SUPPLEMENT ARTICLE

Antiretroviral Agents Used by HIV-Uninfected Persons for Prevention: Pre- and Postexposure Prophylaxis

Robert M. Grant

Gladstone Institute of Virology and Immunology and University of California, San Francisco

Prophylactic use of antimicrobial agents and microbicides has been proven for many infections, including surgical, gastrointestinal, upper respiratory, and meningococcal infections. Antiretroviral therapy for pregnant women prevents mother-to-child transmission of human immunodeficiency virus (HIV), which has become rare in settings where access to therapy is widespread. Postexposure prophylaxis after needlestick injury or significant sexual exposure is recommended on the basis of animal studies and case-control observational studies, although use of these interventions is limited to those who recognize exposure, have access, and have the power to use the interventions. Clinical trials are evaluating whether regular or preexposure use of antiretroviral therapy provides additional protection for persons at high risk of infection who are also offered standard prevention care, including HIV testing, counseling, condoms, and management of sexually transmitted infections. Trials are evaluating topical or oral use. Concerns have arisen with regard to optimal dosing strategies, costs, access, drug resistance, risk behavior, and the role of communities. Future implementation, if warranted, will be guided by the results of clinical trials in progress and engagement of communities exposed to HIV.

CHEMOPROPHYLAXIS FOR HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION AND AIDS

Antiretroviral therapy (ART) has a proven capacity to prolong life and to allow HIV-infected persons to return to work and engage in relationships with families and partners. By preventing AIDS among persons with HIV infection, effective therapies can be said to play a prophylactic role.

Prevention of mother-to-child transmission. Prevention of transmission of HIV infection from infected mothers to infants has been demonstrated using a variety of regimens, including zidovudine [1], short-course nevirapine [2], and combination therapy [2–8], and was recently reviewed [9]. Short-course regimens involving peripartum administration of nevirapine, zidovudine, combination zidovudine and lamivudine, or combination nevirapine and zidovudine provide substantial protection but appear to be less protective than is zidovudine given prepartum, intrapartum, and postpartum, as in AIDS Clinical Trials Group 076 [10]. Analysis of prospective data from 2876 pregnancies in Europe indicated that vertical transmission rates decreases from 15.5% to 2.6% with increasing use of zidovudine chemoprophylaxis (the 076 regimen), combination ART that aims to fully suppress plasma RNA level in the mother, and cesarian delivery [11]. In that review, use of fully suppressive regimens was associated with more protection, compared with zidovudine alone (adjusted odds ratios, 0.15 and 0.34, respectively). Drug resistance occurs frequently with use of single-dose nevirapine, which has a low genetic barrier to resistance [12]. ART use during breast feeding is also associated with protection from transmission to infants, although use of breast milk substitutes is preferred if safe products are available (reviewed in [13]). For prevention of mother-to-child transmission, multiple agents used in

Reprints or correspondence: Dr Robert M. Grant, 1650 Owens St, San Francisco, CA 94158 (robert.grant@ucsf.edu).

Clinical Infectious Diseases 2010; 50(S3):S96–S101

1058-4838/2010/5010S3-0005$15.00
DOI: 10.1086/651479

combination are associated with greater protection, greater therapeutic benefit for the mother, and decreased risk of drug resistance and are recommended if available [14, 15]. Infection of infants is extremely rare in urban centers and well-resourced settings where standards of care are widely implemented.

Postexposure prophylaxis (PEP). PEP is recommended after substantial exposure to HIV because of a needlestick injury or unprotected sexual intercourse [16]. Substantial exposures include exposure of the vagina, rectum, eye, mouth, or other mucous membranes; exposure of nonintact skin; or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood when the source is known to be HIV infected. PEP is recommended if the source is known to be HIV-1 infected and should be considered if the serostatus of the source is not known. PEP is not recommended if the exposure involves negligible risk for HIV exposure, including contact with urine, nasal secretions, saliva, sweat, or tears, if not visibly contaminated with blood.

