



NEW APPROACHES TO HIV PREVENTION

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Just as the 1996 International AIDS Conference in Vancouver ushered in the era of effective combination antiretroviral therapy and the 2000 meeting in Durban focused on the HIV/AIDS epidemic in the developing world, the 2006 conference (held August 13–18 in Toronto) may be remembered as the one that brought HIV prevention to the fore.

Political considerations aside, it has become abundantly clear that efforts to promote behavioral change—the so-called “ABC” approach, relying on abstinence, marital fidelity (“be faithful”), and condoms—has failed to stem the tide of new HIV infections.

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), some four million people worldwide were newly infected in 2005. Even as antiretroviral therapy begins to trickle down to people in resource-limited countries, public health experts estimate that about four people become infected with HIV for each person who starts treatment.

NEW PREVENTION TECHNOLOGIES

Recognizing the limitations of traditional behavioral approaches, researchers and advocates have turned their attention to several experimental prevention technologies, which were discussed at numerous scientific sessions, policy roundtables, and press briefings at the Toronto conference:

- HIV vaccines
- Vaginal and rectal microbicides
- Adult male circumcision
- Treatment of other sexually transmitted infections
- Pre-exposure prophylaxis (PrEP) using antiretroviral drugs

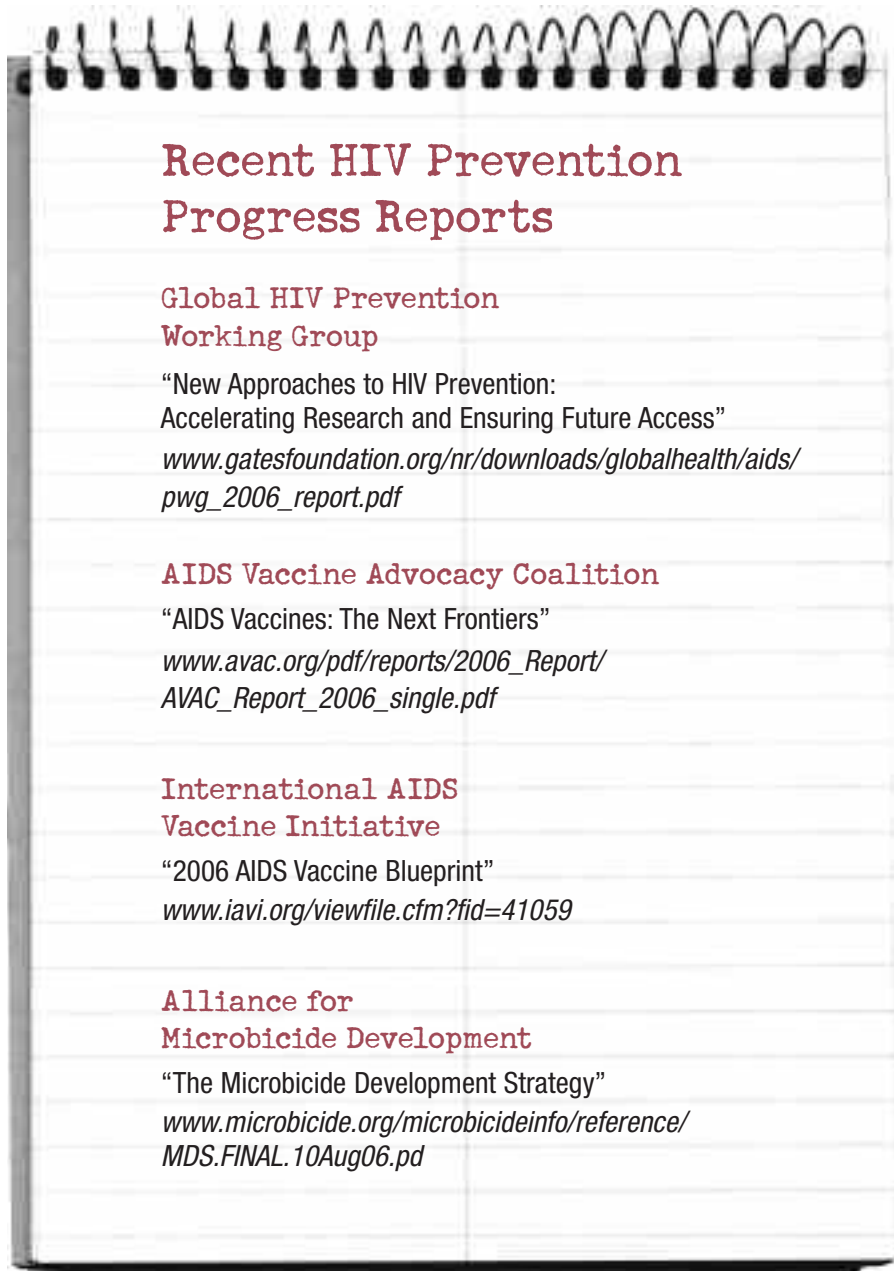
"I would like to believe that HIV prevention soon will be more than 'ABC'," said Gita Ramjee, PhD, of the South African Medical Research Council, speaking at a plenary session on prevention technologies. "We will add one more 'C' for circumcision. We will add 'D' for diaphragm, 'E' for pre- and post-exposure prophylaxis, 'F' for female controlled microbicides, 'G' for genital tract infection control, 'H' for herpes simplex virus suppression, and 'I' for immunity by vaccines."

