Annotated Bibliography:

Pre-Exposure Prophylaxis

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Organization of Entries

This publication is a compilation of select journal articles and reports related to pre-exposure prophylaxis (PrEP), an HIV prevention strategy that shows promise in protecting HIV negative individuals from HIV infection. The bibliography was developed by conducting an extensive literature search utilizing MEDLINE (The National Library of Medicine's premier bibliographic database) and web-based search engines.

Abbas UL, Anderson RM, Mellors JW. Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings. PLoS One. 2007;2(9):e875.

The potential impact of pre-exposure chemoprophylaxis (PrEP) on heterosexual transmission of HIV-1 infection in resource-limited settings is uncertain. A deterministic mathematical model was used to simulate the effects of antiretroviral PrEP on an HIV-1 epidemic in sub-Saharan Africa under different scenarios (optimistic, neutral and pessimistic) both with and without sexual disinhibition. Sensitivity analyses were used to evaluate the effect of uncertainty in input parameters on model output and included calculation of partial rank correlations and standardized rank regressions. In the scenario without sexual disinhibition after PrEP initiation, key parameters influencing infections prevented were effectiveness of PrEP (partial rank correlation coefficient (PRCC) = 0.94), PrEP discontinuation rate (PRCC = -0.94), level of coverage (PRCC = 0.92), and time to achieve target coverage (PRCC = -0.82). In the scenario with sexual disinhibition, PrEP effectiveness and the extent of sexual disinhibition had the greatest impact on prevention. An optimistic scenario of PrEP with 90% effectiveness and 75% coverage of the general population predicted a 74% decline in cumulative HIV-1 infections after 10 years, and a 28.8% decline with PrEP targeted to the highest risk groups (16% of the population). Even with a 100% increase in at-risk behavior from sexual disinhibition, a beneficial effect (23.4% - 62.7% decrease in infections) was seen with 90% effective PrEP across a broad range of coverage (25% - 75%). Similar disinhibition led to a rise in infections with lower effectiveness of PrEP ($\leq$50%). Mathematical modeling supports the potential public health benefit of PrEP. Approximately 2.7 to 3.2 million new HIV-1 infections could be averted in southern sub-Saharan Africa over 10 years by targeting PrEP (having 90% effectiveness) to those at highest behavioral risk and by preventing sexual disinhibition. This benefit could be lost, however, by sexual disinhibition and by high PrEP discontinuation, especially with lower PrEP effectiveness ($\leq$50%).

AIDS Vaccine Advocacy Coalition. Anticipating the results of PrEP trials: A powerful new HIV prevention tool may be on the horizon. Are we prepared? August 2008. Available at: http://www.avac.org/prep08.pdf. Accessed July 7, 2009.

This report provides background on pre-exposure prophylaxis (PrEP) research, the status of current clinical trials, and issues concerning effective delivery should PrEP prove effective. It closes with a list of priority issues that need attention now from governments, global health institutions, donors, researchers, and advocates. This report is part of AVAC's "Anticipating and Understanding Results" series, which provides timely analysis of trials of new HIV prevention options.

Al-Jabri AA, Alenzi FQ. Vaccines, virucides and drugs against HIV/AIDS: Hopes and optimisms for the future. The Open AIDS Journal. 2009;3:1-3. Epub. 2009 Jan. 23.

More than 25 million lives have been claimed by AIDS and 33.2 million people are estimated to have HIV, the majority of which are living in the underdeveloped countries. Failed tests on vaccines, virucides and complete virus eradication have caused scientists to refocus on the basic questions of what makes an effective HIV immune response. The "gloom" over disappointing research results on vaccine development and virucides "threatens to overshadow more positive" HIV/AIDS-related news, such as findings that male circumcision might reduce the likelihood of HIV transmission and that giving antiretroviral drugs to "high-risk" HIV-negative people (pre-exposure prophylaxis) could help protect them from infection. Something like pre-exposure prophylaxis has a good chance of becoming available before we have a 100% efficacious vaccine. The future in the field of HIV/AIDS will be much brighter if global research is appropriately coordinated and sufficient funds are available.

Baeten JM. New biomedical strategies for HIV-1 prevention in women. Current Infectious Disease Reports. 2008;10(6):490-498.

Novel HIV-1 prevention strategies continue to be urgently needed. This article reviews the current state of biomedical prevention against HIV-1, focusing on recently completed and ongoing clinical trials of new prevention interventions, particularly those relevant to prevention of HIV-1 in women. Male circumcision, cervical barrier devices, suppressive therapy against herpes simplex virus type 2, treatment of vaginal infections and other vaginal health interventions, pre-exposure antiretroviral prophylaxis, and topical vaginal microcobicides are discussed.

Centers for Disease Control and Prevention. Q & A: CDC's clinical studies of pre-exposure prophylaxis for HIV prevention. CDC HIV/AIDS Facts, January 2009. Available at: http://origin.cdc.gov/hiv/resources/qa/pdf/prep.pdf. Accessed July 20, 2009.

CDC is sponsoring these trials because safe and effective new approaches to HIV prevention are urgently needed. More than 7,000 people continue to become infected around the world every day (approximately 2.7 million per year). Although behavior change programs have contributed to dramatic reductions in the number of annual infections in the United States and many other nations, far too many people remain at high risk. With an effective vaccine years away, there is mounting evidence that antiretroviral agents may be able to play an important role in reducing the risk for transmission. Researchers believe that an HIV drug approved by the U.S. Food and Drug Administration (FDA) – tenofovir disoproxil fumarate (tenofovir, brand name Viread) used alone or in combination with emtricitabine (together, known by the brand name Truvada) – taken daily as an oral preventive drug, is among the most important new prevention approaches being investigated today. The approach is called pre-exposure prophylaxis, or PrEP. If proven safe and effective, PrEP could help address the urgent

need for a female-controlled prevention method for women worldwide who are unable, because of cultural and other barriers, to negotiate condom use. Furthermore, if effective, it could provide an additional safety net for all men and women at risk due to sexual or drug-using behaviors, when combined with reducing the number of sexual partners, HIV counseling and testing, condom use, use of sterile syringes, and other prevention measures.

