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS. 2012; 7:99–105. [PubMed: 22227585]
43. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of anti-retroviral treatment. N Engl J Med. 2006; 355:2283–2296. [PubMed: 17135583]

44. Phillips AN, Carr A, Neuhaus J, Visnegarwala F, Prineas R, Burman WJ, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. Antiviral Ther. 2008; 13:177–187.
45. Phillips AN, Gazzard B, Gilson R, Easterbrook P, Johnson M, Walsh J, et al. Rate of AIDS diseases or death in HIV-infected antiretroviral therapy-naive individuals with high CD4 cell count. AIDS. 2007; 21:1717–1721. [PubMed: 17690569]
46. PEPFAR Scientific Advisory Board. [13 March 2012] PEPFAR Scientific Advisory Board Recommendations for the Office of the US Global AIDS Coordinator: implications of HPTN 052 for PEPFAR's Treatment Programs. 2011. http://www.pepfar.gov/documents/organization/177126.pdf.
47. World Health Organization. WHO and U.S. NIH Working Group Meeting on treatment for HIV prevention among MSM: what additional evidence is required?; Geneva, Switzerland. 26–27 October 2011; http://www.who.int/hiv/pub/msm_meeting_report.pdf.
48. Bar KJ, Li H, Chamberland A, Tremblay C, Routy JP, Grayson T, et al. Wide variation in the multiplicity of HIV-1 infection among injection drug users. J Virol. 2010; 84:6241–6247. [PubMed: 20375173]
49. [13 March 2012] Copenhagen HIV Program Denmark and Royal Free School and UC Medical School. Partners of people on ART: a New Evaluation of the Risks (PARTNER study). http://www.partnerstudy.eu/.
50. Kirby Institute for Infection and Immunity in Society. [23 April 2012] ‘Opposites Attract: The study of relationships between HIV positive and negative gay men’.. Study website: www.oppositesattract.net.au.
51. Castel, A.; Befus, M.; West-Ojo, T.; Giffin, A.; Hader, S.; Kamanu-Elias, N. Use of community viral load as population-based biomarker of HIV-Washington, DC, 2004–2008.. Proceedings of the 18th Annual Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2011;
52. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One. 2010; 5:e11068. [PubMed: 20548786]
53. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet. 2010; 376:532–539. [PubMed: 20638713]
54. Wood E, Kerr T, Marshall BD, Li K, Zhang R, Hogg RS, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. BMJ. 2009; 338:b1649. [PubMed: 19406887]
55. Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. J Infect Dis. 2004; 190:879–885. [PubMed: 15295691]
56. Katz MH, Schwarcz SK, Kellogg TA, Klausner JD, Dilley JW, Gibson S, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. Am J Public Health. 2002; 92:388–394. [PubMed: 11867317]
57. Law MG, Woolley I, Templeton DJ, Roth N, Chuah J, Mulhall B, et al. Trends in detectable viral load by calendar year in the Australian HIV observational database. J Int AIDS Soc. 2011; 14:10. [PubMed: 21345234]
58. Porco TC, Martin JN, Page-Shafer KA, Cheng A, Charlebois E, Grant RM, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. AIDS. 2004; 18:81–88. [PubMed: 15090833]
59. Stoltz JA, Wood E, Small W, Li K, Tyndall M, Montaner J, et al. Changes in injecting practices associated with the use of a medically supervised safer injection facility. J Public Health (Oxf). 2007; 29:35–39. [PubMed: 17229788]
60. Wood E, Tyndall MW, Montaner JS, Kerr T. Summary of findings from the evaluation of a pilot medically supervised safer injecting facility. CMAJ. 2006; 175:1399–1404. [PubMed: 17116909]
61. Wood E, Montaner J, Yip B, Tyndall M, Schechter M, O'Shaughnessy MV, Hogg RS. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 Infected injection drug users. CMAJ. 2003; 169:656–661. [PubMed: 14517122]