HIV VACCINES

Ever since the virus was identified in the mid-1980s, an effective HIV vaccine has been the "holy grail" of prevention research. But two decades later, progress has been frustratingly slow.

In 1997, then-president Bill Clinton predicted the availability of an HIV vaccine within ten years, recalled Susan Buchbinder, MD, at a session on prevention at the late-September International Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco. "Next year it will be ten years, and we will not have an efficacious vaccine," she said, "but we are making progress."

Clinton may be forgiven for underestimating the difficulty of the task. Development of even a partially



Recent HIV Prevention Progress Reports

Global HIV Prevention Working Group

"New Approaches to HIV Prevention: Accelerating Research and Ensuring Future Access"
www.gatesfoundation.org/nr/downloads/globalhealth/aids/pwg_2006_report.pdf

AIDS Vaccine Advocacy Coalition

"AIDS Vaccines: The Next Frontiers"
www.avac.org/pdf/reports/2006_Report/AVAC_Report_2006_single.pdf

International AIDS Vaccine Initiative

"2006 AIDS Vaccine Blueprint"
www.iavi.org/viewfile.cfm?fid=41059

Alliance for Microbicide Development

"The Microbicide Development Strategy"
www.microbicide.org/microbicideinfo/reference/MDS.FINAL.10Aug06.pdf

effective HIV vaccine must overcome several obstacles, including the natural variability of the virus, its rapid mutation, its ability to lie hidden in long-lived "reservoir" cells, and the fact that it infects the very cells needed to mount an effective immune response.

Nevertheless, several candidates have shown promise in laboratory and animal studies, including both prophylactic vaccines that prevent infection and therapeutic vaccines intended to delay disease progression. The good

news on the vaccine front, Buchbinder added, is that in more than 50 Phase I and II vaccine trials to date, "the safety profile, overall, has been excellent."

Concerns about safety rule out the use of live attenuated or whole inactivated HIV in vaccines, necessitating alternate techniques. The earliest prophylactic vaccine candidates attempted to stimulate production of neutralizing antibodies against HIV by presenting pieces of the virus, such as the gp120 envelope protein. Despite early hints of efficacy, these subunit

vaccines have failed to produce lasting antibody responses in more than 30 clinical trials. Even after years of research, it remains unclear which—if any—HIV antigens might stimulate a robust humoral (antibody-mediated) immune response, and whether this is enough to prevent infection.

Most current vaccine trials focus on therapeutic candidates that aim to stimulate the body's natural immune response to HIV after infection. Several are designed to promote cellular immunity mediated by CD8 cytotoxic T-lymphocytes, or killer T-cells, by presenting bits of HIV DNA (plasmids) or HIV genes carried by harmless genetically engineered vector viruses. A combination vaccine—for example, a DNA “primer” followed by a viral vector “booster”—may prove most effective.

Vaccines using canarypox and smallpox vectors have shown limited effectiveness, producing only weak and transient immune responses. About a dozen candidates use the modified Vaccinia Ankara (MVA) poxvirus. At the AIDS Vaccine 2006 conference in Amsterdam in early September, Swedish researchers reported that a DNA plasmid primer combined with an MVA booster containing HIV subtype AE *env*, *gag*, and *pol* genes produced strong CD8 cell responses in more than 90% of vaccinated participants in a small Phase I trial.

Adenovirus vectors appear to be the most promising current therapeutic vaccine approach. A potential drawback is that many people are already immune to adenoviruses—responsible for the common cold and other respiratory infections—which may limit their use as vaccine vectors.

Two adenovirus HIV vaccines are now in large clinical trials. Early data reported at the Amsterdam meeting indicate that both stimulate CD8 cell responses in a majority of vaccinated volunteers. Merck's candidate, a trivalent adenovirus type 5 vector encoding HIV subtype B *gag*, *pol*, and *nef* genes, is under study in the STEP

trial in North and South America and Australia. Another candidate, which expresses subtype B *gag* and *pol* proteins plus *env* proteins from subtypes A, B, and C, is being tested in HIV Vaccine Trials Network (HVTN) Study 054 in the United States, South America, and South Africa. (For currently enrolling vaccine trials, see “Open Clinical Trials,” page 54).