Cohen MS, Gay C, Kashuba AD, et al. Narrative review: Antiretroviral therapy to prevent the sexual transmission of HIV-1. Annals of Internal Medicine. 2007;146(8):591-601.

Antiretroviral therapy (ART) has prolonged and improved the lives of persons infected with HIV. Theoretically, it can also be used to prevent the transmission of HIV. The pharmacology of ART in the male and female genital tract can be expected to affect the success of the intervention, and ART agents differ considerably in their ability to concentrate in genital tract secretions. Emergency ART is considered to be the standard of care after occupational exposures to fluids or tissues infected with HIV. More recently, ART for prophylaxis after nonoccupational HIV exposures has been widely used and most countries have developed specific guidelines for its implementation. However, developing clinical trials to prove the efficacy of ART postexposure prophylaxis has not been possible. Experiments with rhesus macaques suggest that therapy must be offered as soon as possible after exposure (within 72 hours) and must be continued for 28 days. Additional nonhuman primate experiments have demonstrated protection from HIV infection with ART preexposure prophylaxis, and several clinical trials are under way to evaluate the safety and efficacy of this approach. The degree to which ART offered to infected persons reduces infectiousness is of considerable public health importance, but the question has not been sufficiently answered. This article provides a review of the data on the use of ART to prevent the sexual transmission of HIV and identify challenges to improving and clarifying this approach.

Cohen MS, Kashuba AD. Antiretroviral therapy for prevention of HIV infection: New clues from an animal model. PLoS Medicine. 2008;5(2):e30.

The introduction of antiretroviral therapy (ART) in the early 1990s profoundly changed the face of HIV infection by improving survival rates [1]. But ART has equal potential for prevention, since it reduces the probability of HIV transmission from an infected person to their sexual partner(s). Although there have been no randomized controlled clinical trials on the subject, antiretroviral drugs are currently used in clinical practice for post-exposure prophylaxis after inadvertent occupational exposure (based on the results of a case control study [2]) or after sexual exposure to the virus [3]. Pre- and post-exposure prophylaxis (PrEP and PEP, respectively) have been used successfully to interrupt transmission of HIV from infected mothers to their babies [4].

Denton PW, Estes JD, Sun Z, et al. Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice. PLoS Medicine. 2008;5(1):e16.

Worldwide, vaginal transmission now accounts for more than half of newly acquired HIV-1 infections. Despite the urgency to develop and implement novel approaches capable of preventing HIV transmission, this process has been hindered by the lack of adequate small animal models for preclinical efficacy and safety testing. Given the importance of this route of transmission, we investigated the susceptibility of humanized mice to intravaginal HIV-1 infection. We show that the female reproductive tract of humanized bone marrow-liver-thymus (BLT) mice is reconstituted with human CD4+ T and other relevant human cells, rendering these humanized mice susceptible to intravaginal infection by HIV-1. Effects of HIV-1 infection include CD4+ T cell depletion in gut-associated lymphoid tissue (GALT) that closely mimics what is observed in HIV-1-infected humans. We also show that pre-exposure prophylaxis with antiretroviral drugs is a highly effective method for preventing vaginal HIV-1 transmission. Whereas 88% (7/8) of BLT mice inoculated vaginally with HIV-1 became infected, none of the animals (0/5) given pre-exposure prophylaxis of emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) showed evidence of infection (Chi square = 7.5, $df = 1$, $p = 0.006$). The fact that humanized BLT mice are susceptible to intravaginal infection makes this system an excellent candidate for preclinical evaluation of both microbicides and pre-exposure prophylactic regimens. The utility of humanized mice to study intravaginal HIV-1 transmission is particularly highlighted by the demonstration that pre-exposure prophylaxis can prevent intravaginal HIV-1 transmission in the BLT mouse model.

Derdelinckx I, Wainberg MA, Lange JM, et al. Criteria for drugs used in pre-exposure prophylaxis trials against HIV infection. PLoS Medicine. 2006; 3(11): e454.

In 2004, almost 5 million people became newly infected with HIV, emphasizing the continuous need for effective prevention strategies. The development of an effective preventive vaccine faces many difficulties and is not likely to occur within the next decade. Behavioural changes, such as consistent and correct condom use and abstinence from high-risk behaviour, probably contributed to the fall in HIV incidence recently reported in several African countries and in India [1]. Recently, it was shown that male circumcision reduced the risk of acquiring HIV by 60% [2] and the risk of male-to-female transmission by 30% [3]. However, behavioural interventions may not be able to curb the HIV epidemic as much as needed, prompting the need to find additional, more effective preventive strategies. There is also a need for “female-initiated intervention”. Women around the globe continue to be infected with HIV by their male partners and often feel unable to insist on condom use. Alternatives to behavioural strategies include those that are based on drugs. Anti-HIV vaginal microbicides, which may offer women a means of protecting themselves from infection, are currently being evaluated [4]. Also, rectally applied microbicides have proven to effectively prevent infection in macaques challenged via this transmission route [5]. However, like male circumcision, this strategy

may not provide protection against other routes of HIV transmission, such as oral or intravenous transmission. Oral antiretroviral pre-exposure prophylaxis (PREP) in high-risk populations may be a more reliable tool in preventing transmission of HIV [6]. Limited animal model data suggest that antiretroviral drugs may prevent infection when taken prior to, at the time of, and/or after HIV exposure [7-10]. Theoretically, preventing HIV infection could be done by blocking any step in the HIV life cycle. Blocking a step prior to integration of proviral DNA into the host DNA is believed to have greater potential since this way the permanent integration of proviral HIV is averted.