Efficacy after needlestick injury is thought to be as high as 80%, on the basis of case-control observational studies; randomized evaluation of PEP has not been performed. Recommendations based on preclinical studies involving nonhuman primates are that PEP should be started as soon as possible after a substantial exposure (no later than 72 h after exposure) and should be continued for 28 days after exposure. Use of PEP has been limited, because persons have difficulty recognizing exposure to HIV-1 as the result of incomplete information, anxiety, substance use, or preference to focus on goals other than aversion of acquisition of HIV infection during sexual conduct [17]. Failure of PEP to prevent acquisition of HIV infection has been described and most likely resulted from initiation of prophylaxis after the 72-h period after exposure [18]. There is no information available regarding the relative efficacy of different PEP regimens after different types of exposure or after exposure to drug-resistant mutants. PEP is not universally available because of limited resources, limited evidence demonstrating efficacy, the absence of Food and Drug Administration–cleared indications for PEP agents, and concerns about how biomedical safeguards might increase risk behavior.

Preexposure prophylaxis (PrEP): oral and topical. PrEP has been proposed to address some of the limitations of PEP [19]. Clinical trials are currently evaluating whether daily oral tenofovir disoproxil fumarate (TDF) with or without emtricitabine provides additional protection to persons who already receive standard prevention care, including HIV testing, counseling, condoms, and management of sexually transmitted infections [20]. The recommended daily dose does not require that individuals recognize and act on specific HIV exposures—a known challenge. Preexposure administration may also increase efficacy by allowing time for the drug to enter target cells and be metabolized to the active phosphorylated forms before viral exposure. For persons who are possibly exposed to HIV-1 more frequently than once a month, which includes most groups at high risk, preexposure and postexposure administration periods overlap.

A blinded and placebo-controlled randomized trial confirmed safety of daily oral receipt of TDF for African women at high risk of infection [21]. Overall, 936 women were studied for periods as long as 12 months. Liver function tests and tests for kidney function were monitored. Of importance, there were no serious flares after stopping TDF in a subgroup of 23 women who were found to have hepatitis B, and the rate of low-grade abnormalities was comparable in the placebo and active arms of the study. The absence of hepatitis B flares after stopping active drugs in the PrEP study likely reflects the relatively preserved liver function expected in healthy volunteers enrolled in HIV prevention research [22, 23].

Microbicide and PrEP studies have different historical roots but are now converging to evaluate similar concepts. The feasibility and tolerability of topical (vaginal) use of TDF gels has been evaluated in the short term (14 days) and the intermediate term (24 weeks), with acceptable results [24, 25]. An efficacy trial of exposure-driven use of a topical TDF gel is fully enrolled in South Africa (Caprisa 004), and an efficacy trial of daily vaginal TDF gel use is planned (VOICE).

CHALLENGES

Research on prevention of HIV infection faces substantial challenges in the preclinical and clinical phases, regulatory environment, and implementation. Although substantial progress in the development of animal models has been made, few of the available models have been standardized for use in different laboratories, and none have been validated by correlation with protective effects observed in persons. Although plasma RNA level has become an accepted primary outcome for HIV treatment trials, the prevention field has not identified a surrogate marker that can be used in lieu of incidence of new HIV infection. As such, prevention trials must be large, enrolling many thousands of participants who are followed up for several years at great expense. The regulatory environment for prevention is not well defined, which leaves trial sponsors with little guidance regarding standards of evidence. Finally, potential beneficiaries of prevention methods have competing demands for limited resources, and disease prevention is not the highest priority when food, shelter, education, and safety are not assured. In summary, development pathways in prevention of HIV infection are not well established, and path-finding successes are scarce.

Animal models for development of prevention concepts. Nonhuman primates challenged with some strains of simian

immunodeficiency virus (SIV) recapitulate many of the features of HIV infection, including persistent infection after mucosal challenge; rapid depletion of gut-associated lymphoid tissues, followed by systemic decrease in $CD4^+$ T cell count; and ultimately, systemic immunodeficiency. SIV strains are susceptible to nucleoside and nucleotide reverse-transcriptase inhibitors but are naturally resistant to nonnucleoside reverse-transcriptase inhibitors. Although both SIV and HIV are classified as primate lentiviruses, there are differences in genomic structure, coreceptor use, and accessory genes and target enzymes. To address these differences, virus strains that are chimeras between HIV and SIV have been developed for nonhuman primate experiments. Although they have some theoretical advantages, these virus chimeras typically have an attenuated course of infection in the animals: concepts that may protect against attenuated infections may not be protective against fully virulent challenges, as occurs when persons are exposed to HIV-1. Treatment with progesterone to thin mucosal walls to make nonhuman primate susceptibility more similar to human susceptibility may help [26].