Importantly, a prophylactic HIV vaccine need not be completely effective to have a major impact on the epidemic. According to one mathematical model recently developed by the International AIDS Vaccine Initiative (IAVI) and the Futures Group, a 30% effective vaccine given to just 20% of the at-risk population could reduce new infections by 17%.

Yet even a partially effective vaccine is not on the near horizon, underlining the need for alternative prevention methods. “Unless there's some striking breakthrough that we're not aware of,” cautions UNAIDS chief scientific advisor Cate Hankins, “it's likely to be another ten years before one is commercially available.”

MICROBICIDES

Microbicides—chemicals that work by various mechanisms such as forming a physical barrier to viral entry, increasing acidity in the vagina, blocking HIV entry into cells, or interfering with viral replication—have gained increasing attention as an HIV prevention strategy.

Vaginal microbicides have been promoted since the early 1990s as a female-controlled method that women could use without the knowledge or consent of their male partners—a crucial consideration, given that many women worldwide lack the social and economic power to refuse sex or demand that their partners use condoms.

“Abstinence is not an option for some poor women and girls who have no choice but to marry at an early age. Being faithful will not protect a woman whose partner is not faithful. And using condoms is not a decision

that a woman can make by herself,” said philanthropist Bill Gates during his opening keynote address at the Toronto conference. “No matter where she lives or what she does, a woman should never need her partner's permission to save her own life.”

Rectal microbicides are equally important, for both men who have sex with men and for women who practice anal sex, but they have less political support and thus have not been studied as extensively as vaginal microbicides. Many microbicide candidates (such as those that block viral entry or replication) should in principle work both vaginally and rectally, but it is important that such products be specifically tested for rectal as well as vaginal use, since the delicate mucous membranes of the rectum are more prone to irritation and damage. To date, however, though numerous animal studies have tested rectal use of microbicides, all large human trials involve only vaginal use.

As noted in a recent review article by John Moore, PhD, and colleagues in the open-access journal *PLoS Medicine*, a successful microbicide will have to fulfill four criteria: safety, efficacy, acceptability, and affordability.

The first major microbicide candidates, containing the spermicidal agent nonoxynol-9, proved a dismal failure. Repeated use of the chemical irritated vaginal and rectal mucous membranes, thereby actually increasing the likelihood of HIV infection. Agents that cause local inflammation are also potentially hazardous, since an inflammatory response draws immune cells to the mucous membranes, where they are more susceptible to viral entry during sex. More recently, in January 2007, a Phase III trial of UsherCell gel (cellulose sulfate) involving more than 1300 women in Africa and India was discontinued after preliminary data showed that women using the product had a higher risk of HIV infection than those using a placebo gel; a similar trial in Nigeria was also halted as a precaution.

Microbicide Candidates in Development

Preclinical

BMS-378806: gp120 attachment inhibitor

CMRD 167: small molecule CCR5 inhibitor

C52L: peptide fusion inhibitor

T-1249: fusion inhibitor related to T-20

Phase I

Cellulose acetate: entry inhibitor

MIV-150: NNRTI

PC 815: combination Carraguard plus MIV-150

UC-781: NNRTI

VivaGel (SPL7013): entry inhibitor

Phase II

AcidForm (Amphora) gel: vaginal defense enhancer

Dapivirine (TMC120): NNRTI

Invisible Condom: entry inhibitor

Praneem: herbal product, mechanism unknown

Tenofovir (PMPA) gel: nucleotide reverse transcriptase inhibitor (NRTI)

Phase III

BufferGel: vaginal defense enhancer

Carraguard: non-specific entry inhibitor

PRO2000: non-specific entry inhibitor

Savvy (C31G) gel: surfactant

UsherCell (cellulose sulfate): non-specific entry inhibitor
[studies halted in January 2007 due to safety concerns]

According to Ramjee, there are some 30–40 microbicide candidates in preclinical development, 14 in early safety studies, and five undergoing efficacy trials in humans (including the now-cancelled UsherCell studies); the Alliance for Microbicide Development

lists more than a dozen products currently in Phase I, II, or III trials (see sidebar above). Some candidates are active against other sexually transmitted pathogens in addition to HIV. Some are contraceptives, while others may be used by women who wish to become pregnant.

Microbicides of various types have demonstrated preliminary efficacy in animal studies, which typically involve monkeys vaginally or rectally exposed to simian immunodeficiency virus (SIV) or a hybrid simian/human immunodeficiency virus (SHIV).

Several microbicide candidates are similar to HIV entry and replication inhibitors currently used for antiretroviral therapy. The nucleotide reverse transcriptase inhibitor tenofovir DF (Viread)—lately in the news as a candidate for PrEP—has also been tested in gel form. This past December, Gilead Sciences granted the non-profit International Partnership for Microbicides and CONRAD the right to develop, manufacture, and distribute the agent as a microbicide in resource-limited countries.