62. Dukers NH, Spaargaren J, Geskus RB, Beijnen J, Coutinho RA, Fennema HS. HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. AIDS. 2002; 16:F19–F24. [PubMed: 12131206]
63. Wand H, Yan P, Wilson D, McDonald A, Middleton M, Kaldor J, et al. Increasing HIV transmission through male homosexual and heterosexual contact in Australia: results from an extended back-projection approach. HIV Med. 2010; 11:395–403. [PubMed: 20136660]
64. Murray JM, Prestage G, Grierson J, Middleton M, McDonald A. Increasing HIV diagnoses in Australia among men who have sex with men correlated with the growing number not taking antiretroviral therapy. Sexual Health. 2011; 8:304–310. [PubMed: 21851769]
65. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006–2009. PLoS One. 2011; 6:e17502. [PubMed: 21826193]
66. Le Vu S, Le Strat Y, Barin F, Pillonel J, Cazein F, Bousquet V, et al. Population-based HIV-1 incidence in France, 2003–08: a modelling analysis. Lancet Infect Dis. 2010; 10:682–687. [PubMed: 20832367]
67. British Columbia Center for Disease Control. [13 March 2012] HIV and sexually transmitted infections. 2010. http://www.bccdc.ca/util/about/annreport/default.htm#heading1.
68. UNAIDS. [13 March 2012] 2011–2015 strategy: getting to zero. Joint United Nations Programme on HIV/AIDS. http://www.unodc.org/documents/eastasiaandpacific/Publications/2011/JC2034_UNAIDS_Strategy_en.pdf.
69. Tanser, F.; Barnighausen, T.; Grapsa, E.; Newell, ML. Effect of ART coverage on rate of new HIV infections in a hyper endemic, rural population: South Africa.. Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2012;
70. Granich R, Gupta S, Suthar AB, Smyth C, Hoos D, Vitoria M, et al. Antiretrovirals therapy in prevention of HIV and TB: update on current research efforts. Curr HIV Res. 2011; 9:446–469. [PubMed: 21999779]
71. US National Institute of Allergy and Infectious Diseases, US National Institutes of Health. [13 March 2012] HPTN 065 TLC-Plus: a study to evaluate the feasibility of an enhanced test, link to care, plus treat approach for HIV prevention in the United States. 2010. http://www.hptn.org/research_studies/hptn065.asp.
72. Novitsky V, Wang R, Bussmann H, Lockman S, Baum M, Shapiro R, et al. HIV-1 subtype C-infected individuals maintaining high viral load as potential targets for the 'test-and-treat' approach to reduce HIV transmission. PLoS One. 2010; 5:e10148. [PubMed: 20405044]
73. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011; 52:793–800. [PubMed: 21367734]
74. Burns DN, Dieffenbach CW, Vermund SH. Rethinking prevention of HIV type 1 infection. Clin Infect Dis. 2010; 51:725–731. [PubMed: 20707698]
75. US Centers for Disease Control. [13 March 2012] Only one quarter of Americans with HIV have virus under control. 2011. http://www.cdc.gov/nchhstp/newsroom/WAD2011PressRelease.html.
76. Miller WC, Rosenberg NE, Rutstein SE, Powers KA. Role of acute and early HIV infection in the sexual transmission of HIV. Curr Opin HIV AIDS. 2010; 5:277–282. [PubMed: 20543601]
77. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. N Engl J Med. 2011; 364:1943–1954. [PubMed: 21591946]
78. Brenner BG, Roger M, Routy JP, Moisi D, Ntemgwa M, Matte C, et al. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis. 2007; 195:951–959. [PubMed: 17330784]
79. Frange P, Meyer L, Deveau C, Tran L, Goujard C, Ghosn J, et al. Recent HIV-1 infection contributes to the viral diffusion over the French territory with a recent increasing frequency. PLoS One. 2012; 7:e31695. [PubMed: 22348121]
80. Cohen M, Dye C, Fraser C, Miller W, Powers K, Williams B. Does transmission during early HIV infection compromise treatment as prevention? PLoS Med. (in press).

81. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329:1168–1174. [PubMed: 20643915]
82. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363:2587–2599. [PubMed: 21091279]
83. Thigpen, M.; Kebaabetswe, P.; Smith, D., et al. Daily oral anti-retroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study.. Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; Rome. 17–20 July 2011; WELBC01 oral abstract
84. Baeten, J.; Celum, C. Antiretroviral preexposure prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP study.. Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; Rome. 17–20 July 2011;
85. FEMem-PrEP Project. [13 March 2012] FHI360. http://www.fhi.org/en/Research/Projects/FEM-PrEP.htm.
86. Microbicide Trials Network. [13 March 2012] VOICE (MTN-003) Study. http://www.mtnstopshiv.org/news/studies/mtn003.
87. Garcia-Lerma JG, Otten RA, Qari SH, Jackson E, Cong ME, Masciotra S, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Med. 2008; 5:e28. [PubMed: 18254653]
88. Garcia-Lerma JG, Cong ME, Mitchell J, Youngpairoj AS, Zheng Q, Masciotra S, et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Sci Transl Med. 2010; 2:14ra14.
89. Scherzer R, Estrella M, Li Y, Deeks SG, Grunfeld C, Shlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012 [Epub ahead of print].
90. Van Damme, L.; Corneli, A.; Ahmed, K.; Agot, K.; Lombaard, J.; Kapiga, S., et al. The FEM-PrEP Trial of emtricitabine/tenofovir disoproxil fumarate (Truvada) among African women.. Proceedings of the 19th Conference on Retrovirusus and Opportunistic Infections; Seattle, WA. 2012;
91. Baeten, J.; Donnell, D.; Ndase, P.; Mugo, N.; Mujugira, A.; Celum, C., et al. ARV PrEP for HIV-1 Prevention among Heterosexual Men and Women.. Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections; Seattle, WA. 2012;
92. Brown KC, Patterson KB, Malone SA, Shaheen NJ, Prince HM, Dumond JB, et al. Single and multiple dose pharmacokinetics of maraviroc in saliva, semen, and rectal tissue of healthy HIV-negative men. J Infect Dis. 2011; 203:1484–1490. [PubMed: 21502084]
93. Kashuba AD, Patterson KB, Dumond JB, Cohen MS. Preexposure prophylaxis for HIV prevention: how to predict success. Lancet. 2011 [Epub ahead of print].
94. HIV Prevention Trials Network. [13 March 2012] HPTN 067: the ADAPT study. http://www.hptn.org/research_studies/hptn067.asp.
95. iPrEx, OLE. [13 March 2012] What is iPrEx OLE?. http://iprexole.com/1pages/aboutus/aboutus-whatisiprexole.php.
96. The French National Agency for Research on AIDS and viral hepatitis. [13 March 2012] IPERGAY un essai ANRS. http://www.ipergay.fr/.
97. HIV Prevention Trials Network. [13 March 2012] HPTN 069: next PrEP study. http://www.hptn.org/research_studies/hptn069.asp.
98. Malcolm RK, Edwards KL, Kiser P, Romano J, Smith TJ. Advances in microbicide vaginal rings. Antiviral Res. 2010; 88(Suppl 1):S30–S39. [PubMed: 21109066]
99. International Partnership for Microbicides. [13 March 2012] Dapivirine (TMC120). http://www.ipmglobal.org/our-work/ipm-product-pipeline/dapivirine-tmc120.
100. Nel, A.; Habibi, S.; Smythe, S.; Nuttall, J.; Lloyd, P. Pharmacokinetics and safety assessment of monthly anti-HIV DPV vaginal microbicide rings with multiple dosing.. Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections; Boston, MA. 2011; paper 1001

101. Romano J, Variano B, Coplan P, Van Roey J, Douville K, Rosenberg Z, et al. Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. AIDS Res Hum Retroviruses. 2009; 25:483–488. [PubMed: 19388819]
102. van't Klooster G, Hoeben E, Borghys H, Looszova A, Bouche MP, van Velsen F, et al. Pharmacokinetics and disposition of rilpivirine (TMC278) nanosuspension as a long-acting injectable antiretroviral formulation. Antimicrob Agents Chemother. 2010; 54:2042–2050. [PubMed: 20160045]
103. Jackson, A.; Else, L.; Tjia, J.; Seymour, N.; Stafford, M.; Back, D., et al. Rilpavirine-LA formulation: pharmacokinetics in plasma, genital tract in HIV-negative females and rectum in males.. Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections; Seattle. 2012;
104. Marcus D, McKay B. Fight over use of HIV drugs. The Wall Street Journal. Mar 7.2012
105. Hurt CB, Eron JJ, Cohen MS. Preexposure prophylaxis and antiretroviral resistance: HIV prevention at a cost? Clin Infect Dis. 2011; 53:1265–1270. [PubMed: 21976467]
106. Grant R. Preexposure chemoprophylaxis for HIV prevention (author reply). N Engl J Med. 2011; 364:1374–1375.
107. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010; 51:496–505. [PubMed: 20673002]
108. Jacobson DL, Spiegelman D, Knox TK, Wilson IB. Evolution and predictors of change in total bone mineral density over time in HIV-infected men and women in the nutrition for healthy living study. J Acquir Immune Defic Syndr. 2008; 49:298–308. [PubMed: 18845956]
109. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007; 2:e27. [PubMed: 17525796]
110. Grohskopf, L.; Pathak, S. Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 preexposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM).. Proceedings of the XVIII International AIDS Conference; Vienna, Austria. 2010;
111. Mulligan, K.; Glidden, DV.; Gonzales, P. Effects of FTC/TDF on bone mineral density in seronegative men from 4 continents: DEXA results of the Global iPrEx Study.. Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections; Boston. 2011;
112. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? BMJ. 2006; 332:605–607. [PubMed: 16528088]
113. Eaton LA, Kalichman S. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. Curr HIV/AIDS Rep. 2007; 4:165–172. [PubMed: 18366947]
114. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active anti-retroviral therapy: a longitudinal study. AIDS. 2004; 18:303–309. [PubMed: 15075549]
115. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. JAMA. 2004; 292:224–236. [PubMed: 15249572]
116. Celum CL. HIV preexposure prophylaxis: new data and potential use. Top Antivir Med. 2011; 19:181–185. [PubMed: 22298887]
117. Blower SM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science. 2000; 287:650–654. [PubMed: 10649998]
118. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, et al. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. AIDS. 2003; 17:1941–1951. [PubMed: 12960827]
119. Baggaley RF, Garnett GP, Ferguson NM. Modelling the impact of antiretroviral use in resource-poor settings. PLoS Med. 2006; 3:e124. [PubMed: 16519553]
120. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009; 373:48–57. [PubMed: 19038438]

121. Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Fraser C. 27 years of the HIV epidemic amongst men having sex with men in the Netherlands: an in depth mathematical model-based analysis. Epidemics. 2010; 2:66–79. [PubMed: 21352777]
122. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS. 2010; 24:729–735. [PubMed: 20154580]
123. Long EF, Brandeau ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and anti-retroviral treatment in the United States. Ann Intern Med. 2010; 153:778–789. [PubMed: 21173412]
124. Smith RJ, Okano JT, Kahn JS, Bodine EN, Blower S. Evolutionary dynamics of complex networks of HIV drug-resistant strains: the case of San Francisco. Science. 2010; 327:697–701. [PubMed: 20075214]
125. Walensky RP, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. Clin Infect Dis. 2010; 51:392–400. [PubMed: 20617921]
126. Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. Emerg Themes Epidemiol. 2005; 2:9. [PubMed: 16153307]
127. Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. AIDS. 2005; 19:1–14. [PubMed: 15627028]
128. Cambiano V, Phillips AN. Modelling the impact of treatment with individual antiretrovirals. Curr Opin HIV AIDS. 2011; 6:124–130. [PubMed: 21505387]
129. Charlebois ED, Das M, Porco TC, Havlir DV. The effect of expanded antiretroviral treatment strategies on the HIV epidemic among men who have sex with men in San Francisco. Clin Infect Dis. 2011; 52:1046–1049. [PubMed: 21460322]
130. Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Prins M, et al. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. AIDS. 2008; 22:1071–1077. [PubMed: 18520351]
131. Xiridou M, Geskus R, de Wit J, Coutinho R. The contribution of steady and casual partnerships to the incidence of HIV infection among homosexual men in Amsterdam. AIDS. 2003; 17:1029–1038. [PubMed: 12700453]
132. Law MG, Prestage G, Grulich A, Van de Ven P, Kippax S. Modelling the effect of combination antiretroviral treatments on HIV incidence. AIDS. 2001; 15:1287–1294. [PubMed: 11426074]
133. Powers KA, Ghani AC, Miller WC, Hoffman IF, Pettifor AE, Kamanga G, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet. 2011; 378:256–268. [PubMed: 21684591]
134. Bendavid E, Brandeau ML, Wood R, Owens DK. Comparative effectiveness of HIV testing and treatment in highly endemic regions. Arch Intern Med. 2010; 170:1347–1354. [PubMed: 20696960]
135. Hallett TB, Baeten JM, Heffron R, Barnabas R, de Bruyn G, Cremin I, et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. PLoS Med. 2011; 8:e1001123. [PubMed: 22110407]
136. Pretorius C, Stover J, Bollinger L, Bacaer N, Williams B. Evaluating the cost-effectiveness of preexposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. PLoS One. 2010; 5:e13646. [PubMed: 21079767]
137. El-Sadr WM, Coburn BJ, Blower S. Modeling the impact on the HIV epidemic of treating discordant couples with antiretrovirals to prevent transmission. AIDS. 2011; 25:2295–2299. [PubMed: 21993304]
138. Shelton JD. HIV/AIDS. ARVs as HIV prevention: a tough road to wide impact. Science. 2011; 334:1645–1646. [PubMed: 22194560]
139. McNeil, DG. [13 March 2012] Clinton aims for 'AIDS-free generation'.. The New York Times. Nov 8. 2011 http://www.nytimes.com/2011/11/09/health/policy/hillary-rodham-clinton-aims-for-aids-free-generation.html.