The more recent development of humanized mice is promising [27]. These small animals have been bred to have genetic systemic immunodeficiency, which allows them to accept grafts of human immune cells. The animals are susceptible to HIV-1 strains, although questions remain about which laboratory adapted stocks of HIV-1 are best suited for modeling natural human infection. Drug and viral administration is feasible, but the doses are still being optimized [28].

Tenofovir and emtricitabine have demonstrated protective effects in these animal models [29–33]. Keeping in mind that animal models do not have proven predictive value, the following signals have been observed and have informed the design of PEP and PREP programs and research in the absence of other information: (1) higher tenofovir dose is associated with higher protection; (2) either emtricitabine or tenofovir alone were associated with partial protection; (3) use of both drugs together increased the level of protection; (4) emtricitabine resistance was observed in some animals that became infected despite use of emtricitabine alone or in combination with tenofovir, whereas tenofovir resistance has not been observed; and (5) tenofovir chemoprophylaxis was partially effective against tenofovir resistant challenge [34].

Clinical research on oral PrEP has used findings from nonhuman primate models for drug regimen selection and study design. Clinical trials currently in progress will evaluate whether the insights from these models were helpful.

Community engagement. The state of the art of community engagement has advanced enormously over the past 25 years of HIV research, most recently during microbicide and PrEP research [35]. Prevention researchers have growing appreciation for starting discussions with community leaders and potential participants beginning at the conception of projects, even before the concept starts the formal process of review for funding, ethics, and regulatory compliance. Starting community engagement at conception allows for input to be reflected in the study design and gives communities time to consider difficult and important questions. Early engagement also allows broader input, to include leaders and constituencies who may have concerns about research concepts and practices. Their input is essential especially if there is insufficient trust to allow participation in formal consultative processes. Broad input ultimately improves the science, with little delay if started early, because issues related to feasibility and acceptability, once identified, can be addressed by altering the study design and through community education programs.

Many prevention trial sites around the world use clinics where participants receive information, study products, testing, counseling, and other services. This is a model of clinical research that derives from treatment trials of persons with a disease. This model is not optimal for prevention research, in which the desired population does not define itself by a disease and often denies their at-risk status. To more fully engage communities, the most successful prevention research sites are based in communities and provide a variety of services and information that are directly relevant to the communities. This model of prevention services provided by community centers may prove to be required for the widespread use of proven methods, just as they have facilitated the conduct of prevention research.

Communication through mass media needs to be interpreted with caution, in that some stories arise because of their appeal to urban myths and conventional thinking rather than because of new information [36, 37]. For example, although news articles suggested that off-label use of PrEP during sex parties in the United States was already common, careful research in the same places during the subsequent year indicated that PrEP use was actually extremely rare [38, 39]. Of importance, persons said that they would be interested in PrEP only if evidence of safety and efficacy for prevention became available, which shows judgment that was not reflected in the news report. Pitfalls are inherent in communication on any scale (both mass media and interpersonal); thus, caution should not prevent engagement with interested reporters who wish to share new information of general interest.

Adherence and therapy. Although vaccines, PEP, and PrEP are sometimes called biomedical prevention methods, these interventions are only helpful if persons use them and understand their limitations; all prevention of HIV infection is behavioral. Use requires access, and access requires both supply and demand; thus, prevention of HIV infection is also social and economic. The possible advent of prophylactic oral medications

or gels would not change the social and behavioral essence of prevention of HIV infection.

Adherence to therapy recommendations is a well-known problem in treatment; it is a common cause of failure of therapy for tuberculosis, HIV infection, systemic hypertension, and other diseases. Lack of adherence underlies much of the failure of condoms and oral hormones for contraception. Adherence is expected to be a still greater challenge in prevention of HIV infection, because the disease and antiretroviral agents are stigmatized and because individuals' social roles are not typically defined by HIV, much less the risk of acquiring HIV infection. Twenty-eight–day PEP regimens are completed by 78%–89% of recipients [17, 40], and adherence was 74% in a study of oral PrEP [21]. Gel adherence is also challenging; 44%–80% of individuals use gels, depending on the study and method of adherence measurement [41, 42]. The lack of a gold standard for measuring adherence makes adherence promotion still more challenging, although electronic devices and home visits are helpful if accepted [43, 44]. Oral and gel medication use has been hard to foster in trials. Evidence of efficacy and confirmation of safety may enhance adherence if this information becomes available.