Studies have shown that a 1% tenofovir gel protected macaque monkeys from SIV infection, and that tenofovir reaches high concentrations in the human male and female genital tracts. It also appears generally safe as a vaginal microbicide. In one study, most women reported mild side effects such as genital irritation, but said they would use the product if available; such irritation is a concern, however, because any damage to vaginal or rectal membranes could facilitate HIV infection if a microbicide is less than 100% effective.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine, or TMC120, appeared safe in a recently completed Phase I trial. Entry inhibitors, several of which are moving through the pipeline as oral agents for HIV treatment, are also being developed as microbicides, including fusion inhibitors related to T-20 (enfuvirtide, Fuzeon) and CCR5 inhibitors.

It is likely that the best results will be achieved using combination microbicides that work by multiple mechanisms (e.g., providing a physical barrier, inhibiting viral entry into cells, and suppressing HIV replication). Combination therapy would also help allay concerns about resistance,

should agents used as microbicides later be needed for treatment.

With regard to acceptability, a recent study in Thailand found a high rate of continued use of Carraguard, a microbicide gel derived from seaweed, among monogamous couples who did not regularly use condoms. Most respondents (92% of women and 83% of men) reported that they liked the product somewhat or very much; only 15% of the women, but 43% of the men, thought the gel could be used without the man's knowledge.

Other microbicide delivery methods are also being explored in addition to the more common topical gels and creams. These include cervical caps and vaginal sponges or rings that could be left in place to release chemicals over time, thereby avoiding the need to administer an obvious and possibly messy product immediately before having sex. As Alex Coutinho of the AIDS Support Organization in Uganda put it, "women need something they can fit and forget."

The development of microbicides has been challenging due to myriad technical, logistical, and ethical issues, some of which were discussed in an article in the Summer 2006 issue of *BETA* covering the Microbicides 2006 conference last April. Nevertheless, Ramjee estimates that the first microbicides could be commercially available by 2010—well ahead of an effective HIV vaccine. Phase III trials of Carraguard are expected to be completed by the first quarter of this year.

MALE CIRCUMCISION

Adult male circumcision has also taken its place at the forefront of HIV prevention strategies. More than two dozen abstracts at the Toronto conference were devoted to the topic, and in December, two controlled studies in Africa were halted after interim data showed that circumcision cut the risk of HIV acquisition by half.

Circumcision has been proposed as a protective measure since the late 1980s, based on the observation that

in the developing world, HIV prevalence tends to be lower among groups that practice routine circumcision of male children or adolescents. One meta-analysis, for example, showed that across 27 studies, circumcision was associated with a significantly reduced risk of HIV infection among men in sub-Saharan Africa. But it is difficult to separate out the effects of the procedure itself versus associated factors such as cultural and religious attitudes about sex. (Female genital cutting, sometimes referred to as "female circumcision," involves reduction or excision of the clitoris and labia; this procedure is not associated with lower risk of HIV infection, and may in fact facilitate transmission.)

Adding to the epidemiological evidence, there are plausible biological mechanisms by which male circumcision could reduce the likelihood of HIV infection. In uncircumcised men, the foreskin provides an additional area of mucous membrane susceptible to viral entry. A recent anatomical analysis found that Langerhans' cells with HIV-1 receptors (a type of immune cell that takes up invading pathogens) were present close to the surface in the inner foreskin, and that the inner foreskin had a thinner protective keratin layer than either the outer foreskin or the glans of the penis.

Data from randomized controlled trials of circumcision as an HIV prevention method have so far been encouraging. In the November 2005 issue of *PLoS Medicine*, Bertrand Auvert, MD, reported on a study that included more than 3000 young men in the Orange Farm township near Soweto, South Africa. The men, all of whom expressed an interest in adult circumcision, were randomly assigned to undergo the procedure immediately or at the end of the two-year study period. The trial was stopped early after an interim analysis at 18 months showed that men in the immediate circumcision group experienced 60% fewer HIV infections compared with the delayed group (incidence rates of

0.85 and 2.1 per 100 person-years, respectively).

In a follow-up analysis, Auvert and an international group of public health experts estimated that over the next ten years, routine circumcision of men throughout Africa could avert two million HIV infections and prevent 300,000 deaths. Likewise, a mathematical model presented in Toronto showed that in a high-prevalence area such as Soweto, a five-year program in which 10% of currently uncircumcised men underwent the procedure each year could prevent an estimated 32,000 infections and decrease the HIV prevalence rate to 14% after 20 years; even if condom use fell to zero, the model found, circumcision would still provide a net benefit.