Desai K, Sansom SL, Ackers ML, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS. 2008;22(14):1829-1839.

HIV chemoprophylaxis may be a future prevention strategy to help control the global epidemic of HIV/AIDS. Safety and efficacy trials of two agents are currently underway. We assess the expected number of HIV cases prevented and cost-effectiveness of a hypothetical HIV chemoprophylaxis program among men who have sex with men in a large US city. We developed a stochastic compartmental mathematical model using HIV/AIDS surveillance data to simulate the HIV epidemic and the impact of a 5-year chemoprophylaxis program under varying assumptions for epidemiological, behavioral, programmatic and cost parameters. We estimated program effectiveness and costs from the perspective of the US healthcare system compared with current HIV prevention practices. The main outcome measures were number of HIV infections prevented and incremental cost per quality-adjusted life-years saved. A chemoprophylaxis program targeting 25% of high-risk men who have sex with men in New York City could prevent 780 (4%) to 4510 (23%) of the 19,510 HIV infections predicted to occur among all men who have sex with men in New York City in 5 years. More than half of prevented infections would be among those not taking chemoprophylaxis but who benefit from reduced HIV prevalence in the community. Under base-case assumptions, incremental cost was US$ 31,970 per quality-adjusted life-years saved. The program was cost-effective under most variations in efficacy, mechanism of protection and adherence. HIV chemoprophylaxis among high-risk men who have sex with men in a major US city could prevent a significant number of HIV infections and be cost-effective.

Dumond JB, Yeh RF, Patterson KB, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. AIDS. 2007;21(14):1899-1907.

The objective of this study was to describe first dose and steady state antiretroviral drug exposure in the female genital tract. Twenty-seven women initiating combination antiretroviral therapy underwent comprehensive blood plasma and cervicovaginal fluid sampling for drug concentrations during the first dose of antiretroviral therapy and at steady-state. Drug concentrations were measured by validated HPLC/UV or HPLC-MS/MS methods. Pharmacokinetic parameters were estimated for 11 drugs by non-compartmental analysis. Descriptive statistics and 95% confidence intervals were

generated using Intercooled STATA Release 8.0 (Stata Corporation, College Station, Texas, USA). For all antiretroviral drugs, genital tract concentrations were detected rapidly after the first dose. Drugs were stratified according to the genital tract concentrations achieved relative to blood plasma. Median rank order of highest to lowest genital tract concentrations relative to blood plasma at steady state were: lamivudine (concentrations achieved were 411% greater than blood plasma), emtricitabine (395%), zidovudine (235%) tenofovir (75%), ritonavir (26%), didanosine (21%), atazanavir (18%), lopinavir (8%), abacavir (8%), stavudine (5%), and efavirenz (0.4%). This is the first study to comprehensively evaluate antiretroviral drug exposure in the female genital tract. These findings support the use of lamivudine, zidovudine, tenofovir and emtricitabine as excellent pre-exposure/post-exposure prophylaxis (PrEP/PEP) candidates. Atazanavir and lopinavir might be useful agents for these applications due to favorable therapeutic indices, despite lower genital tract concentrations. Agents such as stavudine, abacavir, and efavirenz that achieve genital tract exposures less than 10% of blood plasma are less attractive PrEP/PEP candidates.

Fauci AS. Pathogenesis of HIV disease: Opportunities for new prevention interventions. Clinical Infectious Diseases. 2007;45(Suppl. 4):S206-S212.

Current efforts to prevent human immunodeficiency virus (HIV) disease, which largely focus on altering human behavior, have had some notable successes yet have failed to halt the spread of the acquired immunodeficiency syndrome pandemic. A greater understanding of the pathogenesis of HIV disease is providing us with the scientific rationale for additional approaches to prevention. Some of the approaches discussed in this article are available now. For example, we have the means to screen for and treat other sexually transmitted diseases that increase vulnerability to HIV, adult male circumcision is readily available in most properly equipped hospitals, and antiretroviral agents that decrease the viral load help prevent transmission from pregnant women to their infants. Other approaches discussed are under investigation. For instance, numerous topical microbicides are in various stages of development, incremental progress is being made toward creation of an HIV vaccine designed to prevent HIV transmission or slow the course of disease in people who become infected, and studies are under way to evaluate the risks and benefits of prophylactic antiretroviral therapy in individuals at high risk for HIV disease.

Garcia-Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Medicine. 2008;5(2):e28.

In the absence of an effective vaccine, HIV continues to spread globally, emphasizing the need for novel strategies to limit its transmission. Pre-exposure prophylaxis (PrEP) with antiretroviral drugs could prove to be an effective intervention strategy if highly efficacious and cost-effective PrEP modalities are identified. We evaluated daily and intermittent PrEP regimens of increasing antiviral activity in a macaque model that closely resembles human transmission. We used a repeat-exposure macaque model with 14 weekly rectal virus challenges. Three drug treatments were given once daily, each to

a different group of six rhesus macaques. Group 1 was treated subcutaneously with a human-equivalent dose of emtricitabine (FTC), group 2 received orally the human-equivalent dosing of both FTC and tenofovir-disoproxil fumarate (TDF), and group 3 received subcutaneously a similar dosing of FTC and a higher dose of tenofovir. A fourth group of six rhesus macaques (group 4) received intermittently a PrEP regimen similar to group 3 only 2 h before and 24 h after each weekly virus challenge. Results were compared to 18 control macaques that did not receive any drug treatment. The risk of infection in macaques treated in groups 1 and 2 was 3.8- and 7.8-fold lower than in untreated macaques ($p = 0.02$ and $p = 0.008$, respectively). All six macaques in group 3 were protected. Breakthrough infections had blunted acute viremias; drug resistance was seen in two of six animals. All six animals in group 4 that received intermittent PrEP were protected. This model suggests that single drugs for daily PrEP can be protective but a combination of antiretroviral drugs may be required to increase the level of protection. Short but potent intermittent PrEP can provide protection comparable to that of daily PrEP in this SHIV/macaque model. These findings support PrEP trials for HIV prevention in humans and identify promising PrEP modalities.

