

HIV prevention 2010: where are we now and where are we going?

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The world-wide spread of HIV continues at an unacceptable pace. For every person who initiates treatment, three or more people become infected and most people who are infected have never been tested or are unaware of their status [1].

This issue of *Current Opinion in HIV and AIDS* is devoted to prevention of sexual transmission of HIV. As previously reviewed [1], prevention efforts can be divided into windows of opportunity focused on moments in time (Fig. 1).

The greatest efforts in HIV prevention have been devoted to keeping people negative, and success has been witnessed in some countries, including countries in sub-Saharan Africa. The cultural and behavioral forces that lead to reduced incidence of HIV in Uganda, for example, are complex and perhaps difficult to sort out [2], and the benefits of the ABC (abstinence, behavior change, and condom) strategy have not reduced urgent need for biological prevention. Indeed, in this issue McDonald and Hart have emphasized the great difficulty in preventing the spread of HIV among men-having-sex-with-men (MSM), regardless of intensive efforts to inspire behavior change [3]. And these data are even more alarming as we learn more about MSM behaviors in China [4] and Africa [5], where stigma has, heretofore, almost completely obscured this risk population.

Among the people who are HIV negative the two most credible interventions have included treatment of classical sexually transmitted diseases (STDs) (especially HSV-2) and male circumcision. STD interventions to prevent HIV have simply not worked well. Of multiple randomized controlled trials only one has actually reduced HIV-1 incidence [6]. Yet it remains very likely that STDs facilitate HIV transmission [7]. Perhaps the key problem lies with STD (therapeutic) interventions themselves. They are not good enough. A successful STD intervention must include just the right drugs at just the right times, and the drugs need to work well [7].

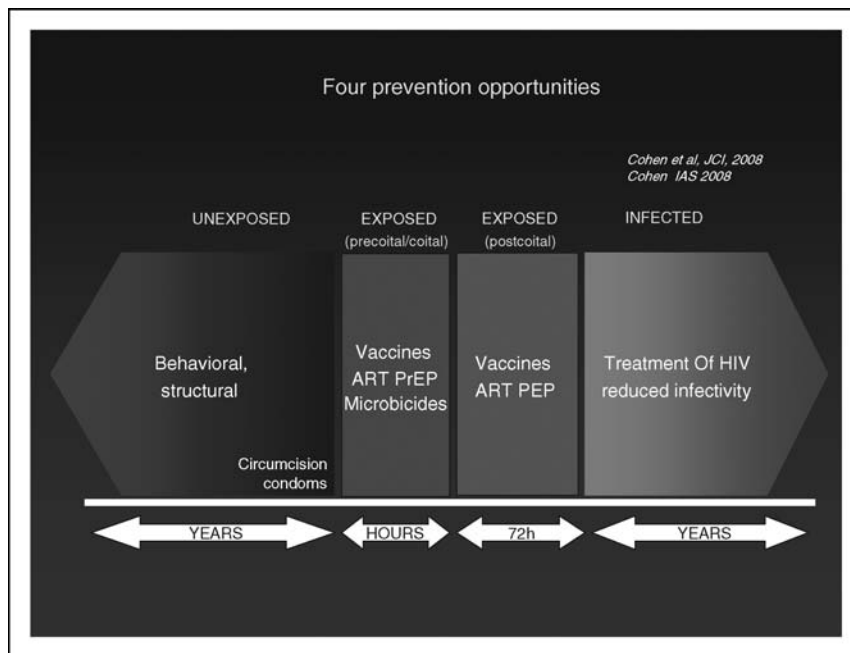
Acyclovir treatment for people who have HIV/HSV co-infection failed to prevent HIV transmission [8]; and acyclovir provided to people who have HSV-2 infection failed to prevent HIV acquisition from a sexual partner [9]. These results do not mean that HSV-2 does not facilitate HIV-1 transmission. Rather, acyclovir fails to adequately suppress reactivation of HSV-2 lesions [10]; in a study designed to demonstrate the power of acyclovir to prevent HIV transmission [9], more than 60% of women continued to experience recurrences of lesions [10]. And HSV-2 causes chronic tissue inflammation that includes infiltration of mononuclear cells expressing greatly increased numbers of CCR5 and CXCR4 receptors (available for acquisition of HIV) that can be detected long after cutaneous lesions have resolved [11].

On the other hand, male circumcision provides powerful protection against HIV. As reviewed by Templeton in this issue [12], male circumcision trials have demonstrated more than 50% reduction of HIV acquisition, and circumcision rollout is underway. The key question is whether enough men in the riskiest environments can be circumcised with the safety and efficiency demanded to stop the spread of HIV.

The acquisition of HIV occurs at a single moment in time, and sexual transmission of HIV reflects critical local events [13]. Keele [14] has summarized very recent data about the transmitted HIV variant(s). Surprisingly, regardless of exposure to a vast and diverse number of HIV variants more than 80% of people acquire a single HIV viral variant, and very few patients acquire more than two or three. These results demonstrate a transmission ‘bottleneck’ that is not yet understood.