Drug resistance. Any use of ART involves a risk of drug resistance. The ultimate goal of chemoprophylaxis is to prevent the majority of infections. In this way, perioperative chemoprophylaxis for bacterial infections, long resisted because of fears of drug resistance, is now the standard of care for many procedures, because the number of infections averted far exceeds the incidence of drug resistance [45]. Similarly, the best way to prevent HIV drug resistance is to prevent HIV infection.

Use of ART to prevent mother-to-child transmission has been associated with drug resistance in mothers, especially when regimens are used that do not fully suppress plasma viral load [14]. Therefore, fully suppressive regimens are now recommended whenever they are feasible. Infants who become infected despite ART use also tend to be infected with drug-resistant virus. Failure of PEP was also associated with development of drug-resistant virus [18] in a person who was already viremic, but without detectable anti-HIV antibodies, at the time that PEP was initiated.

Minimizing the risk of drug resistance during PEP or PREP requires that steps be taken to identify infection at baseline so that referrals can be made for appropriately suppressive therapies. Rapid point-of-care tests for HIV antibodies have excellent sensitivity but will still miss infections in the window period before antibodies develop, which may last for a few weeks. Whether addition of emtricitabine to TDF in PREP regimens is associated with more or less risk of drug resistance is an open question; resistance during treatment often occurs to only 1 drug in the regimen, and the added efficacy of adding emtricitabine that was seen in nonhuman primates may not occur in persons. Viral RNA testing before initiation of PEP, which allows detection of acute infections, has been increasingly used. The development of more-sensitive point-of-care tests for early HIV infection, based on antigen or RNA detection, should be a high priority for research.

Sexual behavior. There is concern that any benefits of biomedical prevention methods could be offset by behavioral disinhibition or risk compensation. Individuals may increase risk behavior if fear of HIV infection is diminished by the advent of new prevention methods [46].

Feared increases in sexual behavior were not observed in trials of male circumcision, trials of daily oral PrEP, open-label PEP studies, herpes suppression studies, and most vaccine studies [17, 21, 47–52]. A small vaccine trial found increased reported insertive, but not receptive, intercourse, although this trend probably reflected population-wide trends in "strategic positioning" [53]. Sexual behavior tends to be safer over time during prevention trials, possibly reflecting real effects of counseling and condom promotion, which are standard in all prevention trials. Alternatively, reported decreases in risk behavior may reflect "social desirability" reporting bias or regression toward the mean in cohorts selected for having "high risk" at the start of the study. Therefore, whether risk compensation will occur remains an open question that should be actively investigated.

On the basis of the evidence accumulated from the majority of prevention trials, ways that biomedical prevention tools could enhance behavioral approaches to prevention of HIV infection should also be considered. Persons with very high exposure may be attracted to prevention services if a wider range of services is available. Fatalistic attitudes may be replaced by prevention activism if highly effective and feasible prevention tools are identified and accepted in communities. Finally, the community engagement that is required for current prevention research may have additional benefits that arise from more organized communities.

Costs. Cost considerations are particularly important when drugs are used. The cost-effectiveness of daily oral PrEP has been considered in speculative "what if" analyses for sub-Saharan Africa and the United States [54, 55]. In both settings, the majority of PrEP program costs are for the drug, but other costs include community education, pharmacy storage and shipping, HIV testing and counseling, monitoring and management of adverse events, and use of second-line treatment regimens if drug resistance occurs. In both settings, daily oral PrEP would be cost-effective only if the following conditions are met: (1) PrEP is highly effective, (2) PrEP is targeted to highly exposed persons, (3) monitoring and treatment of adverse events is manageable, and (4) increases in sexual behavior are modest, relative to the efficacy of PrEP. Decreasing the cost of drugs will also be important, especially in settings where

generic-level pricing is not already available [54]. Intermittent or exposure-driven treatment administration is expected to be more cost-effective, if found to be feasible and efficacious. The relative costs of topical administration, compared with oral administration, would be sensitive to differences in efficacy, toxicity, and manufacturing costs, for which information is incomplete. Current clinical trials will provide essential information needed to inform the cost-effectiveness analysis.