Gay CL, Cohen MS. Antiretrovirals to prevent HIV infection: Pre- and postexposure prophylaxis. Current Infectious Disease Reports. 2008;10(4):323-331.

The public health impact of using antiretroviral therapy (ART) has been largely ignored as a strategy for HIV prevention. ART can be used to prevent HIV transmission through three mechanisms: 1) reduction of HIV viral load in individuals aware of their status; 2) postexposure prophylaxis following risk exposures; and 3) as pre-exposure prophylaxis with oral and/or topical microbicides. The concept of using ART to decrease infectiousness in an HIV-infected individual stems from the strong association between risk of HIV transmission by all exposure routes and HIV viral levels in the blood [1-3]. The use of postexposure prophylaxis following occupational exposures is now the standard of care in many settings, and accumulating evidence from large registries will further inform this practice. Postexposure prophylaxis following nonoccupational exposure and studies on its feasibility and acceptability are expanding, as is the development of guidelines for its use based on exposure risk. To date, ART as pre-exposure prophylaxis to prevent HIV infection has primarily been studied in animals, but human studies of its safety and efficacy are ongoing.

Grant RM, Buchbinder S, Cates W, et al. Promote HIV chemoprophylaxis research, don't prevent it. Science. 2005;309(5744):2170-2171.

HIV infects more than 40 million people worldwide, and there are 14,000 new infections per day (1). No preventive vaccine is yet in sight (2). Even as available and proven prevention interventions are used, the HIV pandemic will not be stopped solely by talking to those at risk (3). Chemoprophylaxis with antiretroviral agents is a promising new approach (4). Clinical trials of daily oral antiretroviral dosing as pre-exposure prophylaxis (PrEP) have been initiated in Africa, Asia, and the United States and are planned in Latin America. Unfortunately, these trials have become controversial.

Guest G, Shattuck D, Johnson L, et al. Changes in sexual risk behavior among participants in a PrEP HIV prevention trial. Sexually Transmitted Diseases. 2008;35(12):1002-1008.

One of the concerns raised regarding the introduction of any new HIV-prevention measure, such as PrEP, is the potential for risk disinhibition or sexual risk compensation. The oral tenofovir HIV prevention trial has been the subject of international discussion in this regard. This article maps the changes in sexual risk behavior among women participating in the oral tenofovir HIV prevention trial in Ghana. Content-driven, thematic analysis was carried out on qualitative data obtained from in-depth interviews with study participants. Growth curve analysis was the primary method used to document trends over time in self-reported sexual behavior collected monthly. Overall, the study found that sexual risk behavior did not increase during the trial. Number of sexual partners and rate of unprotected sex acts decreased across the 12-month period of study enrollment. Certain subgroups of women, however, exhibited different growth curves. Data indicate that the HIV prevention counseling associated with the trial was effective. Counseling during the trial was effective. Different types of counseling and messaging may be needed for different subgroups within a population. These findings also have implications for required sample sizes for future HIV prevention trials where seroconversion is the main outcome.

Hill A, Youle M, Boucher C. Cost-effectiveness analysis of ART for pre-exposure prophylaxis. Presented at the 13th Conference on Retroviruses and Opportunistic Infections. Abstract 901. Denver, CO, February 5-8, 2006. Available at: http://www.aegis.com/conferences/croi/2006/901.pdf. Accessed July 20, 2009.

Clinical trials of antiretrovirals for PrEP are planned or ongoing. Even if these trials show PrEP to significantly lower rates of HIV infection, high drug costs and safety concerns could limit wide-scale introduction of PrEP in developing countries. The objective of this study was to calculate the range of possible costs for preventing HIV infection with PREP treatment, given different HIV incidence and treatment cost estimates. 80% efficacy for PrEP was assumed, as this is the basis for several PrEP trial protocols. A MEDLINE search identified epidemiological studies evaluating the incidence of new HIV-infections worldwide, by country and risk group. These incidence estimates were used to calculate the number of people who need to be treated with PrEP to prevent one HIV infection (NNTB). Lowest published antiretroviral drug prices in US$ (Medecins Sans Frontieres 2005) were combined with HIV incidence estimates to calculate the cost per HIV infection prevented with PrEP. An additional $30 per year was included to cover routine HIV antibody testing and clinic visits during PrEP treatment. Lifetime costs of ARV treatment and care were stimated at US $10,000 per HIV infected person (based on 20 years of HAART, diagnositics and care at $500 per year in a developing country setting). The effectiveness of PrEP can also be contrasted with potential drug toxicities – the number of people needed to treat to prevent one HIV infection (NNTB) can be compared with the number of people to treat to cause one major toxicity (NNTH) (eg hepatic failure on NVP, flare of Hepatitis B on 3TC, lactic acidosis on NRTI treatment). This type of analysis needs to be adapted for PrEP drug candidates.

Jackson JB, Barnett S, Piwowar-Manning E, et al. A phase I/II study of nevirapine for pre-exposure prophylaxis of HIV-1 transmission in uninfected subjects at high risk. AIDS. 2003;17(4):547-553.