On December 12, the National Institutes of Health (NIH) halted two similar controlled circumcision trials after interim analyses showed that the intervention significantly reduced the risk of HIV infection. In a trial of 4996 HIV negative men aged 15–49 in Rakai, Uganda, the rate of HIV acquisition fell by 48%; the infection rate decreased even more—by 53%—in a study of 2784 young men aged 18–24 in Kisumu, Kenya. In both studies, participants received condoms and HIV prevention counseling. The trials were scheduled to continue through mid-2007, but given the clear benefit shown by the interim data, a Data Safety and Monitoring Board determined that it would be unethical to continue the trials, and the men who were initially assigned to the non-circumcision arms will be offered the procedure.

"We now have confirmation—from large, carefully controlled, randomized clinical trials—showing definitively that medically performed circumcision can significantly lower the risk of adult males contracting HIV through heterosexual intercourse," said National Institutes of Allergy and Infectious Diseases director Anthony Fauci, MD. "While the initial benefit will be fewer HIV infections in men, ultimately adult male circumcision

could lead to fewer infections in women in those areas of the world where HIV is spread primarily through heterosexual intercourse.”

However, the World Health Organization (WHO), UNAIDS, other United Nations agencies, and the World Bank issued a joint statement declaring that despite these promising results, circumcision does not provide complete protection against HIV infection. “Circumcised men can still become infected with the virus and, if HIV positive, can infect their sexual partners,” the agencies warned. “Male circumcision should never replace other known effective prevention methods and should always be considered as part of a comprehensive prevention package, which includes correct and consistent use of male or female condoms, reduction in the number of sexual partners, delaying the onset of sexual relations, and HIV testing and counseling.”

It may seem questionable whether men who are reluctant to use condoms to prevent HIV infection will eagerly undergo a painful operation, but in surveys, as many as 80% of men expressed an interest in adult circumcision if it would lower their risk; indeed, in some parts of Africa there are already waiting lists for the procedure.

ROLE OF SEXUALLY TRANSMITTED INFECTIONS

Though hardly a new observation, evidence continues to accumulate that sexually transmitted infections (STIs)—including syphilis, herpes simplex virus (HSV), gonorrhea, and human papillomavirus (HPV)—can facilitate HIV infection, and that STI treatment is an important strategy for HIV prevention.

STIs facilitate infection by producing sores that provide a route for HIV to enter the body, as well as by mobilizing immune cells to the genital tract, where they are susceptible to HIV entry. Research has also shown that certain STIs are associated with

higher HIV viral load in semen and female genital fluids, which increases the likelihood of transmitting the virus either during sex or to an infant during delivery.

“There is no doubt that other genital infections increase the risk of HIV infection,” explains Victoria Cargill-Swiren, MD, of the NIH Office of AIDS Research. “Whenever you have an outbreak like this, you have a burst of HIV activity. Dendritic cells in the genital mucosa provide a perfect Trojan horse for HIV.”

A recent prospective study in Malawi showed that maternal syphilis was associated with greater risk of mother-to-child HIV transmission. Similarly, another study found that among 21 HIV positive New York City women diagnosed with genital HSV infection during pregnancy, six gave birth to HIV-infected infants—nearly five times the transmission rate observed in mothers without HSV.

Several studies have shown that HSV and other STIs also increase rates of sexual transmission of HIV among heterosexual couples and among men who have sex with men. One study, for example, found that genital ulcer disease quintupled the risk of HIV transmission per sex act. A recent Australian study of more than 1400 initially HIV negative gay men found that anal gonorrhea and anal warts (caused by HPV) were linked to higher rates of HIV seroconversion, even after controlling for differences in sexual behavior.

Fortunately, this principle also works in reverse: treating STIs can reduce the risk of contracting or transmitting HIV. As early as the mid-1990s, a Tanzanian study showed that STI treatment was associated with a 40% reduction in HIV transmission. More recently, a study in Burkina Faso showed that daily use of valacyclovir (Valtrex) for the treatment of HSV type 2 decreased vaginal shedding of HIV, which could potentially reduce the risk of both sexual and mother-to-child transmission.

PRE-EXPOSURE PROPHYLAXIS

Of all the new prevention technologies discussed at the Toronto conference, pre-exposure prophylaxis (PrEP) has generated the most interest—and the most controversy.

The latest biomedical approach to HIV prevention, PrEP refers to the use of antiretroviral drugs by HIV negative individuals to prevent infection. PrEP should not be confused with post-exposure prophylaxis (PEP), which refers to the use of drugs for a short period following a potential exposure to HIV, for example through an accidental needle-stick, broken condom, or sexual assault.

PrEP and PEP are based on a similar principle: that confronting HIV with antiretroviral agents before or immediately after exposure may prevent the virus from taking hold in the body. Unlike microbicides and circumcision, PrEP could potentially prevent HIV infection through routes other than sexual transmission, such as sharing drug injection equipment.