140. Office of the Press Secretary, The White House. [13 March 2012] FACT SHEET: the beginning of the end of AIDS. 2011. http://www.white house.gov/the-press-office/2011/12/01/fact-sheet-beginning-end-aids.

141. World Health Organization. [24 April 2012] Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. 2012. http://www.who.int/hiv/pub/guidelines/9789241501972/en/index.html.

142. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. Lancet. 2008; 372:669–684. [PubMed: 18687459]

143. Barouch DH, Liu J, Li H, Maxfield LF, Abbink P, Lynch DM, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. Nature. 2012; 482:89–93. [PubMed: 22217938]

144. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009; 361:2209–2220. [PubMed: 19843557]

AIDS. Author manuscript; available in PMC 2013 May 11.

Table 1

Exposures of antiretrovirals in genital tract fluid, cells, and tissues compared with blood plasma.

	Data under single-dose (multiple-dose) conditions				
Drug	**CVF**	**VCT**	**SP**	**Seminal mononuclear cells**[a]	**Colorectal tissue**
Nucleoside analogue reverse transcriptase inhibitors					
Tenofovir	1.35 (0.75)[b]	5.8[c,e]/0.6[d,e]	4.4 (5.1)	9.4 (17.5)	33[e]
Abacavir	0.21 (0.08)[b]		(1.5)[b]		
Lamivudine	2.41 (4.11)[b]		(6.70)	1.00	
Zidovudine	3.71 (2.35)[b]		(2.30)	0.36	
Didanosine	0.06 (0.21)[b]				
Emtricitabine	1.11 (3.95)[b]	42[c,e]/7[d,e]			4.3[e]
Stavudine	0.04 (0.05)[b]		(3.50)		
Protease inhibitors					
Lopinavir (with RTV)	0.17 (0.08)[b]		(0.05)		
Atazanavir (with RTV)	0.16 (0.18)[b]		(0.10)		
Ritonavir (RTV)	0.18 (0.26)[b]		0.11 (0.07)[b]		5.8 (12.8)[b]
Indinavir (with RTV)	(4.60)		(1.9)[b]		
Darunavir (with RTV)	(1.5)[b]		0.18 (0.20)[b]		1.26 (2.70)[b]
Amprenavir	(0.50) with RTV		(0.20) without RTV		
Nelfinavir			(0.08)[b]		
Saquinavir (with RTV)			(0.03)[b]		
Nonnucleoside reverse transcriptase inhibitors					
Efavirenz	0.005 (0.004)[b]		(0.03)		
Nevirapine	(0.80)		(0.60)		
Delavirdine	(0.40)				
Etravirine	(1.3)[b]		0.17 (0.15)[b]		15.7 (7.5)[b]

Drug	Data under single-dose (multiple-dose) conditions				
	CVF	VCT	SP	Seminal mononuclear cells[a]	Colorectal tissue
Entry inhibitors					
Maraviroc	1.9 (2.7)[b]	1.9[b]	0.6 (0.6)[b]		9 (28)[b]
Integrase inhibitors					
Raltegravir	0.64 (0.93)[b]		(3.20)		39 (239)[b]

Comparisons are tissue/blood plasma (BP) paired samples unless otherwise noted. AUC, area under the concentration–time curve; BP, blood plasma; CVF, cervicovaginal fluid; SP, seminal plasma; VCT, vaginal and/or cervical tissue. Modified from [5].

[a] Seminal mononuclear cells compared to peripheral blood mononuclear cells.

[b] $AUC_{CVF,\ SP,\ or\ tissue} : AUC_{BP}$ ratio.

[c] Cervical.

[d] Vaginal.

[e] $AUC_{tissue\ 1–14\ days} : AUC_{BP\ 1–14\ days}$ ratio.

Table 2

Studies assessing effects of antiretroviral treatment on HIV transmission.