The objective of this study was to evaluate the safety, tolerability, and trough levels of three pre-exposure prophylaxis regimens of nevirapine among HIV-1-uninfected subjects at high risk for HIV-1 infection. A phase I/II trial (HIVHOP 101) in which 33 such uninfected subjects received a 200 mg tablet of nevirapine once weekly (cohort A, n = 12), twice weekly (cohort B, n = 12), or every other day (cohort C, n = 9) for 12 weeks. Clinical signs/symptoms, laboratory parameters, and nevirapine trough levels were assessed at entry and at 1,2,4,6,9, and 12 weeks, with a follow-up sample at 16 weeks. No subject experienced clinical symptoms attributed to nevirapine, including rash. There were no significant changes in liver enzyme levels from baseline to week 12 in the three cohorts, except for glutamyl transpeptidase in chohort B. Median nevirapine trough levels at weeks 1 and 12 were 119 ng/ml (range, <25-205) and 135 ng/ml (range, <25-1065), respectively, for cohort A, 569 ng/ml (range, 135-2641) and 431 ng/ml (range, 42-2454) for cohort B, and 1942 ng/ml (range, 1214-2482) and 943 ng/ml (range, 262-5281) for cohort C. No subject became HIV-1 antibody positive by week 16. A single dose of nevirapine taken once weekly, twice weekly, or every other day for 12 weeks was safely tolerated by the subjects in this small study, and resulted in nevirapine levels well above the IC_{50} (inhibitory concentration of 50%: 10 ng/ml) over the 12-week period in nearly all evaluable subjects.

Karim SSA, Baxter C. Antiretroviral prophylaxis for the prevention of HIV infection: Future implementation challenges. HIV Therapy. 2009;3(1):3-6.

The search for safe and effective methods of HIV prevention continues 25 years into the HIV/AIDS epidemic. In the last decade, several biomedical prevention technologies have been tested for the prevention of sexual transmission of HIV, but only medical male circumcision has proven to be effective. Trials of microbicides, herpes simplex virus-2 therapy, diaphragms and vaccines have all failed to show protection against HIV infection and, in some instances, may have even enhanced HIV infection. Much hope now rests on efficacy trials of antiretrovirals (ARVs) as pre-exposoure prophylaxis (PrEP). ARVs have been shown to be effective in suppressing HIV replication in infected individuals. However, PrEP involves the long-term use of ARVs prior to HIV exposure so that the ARVs are already biologically active in the target cells when exposure occurs, with the aim of either preventing HIV infection or, at least, favorably altering the natural course of infection to improve prognosis or decrease infectiousness. The concept of PrEP is not new; it builds on the premise that effective therapeutic medications can be used by healthy people to prevent certain infections; for example, chloroquine to prevent malaria or isoniazed prophylaxis to prevent tuberculosis. The use of ARVs as PrEP is effective in animal models; several studies since 1995 have shown that tenofovir used as PrEP can prevent SIV infection. Even a single PrEP dose has been shown to be effective in the macaque model. Further evidence to support the idea of testing ARVs for PrEP in humans comes from two sources: clinical trial data on the

efficacy of ARVs in preventing mother-to-child transmission of HIV, and observational data showing ARVs used as postexposure prophylaxis can prevent HIV infection from needlestick exposure. These create the grounds for cautious optimism as the results of efficacy trials assessing ARVs as PrEP are awaited.

Koblin BA, Murrill C, Xu G, et al. Awareness of HIV prevention strategies under development. Journal of Acquired Immune Deficiency Syndromes. 2008;48(2):232-234.

A number of biomedical interventions to prevent HIV acquisition and transmission are currently being tested in the United States for safety and, for some, efficacy. Three strategies being tested among men who have sex with men (MSM) include preventive HIV vaccines, suppression of herpes simplex virus type 2 (HSV-2) infections, and use of antiretrovirals for prevention of infection. This first approach, preventive HIV vaccines, has been under development in the United States since 1988, and phase 1 and 2 trials are ongoing. Two efficacy trials completed to date have not demonstrated efficacy of test vaccines. The second approach, suppression of HSV-2 infection with acyclovir, is based on evidence that HSV-2 infection increases the risk of HIV infection at least 2-fold. A recently completed trial testing the efficacy of suppressive therapy with acyclovir in preventing HIV acquisition among MSM in the United States and Peru and women in Africa did not show efficacy of this prevention strategy. Lastly, recommendations for nonoccupational postexposure prophylaxis (nPEP) using antiretrovirals were published by the Centers for Disease Control and Prevention (CDC) in 2005, although clinicians and health departments have recommended use of nPEP since 1998. One study of pre-exposure prophylaxis (PrEP) among MSM is underway in the United States and is examining the safety of PrEP, biologically and with regard to potential increases in risk behaviors.

Lange JM. We must not let protestors derail trials of pre-exposure prophylaxis for HIV. PLoS Medicine. 2005;2(9):e248.

One of the great tragedies of our times is the extent to which HIV prevention efforts are falling short. In 2004, more new HIV infections occurred than in any previous year: close to 14,000 a day, 570 per hour, almost ten per minute. The greater part of new infections occurs in young people, over half in persons between 15 and 24 years of age, and over half in women. The increasing feminization of the HIV/AIDS epidemic reflects the vulnerable position of women in many societies. HIV is a virus, but inequity is at the roots of most of its spread.

Liu AY, Grant RM, Buchbinder SP. Pre-exposure prophylaxis for HIV: Unproven promise and potential pitfalls. Journal of the American Medical Association. 2006; 296(7):863-865.

An estimated 11,000 new human immunodeficiency virus (HIV) infections occur worldwide per day and approximately 4 million individuals are infected with HIV per year. Although behavior change has likely led to substantial reductions in HIV incidence

in some populations and risk-reduction counseling will likely remain the cornerstone of HIV prevention programs, new HIV prevention strategies are urgently needed to further reduce incident infections. Pre-exposure chemoprophylaxis (PrEP) has emerged as a promising new biomedical strategy for preventing HIV infection, and clinical trials are planned or under way to evaluate the safety and efficacy of this approach. Because many antiretroviral drugs are licensed in the United States, PrEP could become available for use as a prevention tool more quickly than other experimental prevention strategies, such as an HIV vaccine.