Biological prevention strategies require all defenses in place at the moment of a potential transmission event. Circumcision, of course, requires considerable advance planning, as would a vaccine. And HIV vaccine efforts have been fraught with challenges [15]. However, a very large vaccine trial in Thailand demonstrated modest (31%) protection for a year after vaccination most likely ascribed to antibody formation [16]. These observations have rejuvenated the quest for a truly preventive HIV vaccine, as opposed to a vaccine that allows infection but with reduced peak and set point viral load [15]. Recently it has been possible to identify antibodies that neutralize HIV (reviewed in [17]), and to demonstrate antibody mediated passive protection from infection after a

Figure 1 Four prevention opportunities



Reproduced with permission from [1].

mucosal simian immunodeficiency virus-HIV chimera (SHIV) challenge [18].

Biological prevention strategies for the immediate future all involve antiretroviral therapy (ART). Oral post-exposure prophylaxis for HIV after parenteral (needlestick) or sexual exposure has been widely adopted, as discussed by Barber and Benn in this issue [19]. Pre-exposure ART could be provided by parenteral or oral delivery, or as a topical microbicide. Oral pre-exposure prophylaxis requires that the antiviral agents achieve rapid, reliable and durable concentration(s) in the genital tract. Taylor and Davies have nicely reviewed the pharmacology of ART [20]. Ramjee has reviewed [21] the topical use of antiretroviral agents for the same purpose. The nonspecific agents (Buffergel, PRO2000) tested have been disappointing, and future emphasis will focus on antiretroviral agents, some of which are still in development. The feasibility and capability of current healthcare systems to deliver ART to HIV uninfected individuals globally will be an enormous challenge not only requiring availability of appropriate antiretroviral agents but also necessitating regular HIV testing to ensure PEP and PrEP are only given to uninfected individuals. In summary, although it seems very likely that ART treatment will reduce the transmission of HIV, it is premature to conclude that a population-level benefit is sure, and without feasibility, acceptability and operational studies further mathematical modeling alone will not answer this critical question.

Arguably, turning treatment into prevention is a sensible and compelling prevention strategy. More than 20 years ago investigators started working to demonstrate the biological plausibility of this approach, first by demonstrating the ability of ART to reduce HIV in genital secretions (reviewed in [22]). Very recent observational data have demonstrated that, at least over a short period of time, ART can reduce transmission of HIV in discordant couples [23–25]. A large randomized controlled trial (HPTN052) is underway to try to prove that ART provides durable protection in discordant couples (at www.hptn.org).

Mathematical modeling and ecological studies can be used to examine ‘treatment as prevention’. Model results are entirely determined by the assumptions employed and the math. In one model ART appears poised to end the HIV epidemic if virtually everyone can be tested and if everyone who is HIV positive can be reliably treated [26]. However, other models (reviewed in [27]) do not support this conclusion and at least one model suggests the potential for the spread of HIV-resistant variants [28].

Some ecological studies suggest a benefit [29,30] of widespread use of ART at the population level and others demonstrate no effect [31,32]. Two recent studies [29,30] have used ‘new diagnosis’ of HIV as a surrogate for HIV incidence. In these studies introduction of ART in a community has been associated with reduced newly recognized cases of HIV. In San Francisco [29], reduction

in viral load in people with recognized and treated HIV has been correlated with diminished new cases in the community. Although intriguing, this approach is problematic because the actual presentation of HIV or AIDS often occurs years after infection, and in many cases, HIV must have been acquired in these communities at a time well before many people were treated for HIV. The actual measurement of incident HIV in a cohort of MSM in Amsterdam [30] and by epidemiological methods in France [31] has failed to demonstrate reduced HIV incidence. Indeed, using an imperfect antibody measure of incidence of HIV in San Francisco failed to show a significant change [28]. In summary, although it seems very likely that ART treatment will reduce the transmission of HIV it is premature to conclude that a population-level benefit is sure, and further mathematical modeling will not answer this critical question.

Furthermore, no mathematical model deals well with patients with acute HIV infection, who are very difficult to find [33] but might contribute substantially to the spread of HIV. Modelers have suggested that 8–40% of incident HIV can be ascribed to acute transmission, as reviewed in this issue by Miller *et al.* [34]. Viral phylogeny data in some places support this idea [35]. These results suggest that detection and treatment of patients with early and immediate ART might offer public health benefit [36]. But empiric treatment of HIV in acute infection is debated [36,37]. In reviewing this idea in this issue, Hamlyn *et al.* [37] note that treatment of people with acute infection has not yet demonstrated therapeutic benefit for the individual. Such limitation likely reflects the fact that patients are rarely found early enough to avoid irreparable damage to the immune system [15]. However, the high viral load associated with acute HIV infection coupled with specific characteristics of recently transmitted viral variants provides great potential for HIV transmission that lasts for several months after infection [38].

In summary, this issue of *Current Opinion* offers an impressive and comprehensive view about current HIV prevention efforts, and things are moving very fast. In the near future results of randomized trials using ART as a microbicide for women and as oral pre-exposure prophylaxis for men and women will be available. Several feasibility studies devoted to increased HIV testing and treatment, and immediate treatment, are either in development or underway. It seems likely that biological prevention strategies to that complement the success of ABC and male circumcision will be forthcoming.

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