Author	Study location	No. of couples	Study population	Conclusions
Retrospective cohorts				
Musicco *et al.* [34]	Italy	436	HIV + clinic and HIV surveillance center clients and their seronegative partners	ART in HIV-infected men reduces, but does not eliminate, heterosexual transmission of infection
Castilla *et al.* [28]	Spain	393	HIV clinic patients and their seronegative partners	Combined ART applied according to current guidelines has a great potential for preventing HIV transmission to sexual partners
Prospective cohorts				
Bunnell *et al.* [31]	Uganda	926	ART-naive HIV-positive adults enrolled in home-based ART program reporting on their partners (stable/nonstable, HIV-positive/negative)	ART, prevention counseling, and partner VCT associated with reduced estimated risk of HIV transmission during first 6 months of therapy
Del Romero *et al.* [29]	Spain	424	Couples recruited through HIV-positive patients at an HIV/STI clinic	Heterosexual infectivity of HIV in individuals taking effective antiretroviral treatment is low
Donnell *et al.* [30]	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	3381	HIV-positive and HSV-positive individuals and their HIV-negative partners from the partners in prevention HSV/HIV Transmission Study	Provision of ART to HIV-infected patients could be an effective strategy to achieve population-level reductions in HIV transmission
Hernando *et al.* [32]	Spain	339	HIV-positive patients and their partners attending a HIV/STI clinic	Couples-based safe sex counseling and ART can reduce but not eliminate sexual HIV transmission
Melo *et al.* [33]	Brazil	93	HIV clinic patients and their seronegative partners	Transmitters showed significantly higher median viral loads, suggesting that heterosexual transmission of HIV is more a function of viral load than sex of index case. Antiretroviral use may play a role in the prevention of HIV heterosexual transmission
Reynolds *et al.* [35]	Uganda	250	Serodiscordant couples offered free ART if eligible	HIV transmission may be reduced among HIV-discordant couples after initiation of ART due to reductions in viral load and increased consistent condom use
Sullivan *et al.* [36]	Rwanda, Zambia	2993	Serodiscordant couples initiated on ART if eligible	ART was associated with a 94% reduction in transmission; ART initiation is a critical component of a package of biomedical and behavioral prevention services
Wang *et al.* [37]	China	1927	Former plasma donors and their seronegative spouses	Transmission events occurred with equal frequency in couples regardless of whether the partner was provided ART

ART, antiretroviral therapy; HSV, herpes simplex virus; STI, sexually transmitted infections; VCT, voluntary counseling and testing.

Table 3

Ecological studies.

Author	Analysis method	Statistical analysis results	Conclusions
Castel *et al.* [51]	Negative binomial regression of new diagnoses on mean CVL	Lack of association reported ($P = 0.11$)	No association was found between trends in the mean CVL and newly diagnosed HIV/AIDS cases
Das *et al.* [52]	Poisson regression of new diagnoses on changes in total and mean CVL; meta-regression of estimated incidence on changes in total and mean CVL	Statistically significant trend with new diagnoses noted ($P = 0.003$); lack of association using estimated incidence ($P > 0.30$)	Reductions in CVL were associated with decrease in new HIV diagnoses but not with slight decrease in HIV incidence
Fang *et al.* [55]	Modified back-calculation to estimate reduction in transmission rate (new cases per prevalent case-year) between pre-ART and post-ART eras	Pre-ART transmission rate estimated as 0.391 new infections per prevalent case; post-ART transmission rate estimated as 0.184 new infections per prevalent case	Provision of free ART was associated with a 53% reduction in the estimated HIV transmission rate
Katz *et al.* [56]	Inferences drawn from observation of concurrent changes in HIV incidence rates, reported sexual behavior, STI diagnoses, and ART use among population in clinical care	–	ART impact on HIV transmission countered by increased reported risk behaviors
Law *et al.* [57]	Inferences drawn from predicted changes in prevalence of undetectable VL among population in clinical care and external reports of HIV incidence	–	Declines in predicted detectable viral load 1997–2009 coincide with reports of rising new diagnoses and estimated incidence in the same community
Montaner *et al.* [53]	Poisson regression of estimated new diagnoses on changes in median CVL and numbers receiving ART	Effect of 100 new patients receiving ART on estimated new diagnoses predicted as –0.97 (95% CI 0.96–0.98); effect of 1 log decrease median CVL on the estimated new diagnoses predicted as –0.86 (0.75–0.98)	Increased ART coverage and reduced CVL are associated with decreased number of new HIV diagnoses
Porco *et al.* [58]	Inferences drawn from trends in annual HIV incidence based on antibody testing and time period (pre-ART versus post-ART period) as indicator of ART use	–	Wider availability of ART appears to have slowed transmission in the study population
Wood *et al.* [54]	Unadjusted and adjusted Cox proportional hazards regression of time to seroconversion on median CVL in the preceding 6 months	Unadjusted hazard ratio for effect of median CVL on time to seroconversion estimated as 3.57 (2.03–6.27) per $\log_{10}$ CVL increase; adjusted hazard ratio for effect of median CVL on time to seroconversion estimated as 3.32 (1.82–6.08) per $\log_{10}$ CVL increase	Median CVL predicts HIV incidence independent of HIV risk behaviors