Liu AY, Kittredge PV, Vittinghoff E, et al. Limited knowledge and use of HIV post- and pre-exposure prophylaxis among gay and bisexual men. Journal of Acquired Immune Deficiency Syndromes. 2008;47(2):241-247.

Post-exposure prophylaxis (PEP) is currently recommended after certain high-risk exposures, and pre-exposure prophylaxis (PrEP) is undergoing evaluation in clinical trials. Media reports have suggested substantial levels of community PrEP use despite its unproven effectiveness. We conducted a cross-sectional survey of 1819 HIV-uninfected gay/bisexual men in California to assess PEP and PrEP awareness and use. Overall, 47% reported PEP awareness and 4% ever used PEP. Men who were older than 25 years of age (odds ratio [OR] = 2.2, 95% confidence interval [CI]: 1.5 to 3.1), were white (OR = 2.2, 95% CI: 1.6 to 3.0), had an annual income > $100,000 (OR = 2.0, 95% CI: 1.2 to 3.4), self-identified as gay/homosexual (OR = 2.4, 95% CI: 1.4 to 4.3), and had unprotected anal sex (OR = 1.8, 95% CI: 1.3 to 2.3) or sex under the influence of a drug (OR = 2.0, 95% CI: 1.5 to 2.7) were more likely to be aware of PEP, whereas speed users (OR = 0.6, 95% CI: 0.4 to 0.9) were less likely to be aware of PEP. Only 16% reported PrEP awareness, and < 1% ever used PrEP. Unprotected anal sex (OR = 1.6, 95% CI: 1.1 to 2.3) and sex under the influence of a drug (OR = 1.5, 95% CI: 1.0 to 2.2) were associated with PrEP awareness. PEP awareness and use were modest and PrEP use was rare among gay/bisexual men in California. Although PrEP is not currently recommended, community education on the availability of PEP is suggested.

Okwundu CI, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. Cochrane Database of Systematic Reviews. 2009 (1): CD007189.

Twenty-five years into the global HIV/AIDS epidemic, infection rates remain alarmingly high, with over 4 million people becoming infected every year. There is a need for HIV prevention strategies that are more effective. Oral antiretroviral pre-exposure prophylaxis (PrEP) in high-risk individuals may be a reliable tool in preventing the transmission of HIV. The objective of this study was to evaluate the risk reduction and side effects of antiretroviral chemoprophylaxis in preventing HIV infection in high-risk individuals. We conducted electronic searches of MEDLINE (1980 through June 2008); the Cochrane Central Register of Controlled Trials (March 2008); EMBASE (June 2008); and AIDSearch (June 2008). We also searched the WHO International Clinical Trials Registry Platform in June 2008 for ongoing or prospective trials. Data concerning outcomes, details of the interventions, and other study characteristics were extracted by

two independent authors using a standardized data extraction form. The information gathered from each included trial were location of the trial, data, publication status, demographics of participants (e.g., age, gender, risk behavior), exposure modality, type of antiretroviral drug used, duration of drug use, and outcomes. Relative risk with a 95% confidence interval (CI) was used as the measure of effect. Only one trial met our inclusion criteria, so we did not perform a meta-analysis. One randomized controlled trial met the criteria for the review, although it was not completed as planned. The trial did not have the statistical power to answer questions about the efficacy of antiretroviral PrEP for HIV prevention in the assessed risk group. Presently there is no reliable evidence to support the use of any antiretroviral agent for HIV chemoprophylaxis. The value of chemoprophylaxis for HIV prevention cannot be assessed on the basis of the included trial. The result was not statistically significant and, moreover, the trial was not completed as planned; therefore, the use of antiretroviral agents for HIV chemoprophylaxis cannot be recommended at present. To assess the value of antiretroviral agents for HIV chemoprophylaxis, we advocate well-conducted trials with the statistical power to answer questions about PrEP efficacy and safety in various populations and risk groups. These trials also should evaluate other important issues of concern, such as drug safety, adherence, drug resistance, and the effect of PrEP on risk behaviour.

Paltiel AD, Freedberg KA, Scott CA, et al. HIV pre-exposure prophylaxis in the United States: Impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clinical Infectious Diseases. 2009;48(6):806-815.

The combination of tenofovir and emtricitabine shows promise as HIV pre-exposure prophylaxis (PrEP). We sought to forecast clinical, epidemiologic, and economic outcomes of PrEP, taking into account uncertainties regarding efficacy, the risks of developing drug resistance and toxicity, behavioral disinhibition, and drug costs. We adapted a computer simulation of HIV acquisition, detection, and care to model PrEP among men who have sex with men and are at high risk of HIV infection (i.e., 1.6% mean annual incidence of HIV infection) in the United States. Base-case assumptions included 50% PrEP efficacy and monthly tenofovir-emtricitabine costs of $753. We used sensitivity analyses to examine the stability of results and to identify critical input parameters. In a cohort with a mean age of 34 years, PrEP reduced lifetime HIV infection risk from 44% to 25% and increased mean life expectancy from 39.9 to 40.7 years (21.7 to 22.2 discounted quality-adjusted life-years). Discounted mean lifetime treatment costs increased from $81,100 to $232,700 per person, indicating an incremental cost-effectiveness ratio of $298,000 per quality-adjusted life-year gained. Markedly larger reductions in lifetime infection risk (from 44% to 6%) were observed with the assumption of greater (90%) PrEP efficacy. More-favorable incremental cost-effectiveness ratios were obtained by targeting younger populations with a higher incidence of infection and by improvements in the efficacy and cost of PrEP. PrEP could substantially reduce the incidence of HIV transmission in populations at high risk of HIV infection in the United States. Although it is unlikely to confer sufficient benefits to justify the current costs of tenofovir-emtricitabine, price reductions and/or increases in efficacy could make PrEP a cost-effective option in younger populations or populations

at higher risk of infection. Given recent disappointments in HIV infection prevention and vaccine development, additional study of PrEP-based HIV prevention is warranted.