At the recent ICAAC session on HIV prevention, Diane Havlir, MD, said that PrEP was the “perfect example of the fields of treatment and prevention coming together.” Myron Cohen, MD, added that, compared with vaccines, “we’ve been good at making antiretroviral drugs,” so we should consider how they might be used to aid prevention efforts.

The effectiveness of antiretroviral drugs in preventing HIV infection has been convincingly demonstrated in the area of mother-to-child transmission. In this setting, antiretroviral therapy works in part by lowering HIV levels in the mother’s blood and genital fluids, but it appears to also help prevent the virus from establishing itself in the newborn’s body.

PrEP has been tested in numerous animal studies, most of which have used tenofovir monotherapy. In an early study published in the November 17, 1995, issue of *Science*, C.C. Tsai and colleagues found that

once-daily injections of tenofovir for four weeks starting either 48 hours before, four hours after, or 24 hours after exposure to SIV prevented infection in all treated macaques, while untreated control monkeys became infected.

However, a more recent study by researchers with the Centers for Disease Control and Prevention (CDC), reported in the October 1, 2006, *Journal of Infectious Diseases*, yielded less promising results. Four male macaques received once-daily oral tenofovir, four received once-weekly oral tenofovir, and four received no PrEP. Once weekly for 14 weeks, the monkeys were rectally exposed to SHIV in doses about five times higher than the amount of HIV in human semen during acute infection. The untreated control animals became infected after one to two weeks, compared with an average of six weeks for those receiving once-daily tenofovir and seven weeks for those in the once-weekly tenofovir group; one monkey receiving daily tenofovir remained uninfected after all 14 exposures. While tenofovir delayed infection, the difference did not reach statistical significance, leading the authors to conclude that “oral tenofovir DF provided partial protection against SHIV infection, but ultimately did not protect all tenofovir DF-treated animals against multiple virus challenges.”

In a study reported at the 2006 Conference on Retroviruses and Opportunistic Infections, J. Gerardo Garcia-Lerma, PhD, and colleagues, also from the CDC, found that PrEP using tenofovir plus emtricitabine (Emtriva) was more effective than either drug alone. After receiving injections of antiretroviral drugs for nine days, macaques were repeatedly challenged with weekly rectal exposures to SHIV, in amounts similar to those present during sexual intercourse. After 14 exposures, none of the monkeys receiving tenofovir/emtricitabine became infected, com-

More Information on PrEP and Ongoing Trials

“CDC Trials of Pre-Exposure Prophylaxis for HIV Prevention”
Centers for Disease Control and Prevention:
www.cdc.gov/hiv/resources/factsheets/prep.htm.

“PrEP Watch”
AIDS Vaccine Clearinghouse:
www.aidsvaccineclearinghouse.org/preparewatch.

pared with five out of six untreated control animals. Two out of six monkeys were infected after receiving emtricitabine alone, and a study reported at the 2005 Retrovirus conference showed that all four monkeys who received only tenofovir became infected.

In a late-beaker session at the Toronto conference, Leigh Peterson, PhD, of Family Health International (FHI) presented the first hint that PrEP might be effective in humans. Researchers conducted a double-blind study that enrolled 936 at-risk HIV negative women in Ghana, Cameroon, and Nigeria. Participants were randomly assigned to receive 300 mg daily tenofovir monotherapy or placebo. Among the 731 women with nine months of follow-up data, eight became infected with HIV: two in the tenofovir arm and six in the placebo arm (0.86 vs 2.48 infections per 100 person-years). Although the infection rate was 65% lower in the PrEP arm, the difference did not reach statistical significance due to the small numbers involved. The study also found that adverse events were rare and PrEP did not lead to an increase in high-risk sexual activity.

Over the next few years, further data will be forthcoming from ongoing tenofovir PrEP trials studying young heterosexual couples in Botswana,

injection drug users in Thailand, and men who have sex with men in Peru and the United States (see the “Project T” listing in “Open Clinical Trials,” page 53). The Botswana and Peru studies recently added emtricitabine to their PrEP regimens.

Implications of this strategy were discussed at a special session in Toronto, titled “What If PrEP Works?” One concern is the long-term side effects of antiretroviral drugs used for many years by uninfected individuals, for whom the risk/benefit calculation is different from that for HIV positive patients. With tenofovir, the potential risks include kidney toxicity and bone loss, as well as liver inflammation “flares” in people with hepatitis B.

Another concern is the emergence of drug resistance. In a review article in the August 16, 2006, *Journal of the American Medical Association (JAMA)*, three investigators with the ongoing PrEP trials noted that, “this may be a particular problem if PrEP is taken episodically or even as a single-dose ‘evening before’ or ‘morning after’ pill, resulting in suboptimal plasma and intracellular concentrations.” Indeed, Garcia-Lerma’s team found that within nine weeks, all 11 monkeys who received tenofovir-monotherapy PrEP showed evidence of the K65R mutation, which confers resistance to tenofovir and other



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IN LIGHT OF THE RECENT

emphasis on new prevention technologies, it is important not to neglect traditional prevention tools such as condoms and clean needles, which—however imperfect—have dramatically reduced the rate of new HIV infections over the past two decades.