ART, antiretroviral therapy; CI, confidence interval; CVL, community viral load; IDUs, intravenous drug users; STI, sexually transmitted infection.

Table 4

Preexposure prophylaxis clinical trials.

Study	Study population	Study size	Location	Intervention	Outcome
CAPRISA 004 [81]	Heterosexual women (aged 18–40 years)	898	South Africa	Coitally dependent TFV 1% gel (two doses up to 12 h precoitus and postcoitus)	39% protection; 54% protection calculated in participants using >80% of doses
iPrEx [82]	MSM (mean age in TDF/FTC group 27.5 years)	2499	North and South America, Thailand, South Africa	Daily oral TDF/FTC	44% protection; 92% protection calculated for patients with detectable drug concentrations
TDF2 [83]	Sexually active adults (approximately 90% aged 21–29 years)	1200	Botswana	Daily oral TDF/FTC	63% protection
PIP [84]	Heterosexual HIV serodiscordant couples; (median age 33 years)	4747	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	62% protection with TDF alone; 73% protection with TDF/FTC
FEM-PrEP [85]	Heterosexual women (aged 18–35 years)	1951	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	Trial discontinued for futility in April 2011
VOICE (MTN-003) [86]	Heterosexual women (aged 18–45 years)	5029	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	Oral TDF group discontinued for futility in September, 2011; TFV 1% gel and placebo gel groups discontinued for futility in November 2011; oral TDF/FTC group continues
HPTN 052 [41]	Heterosexual and homosexual HIV serodiscordant couples (60% aged 26–40 years)	1726; 37	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Immediate or delayed ART in HIV-infected partner	96% protection

ART, antiretroviral therapy; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, tenofovir diphosphate.

Table 5

Selected modeling studies examining the impact of treatment as prevention on the HIV epidemic.

Source	Model setting	Model risk group(s)	Main predictions
Blower *et al.* [117]	San Francisco	MSM	Increased ART use could substantially reduce epidemic, but if risk behavior increases as a direct result of increased ART use, net benefit could be ~0
Gray *et al.* [118]	Uganda	Heterosexuals	ART alone cannot control mature HIV epidemics; ART in combination with a low-efficacy vaccine and in the absence of behavioral disinhibition could control the epidemic
Baggaley *et al.* [119]	Southern Africa	Heterosexuals	Increased treatment is unlikely to control the epidemic, regardless of extent of ART roll-out; counseling to reduce risk behaviors is essential
Granich *et al.* [120]	South Africa	Heterosexuals	An annual test-and-treat strategy could eliminate the HIV epidemic within 10 years
Bezemer *et al.* [121]	The Netherlands	MSM	Decreasing risk behavior will have the greatest impact on the HIV epidemic, but earlier diagnosis and treatment can also prevent substantial numbers of infections
Dodd *et al.* [122]	Theoretical	Heterosexuals	Test-and-treat interventions can substantially reduce HIV transmission in some contexts, but inadequate intervention coverage and uneven distribution of risk behaviors could dramatically compromise effectiveness
Long *et al.* [123]	USA	MSM, IDUs, heterosexuals	Substantial reductions in risk behavior will be required to markedly affect the epidemic, even with substantial expansion of HIV screening and treatment
Smith *et al.* [124]	San Francisco	MSM	Transmission of antiretroviral-resistant strains could substantially compromise HIV treatment programs
Walensky *et al.* [125]	Washington, DC	Not specified	A test-and-treat intervention with annual testing and realistic rates of intervention uptake is unlikely to halt the HIV epidemic

ART, antiretroviral therapy; IDUs, intravenous drug users.