Paxton LA, Hope T, Jaffe HW. Pre-exposure prophylaxis for HIV infection: what if it works? The Lancet. 2007;370(9581):89-93.

For all the advances in treatment of HIV infection, the mainstays of prevention have changed little: sexual abstinence, condoms, sterile injection equipment, avoidance of high-risk behaviors, and knowing one's own serostatus and that of any sexual or drug-injecting partners. Although these strategies can be effective and recent years have seen decreases in new infections in some countries and in some risk groups, the 11,000 new infections daily is ample testament that additional methods of prevention are needed. Evidence for successful HIV-prevention technologies is mixed. Randomised studies of male circumcision in South Africa, Kenya, and Uganda were discontinued early after interim review showed reductions in new HIV infections ranging from 60% to 74% in the circumcised men compared with those who were not circumcised. Several topical microbicides are in advanced trials. However, phase III trials of C-31G (originally developed by Cellegy Pharmaceuticals) and cellulose sulphate (Polydex Pharmaceuticals, Nassau, Bahamas) were terminated early because preliminary results suggested no efficacy (C-31G) or increased risk of HIV transmission (cellulose sulphate). HIV-vaccine research continues despite two completed trials of AidsVax (VaxGen, South San Francisco, CA, USA) that showed no efficacy. Proof of efficacy of any present microbicide or vaccine candidate is several years away, and first products will probably be only moderately effective. The need to manufacture such a product in large quantities and distribute it around the world will pose additional challenges.

Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clinical Trials. 2007;2(5):e27.

The objective of this trial was to investigate the safety and preliminary effectiveness of a daily dose of a 300 mg of tenofovir disoproxil fumarate (TDF) versus placebo in preventing HIV infection in women. This was a phase 2, randomized, double-blind, placebo-controlled trial. The study was conducted between June 2004 and March 2006 in Tema, Ghana; Douala, Cameroon; and Ibadan, Nigeria. We enrolled 936 HIV-negative women at high risk of HIV infection into this study. Participants were randomized 1:1 to once daily use of 300 mg of TDF or placebo. The primary safety endpoints were grade 2 or higher serum creatinine elevations (>2.0 mg/dl) for renal function, grade 3 or 4 aspartate aminotransferase or alanine aminotransferase elevations (>170 U/I) for hepatic function, and grade 3 or 4 phosphorus abnormalities (<1.5 mg/dl). The effectiveness endpoint was infection with HIV-1 or HIV-2. Study participants contributed 428 person-years of laboratory testing to the primary safety analysis. No significant differences emerged between treatment groups in clinical or laboratory safety outcomes. Study participants contributed 476 person-years of HIV testing to the primary effectiveness analysis, during which time eight seroconversions occurred. Two were diagnosed in participants randomized to TDF (0.86 per 100 person-years) and six in participants

receiving placebo (2.48 per 100 person-years), yielding a rate ratio of 0.35 (95% confidence interval = 0.03 – 1.93), which did not achieve statistical significance. Owing to premature closures of the Cameroon and Nigeria study sites, the planned person-years of follow-up and study power could not be achieved. Daily oral use of TDF in HIV-uninfected women was not associated with increased clinical or laboratory adverse events. Effectiveness could not be conclusively evaluation because of the small number of HIV infections observed during the study.

Selemogo M. HIV pre-exposure prophylaxis trials: socio-economic and ethical perspectives for sub-Saharan Africa. African Journal of AIDS Research. 2008; 7(2):243-247.

The advent of HIV pre-exposure prophylaxis (PrEP) as a HIV-prevention strategy has received optimistic support among HIV researchers. However, discourse on PrEP trials has tended to be dominated by the disputes arising between some activist groups and researchers about the research methodologies. Instead, this paper discusses other issues oftentimes neglected in discussions relating to PrEP trials. Specifically, I focus on the possible ethical implications and the potential impact of sub-Saharan Africa's socio-economic conditions on the promised benefits of PrEP trials for the region and the continent. I argue that the concept pf PrEP as affordable and practical HIV-prevention intervention presents challenges and questions that urgently need addressing as we await results from several ongoing trials. If research is undertaken with no plans on how the results of specific trials can render actual HIV-prevention-benefits – especially for the world's poor – then such endeavors risk being merely information-acquiring ventures.

Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: What went wrong? PLoS Medicine. 2005;2(9):e234.

New approaches to HIV/AIDS prevention are urgently needed to stem the estimated 5 million new infections that occur worldwide each year. One such promising, novel intervention has been the proposed use of the oral antiretroviral drug tenofovir (Viread) as a pre-exposure prophylaxis (PREP) in high-risk groups (for example, uninfected women who have high-risk commercial sex). However, emerging opposition has halted the progress of at least two important clinical trials of tenofovir as PREP and brought negative attention to tenofovir, somewhat similar to that visited on thalidomide more than four decades ago. This could prove damaging in the long term. If tenofovir is someday proven to be clinically efficacious as a PREP, today's irresponsible reporting and activism surrounding tenofovir could cause those in need to snub the drug if, or when, it becomes licensed for use as a PREP. This unfortunate prospect raises questions about responsible media reporting, responsible conduct on the part of investigators and activists, and what should be done to avert or repair damaging trial-related disputes in the future.

Smith SM. Pre-exposure chemoprophylaxis for HIV: It is time. Retrovirology. 2004;1(16):doi:10.1186/1742-4690-1-16.

The HIV-1 plague continues unabatedly across sub-Saharan Africa. In Botswana and Swaziland, nearly 40% of the entire adult population is already infected. No current program is capable of slowing the advancing tide. An effective vaccine and widespread treatment are years, if not, decades away. In this most urgent situation, I propose that pre-exposure chemoprophylaxis be studied as a means to reduce the spread of HIV-1 among at-risk individuals.