These tools would prevent even more infections if they were more widely available—for example, in prisons. In this regard, political, religious, and cultural barriers may be even more difficult to overcome than the scientific challenges facing biomedical prevention approaches. In the words of UNAIDS Executive Director Peter Piot, MD, “the problem with prevention for many is that you cannot avoid dealing with sex and drugs.”

Speaking at the prevention plenary in Toronto, Cristina Pimenta, PhD, of the Brazilian Interdisciplinary AIDS Association warned against viewing the new biomedical interventions as “magical solutions” that deflect attention away from “the fundamentally political barriers that have been erected in recent years by some governments and agencies

nucleoside/nucleotide reverse transcriptase inhibitors.

If PrEP comes into widespread use, some fear resistance rates may increase community-wide, thereby rendering certain drugs less useful for treatment. Extensive tenofovir resistance would be especially problematic for antiretroviral treatment programs in resource-limited settings, because it is one of the simplest and best-tolerated components of highly active antiretroviral therapy (HAART). As is the case with HAART, however, combination PrEP would likely reduce the emergence of resistance mutations.

Although researchers and advocates have taken pains to emphasize that PrEP has not yet been proven effective, some HIV negative people are nevertheless reportedly already using tenofovir “off label” for this purpose.

“PrEP clinical trials should proceed quickly to provide the evidence required for informed counseling about PrEP,” wrote the authors of the recent *JAMA* article. “While the results of these trials are eagerly awaited, optimism for the future should not replace currently available and proven prevention strategies.”

TREATMENT FOR ALL

Besides PrEP and PEP, another way to use existing antiretroviral drugs to reduce new infections involves treating all HIV positive individuals, whether they currently require therapy or not.

Current U.S. HIV treatment guidelines suggest that people should initiate HAART when their CD4 cell counts fall below 350 cells/mm³ or their viral loads rise above 55,000 copies/mL. While there is some evidence that earlier treatment may be beneficial, most experts do not believe antiretroviral therapy is indicated for individuals with very high CD4 counts and low viral loads.

But there is little question that effective antiretroviral therapy dramatically reduces HIV levels in blood, semen, and female genital fluids, which in turn can significantly lower

the risk of transmission. At ICAAC, Cohen noted that transmissibility is highest during acute or primary infection, then falls during the early and middle stages of HIV disease, only to rise again during late-stage disease. Numerous studies conducted throughout the world have shown that the risk of sexual and mother-to-child HIV transmission is greatly reduced when viral load is low; indeed, several have observed no cases of transmission from people on HAART with undetectable HIV RNA.

In the August 16, 2006, issue of *The Lancet* and at the Toronto conference, Julio Montaner, MD, and colleagues presented a mathematical model suggesting that if all HIV positive people received treatment at once, the rate of new infections could drop by as much as 70% over 45 years.

“The present approach to the management of HIV/AIDS is clearly not sustainable, and the status quo no longer acceptable if we hope to control the continued growth of the HIV global pandemic,” the authors wrote. “Although treating 100% of HIV-infected individuals worldwide might not be feasible or even ethically acceptable at this time, given the state of the pandemic, consideration of this possibility is worthwhile.”

The proposal is not without drawbacks, which (as with PrEP) include long-term toxicities and emergence of drug-resistant virus. In addition, viral load is highest during acute infection, when most people do not yet realize they are infected and therefore would not seek treatment.

Nevertheless, Cohen told clinicians at ICAAC, “providing antiretroviral therapy to HIV positive patients in your clinic has a lot of effect on transmission. It’s inevitable that it will serve as part of our overall prevention strategy.”

TRIBULATIONS OF TRIALS

The development of new HIV prevention strategies is hampered by a vari-

ety of challenges, ranging from inadequate funding to ethical questions, including:

- How can researchers ensure that new methods such as vaccines, microbicides, and PrEP will not harm study participants?
- What types of treatment and care will be provided to participants who become infected despite these interventions?
- If the new methods are proven effective, will trial participants and their communities have access to them?
- Is it ethical to provide limited supplies of antiretroviral drugs for use as PrEP when people who are already infected cannot get them?

Such concerns have already led to the discontinuation of several trials, including a PrEP study of sex workers in Cambodia and the Cameroon arm of the FHI trial.

“Trials of potential microbicides and other new HIV prevention approaches are hugely complex undertakings,” Ramjee said at the Toronto conference. “The world’s ability to conduct these trials is reaching maximum capacity, and current clinical trial ethical guidelines were not written with today’s HIV prevention research in mind.”