Vernazza P, Brenner I, Graf I. Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. Presented at the 4th International AIDS Society Conference on HIV Pathogensis, Treatment and Prevention. Abstract MOPDC01. Sydney, Australia, July 22-25, 2007. Available at: http://www.ias2007.org/abstract.aspx?elementId=200703139. Accessed July 16, 2009.

The objectives of this report is to reduce risk-taking behavior in HIV-discordant couples (male HIV-pos.) willing to conceive a child. HIV-discordant couples expressing the desire to conceive a child received a standardized risk reduction counseling including LH-peak measurement and pre-exposure prophylaxis with tenofovir 36 and 12 h before intercourse. Couples were either included after having previously been counseled for artificial insemination with processed semen and quit the program for any reason or after referral through their HIV-physician. Twenty-two couples were admitted for risk reduction counseling. All male partners have been under a fully suppressive antiretroviral treatment. Six couples admitted that they had previously tried to conceive by unprotected intercourse. Twenty-one couples decided to use the proposed risk reduction strategy with timed intercourse and TDF-pre-exposure-prophylaxis. Pregnancy rates were high with more than 50% pregnancies achieved after 3 cycles (11/21). In 15/21 female partners got pregnant after up to 10 attempts. All women tested negative for HIV-antibodies 3 months after the last exposure. The true number of HIV-discordant couples who practice unprotected sex to conceive is most likely underestimated. The risk of transmission in a couple with a fully treated male partner is low and can further be reduced by timed intercourse and a short pre-exposure prophylaxis with tenofovir. The pregnancy rates of natural conception are substantially higher than with artificial reproduction techniques (40% in our program).

Vissers DC, Voeten HA, Nagelkerke NJ, et al. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: A simulation study. PLoS ONE. 2008;3(5):e2077.

Pre-exposure prophylaxis (PrEP) is a promising new HIV prevention method, especially for women. An urgent demand for implementation of PrEP is expected at the moment efficacy has been demonstrated in clinical trials. We explored the long-term impact of PrEP on HIV transmission in different HIV epidemics. We used a mathematical model that distinguishes the general population, sex workers and their clients. PrEP scenarios

varying in effectiveness, coverage and target group were modeled in the epidemiological settings of Botswana, Nyanza Province in Kenya, and Southern Inda. We also studied the effect of condom addition or condom substitution during PrEP use. Main outcome was number of HIV infections averted over 10 years of PrEP use. PrEP strategies with high effectiveness and high coverage can have a substantial impact in African settings. In Southern India, by contrast, the number of averted HIV infections in different PrEP scenarios would much lower. The impact of PrEP may be strongly diminished or even reversed by behavioral disinhibition, especially in scenarios with low coverage and low effectiveness. However, additional condom use during low coverage and low effective PrEP doubled the amount of averted HIV infections. The public health impact of PrEP can be substantial. However, this impact may be diminished, or even reversed, by changes in risk behavior. Implementation of PrEP strategies should therefore come on top of current condom campaigns, not as a substitution.

Voetsch AC, Heffelfinger JD, Begley EB, et al. Knowledge and use of pre-exposure and post-exposure prophylaxis among attendees of minority gay pride events, 2005 though 2006. Journal of Acquired Immune Deficiency Syndromes. 2007;46(3):378-380.

The use of pre-exposure prophylaxis (PrEP), initiating antiretroviral medication before engaging in high-risk activity, has been suggested as a potential biomedical intervention to prevent HIV infection. However, PrEP remains an unproven intervention. Currently the safety and efficacy of daily use of either tenofovir alone or in combination with emtricitabine for PrEP to prevent HIV infection is being evaluated in randomized, placebo-controlled trials among injection drug users, heterosexual men and women, and men who have sex with men (MSM). Results from a clinical trial in Ghana showed that there were not significant adverse events among women taking daily tenofovir compared to pacebo. The earliest efficacy results of these trials will be available in 2007. Despite the lack of efficacy data in humans, there were press reports in 2005 that PrEP use was already occurring among HIV-negative MSM.

Youle M, Wainberg MA. Could chemoprophylaxis be used as an HIV prevention strategy while we wait for an effective vaccine? AIDS. 2003;17(6):937-938.

A recent presentation by Jackson and co-workers at the XVth World AIDS Conference ushered in a new era of HIV prevention. Their study examined the safety and pharmacokinetics of nevirapine in HIV-uninfected high-risk individuals, showing for the first time that a drug used to treat HIV might have the potential to prevent HIV infection. There is little evidence that there has been a significant reduction in the global rate of infection over time. HIV still spreads like wild-fire in susceptible communities, and is increasingly of multidrug-resistant strains of the virus. The quest for an effective preventative vaccine for the uninfected has been, to date, unfruitful. Indeed, there are some concerns that elicited anti-HIV immune responses may be too narrow for complete protection, severely limiting vaccine efficacy. Significant populations are at high risk of imminent HIV infection, such as HIV-discordant sexual partners or those who chose not

to use condoms. For these individuals a current vaccine strategy may be too far in the future.

Youle M, Wainberg MA. Pre-exposure chemoprophylaxis (PREP) as an HIV prevention strategy. Journal of the International Association of Physicians in AIDS Care. 2003;2(3):102-105.

Chemoprophylaxis may be a prevention strategy for the sexual transmission of human immunodeficiency virus (HIV). Evidence suggests that condom use has waned with the availability of antiretroviral medication, at least in some resource-rich settings. Barrier methods of HIV prevention have inherent problems, and the potential for failure. Microbicide research has focused primarily on male-to-female transmission. Analogous to post-exposure prophylaxis, HIV prevention may be achieved by pre-exposure prophylaxis in some settings. Research in this potential strategy may be rewarding.