Competition for trial subjects is a major stumbling block. Phase III prevention trials require large numbers of participants followed over long periods of time, which presents financial and logistical difficulties. Currently, there are about 30,000 women taking part in microbicide trials worldwide (minus about 3000 in the recently cancelled UsherCell studies), 9000 participants in trials of acyclovir (Zovirax) treatment for herpes, and thousands more in various vaccine and PrEP studies.

There is a need for coordination among researchers so that the most promising avenues may be pursued. The proliferation of simultaneous

studies “offers the opportunity to see how various approaches have multiplicative effects,” Buchbinder noted at ICAAC. But if some or all of these prevention strategies are partially effective in reducing HIV infection rates, it could be difficult or impossible to tease out the relative contributions of each.

Since new interventions may not be completely effective, researchers must offer study participants prevention counseling and proven tools such as condoms, which themselves can reduce the rate of new infections. This is good news for the participants, but can mean that trials no longer have the statistical power to determine whether an intervention actually works. Cellegy Pharmaceuticals, for example, recently discontinued a Phase III trial of its Savvy microbicide in Nigeria after an independent monitoring committee determined that due to a lower-than-expected overall rate of new infections, the trial—which provided condoms—no longer had adequate statistical power. “We don’t know whether the condom is working or whether the product is working,” said Chief Financial Officer Robert Caso. An unexpectedly low HIV infection rate also threatens the statistical power of FHI’s ongoing PrEP study in Ghana.

Perhaps the major barrier to stepped-up prevention research is insufficient funding. According to UNAIDS, about \$11.4 billion annually will be needed for HIV prevention by 2008—more than twice the amount currently being spent. Much of the current outlay comes from the U.S. government (via the CDC, NIH, and HVTN), along with other wealthy country governments and the Global Fund to Fight AIDS, Malaria, and Tuberculosis. Activists have criticized the pharmaceutical industry for failing to contribute more, since the greatest demand for new prevention methods will be in developing countries with limited ability to purchase the resulting

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impeding the implementation of proven effective educational approaches, such as condom use and harm reduction.”

Recognizing the importance of these traditional tools, researchers studying new prevention technologies have placed great emphasis on so-called “behavioral disinhibition”: the concern that people who think they are protected by new methods—even if they are not 100% effective—might revert to high-risk sexual and drug-use practices.

However, this may not be as large a problem as some fear if individuals are offered prevention counseling and condoms along with the new methods. In the FHI PrEP study in Ghana, for example, while women reported more sex acts, the number of reported sexual partners declined and the rate of reported condom use rose from 52% to 94%. In the recently discontinued Kenyan circumcision trial, the rate of reported risky sex (defined as unprotected sex with partners other than wives or regular girlfriends) decreased, while the rate of reported consistent condom use increased from 22% at the start of the study to 35% two years after circumcision.



products. Private charities such as the Gates Foundation and the Clinton Foundation HIV/AIDS Initiative have recently announced large grants—in the hundreds of millions of dollars—to develop vaccines, microbicides, and PrEP. Some advocates are concerned, however, that increased charitable funding will let governments and industry off the hook.

CONCLUSION: OVERCOMING BARRIERS

As successful novel prevention strategies come to the fore, they raise new issues in several areas, among them:

- Approval and licensing
- Cost and access
- Distribution and implementation

Cost is a particular concern with regard to microbicides and PrEP, which must be used consistently over the long term, as compared with vaccines and circumcision, which are delivered only once (or a few times, in the case of prime-boost vaccines). Moore and colleagues predict that microbicides will have to be “priced in cents-per-usage” to make them viable for the developing world. “Some sophisticated, high-tech approaches may represent outstanding science,” they wrote, “but would simply be too expensive to apply.”

Distribution and implementation of new prevention technologies are hampered by limited infrastructure and a shortage of health-care personnel in the developing world. Increased demand for adult circumcision, for example, could overwhelm existing clinics, raising the prospect that men might resort to traditional circumcisers working in less-than-sterile conditions; the WHO plans to meet early this year to discuss the implementation of large-scale circumcision programs in resource-limited settings. To implement widespread PrEP, health-care workers (who may

not be physicians experienced in HIV management) will have to be trained to monitor for side effects of antiretroviral drugs.

Advocates and researchers at the Toronto conference and at ICAAC repeatedly stressed that efforts should begin now—even before trials are completed—to train health-care workers, devise public education campaigns, and develop distribution channels so new technologies can be rolled out rapidly as soon as they are shown to be effective.

“The development of effective new HIV prevention approaches could help millions avoid crippling illness and death,” said David Serwadda of Makerere University in Kampala, Uganda, co-chair of the recently established Global HIV Prevention Working Group. “But unless we prepare now to make new, lifesaving tools accessible in developing countries, this scientific triumph will turn into a moral failure.”

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