CONCLUSIONS

Although current and planned research will address key questions related to efficacy and safety, additional questions will be faced by communities and public health officials who wish to implement new prevention strategies. How will start-up funds for training and facilities be raised? What is the best way to integrate new prevention services with existing prevention and treatment programs, which have different operating styles and goals and limited resources? What is the best way to monitor use of ART-based strategies, including the frequency of HIV testing and effects on drug resistance? What is the best way to target different services to different populations, especially in areas where the drugs, the infection, and the social groups are stigmatized? What is the best way to optimize regimen choice, dosage, dosing interval, and route of administration if one of the early approaches is found to be superior to placebo? Is daily treatment administration required, or is pre- and postexposure administration feasible and effective? When should PrEP be started? When should it be stopped?

Currently, prevention of HIV infection with use of ART remains an unproven promise. Progress is facilitated by avoiding artificial divisions: treatment and prevention enable each other; biomedical prevention requires behavioral change; microbicides are topical PrEP, and PrEP regimens are oral microbicides; and communities and investigators overlap and have mutual interests in making science better and better suited to real needs. Although current clinical trials of chemoprophylaxis aim to find a "magic bullet" for prevention of HIV infection, such bullets will help only if they are used by communities in their struggles to live in a world plagued by HIV infection.

Acknowledgments

Potential conflicts of interest. R.M.G. is an investigator in trials of preexposure prophylaxis that are funded by the National Institutes of Health, the Centers for Disease Control and Prevention, and the Bill and Melinda Gates Foundation. Study medication is donated by Gilead Sciences for this research.

Supplement sponsorship. This article is part of a supplement entitled "Synergistic Pandemics: Confronting the Global HIV and Tuberculosis Epidemics," which was sponsored by the Center for Global Health Policy, a project of the Infectious Diseases Society of America and the HIV Medicine Association, through a grant from the Bill & Melinda Gates Foundation.

References

1. Conner EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med **1994**; 331:1173–1180.
2. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet **1999**; 354(9181):795–802.
3. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. DIminution de la Transmission Mère-Enfant. Lancet **1999**; 353(9155):786–792.
4. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. Lancet **1999**; 353(9155):781–785.
5. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. Lancet **2002**; 359(9313): 1178–1186.
6. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. J Infect Dis **2003**; 187(5):725–735.
7. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet **1999**; 353(9155):773–780.
8. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet **2003**; 362(9391): 1171–1177.
9. Volmink J, Siegfried NL, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev **2007**(1):CD003510.
10. Leroy V, Sakarovitch C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? AIDS **2005**; 19(16): 1865–1875.
11. European CS. Children born to women with HIV-1 infection: natural history and risk of transmission. Lancet **1991**; 337:253.
12. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). AIDS **2001**; 15(15):1951–1957.
13. Horvath T, Madi BC, Iuppa IM, Kennedy GE, Rutherford G, Read JS. Interventions for preventing late postnatal mother-to-child transmission of HIV. Cochrane Database Syst Rev **2009**(1):CD006734.
14. Perinatal HIV Guidelines Working Group. Public health service task force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 29 April 2009:1–90. http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed 28 July 2009.
15. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, 2009:1–161. http://www.aidsinfo.nih.gov/contentfiles/adultandadolescentGL.pdf. Accessed 28 July 2009.
16. Smith DK, Grohskopf LA, Black RJ, et al.; US Department of Health and Human Services. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of

Health and Human Services. MMWR Recomm Rep **2005**; 54(RR-2): 1–20.
17. Schechter M, do Lago RF, Mendelsohn AB, Moreira RI, Moulton LH, Harrison LH. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV. J Acquir Immune Defic Syndr **2004**; 35(5):519–525.
18. Roland ME, Neilands TB, Krone MR, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. Clin Infect Dis **2005**; 41(10):1507–1513.
19. Youle M, Wainberg M. Could chemoprophylaxis be used as an HIV prevention strategy while we wait for an effective vaccine? AIDS **2003**; 17:937–938.
20. PrEP Watch. http://www.prepwatch.org/trials.htm. 28 July 2009.
21. 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 Clin Trials **2007**; 2(5):e27.
22. Levy V, Grant RM. Antiretroviral therapy for hepatitis B virus-HIV-coinfected patients: promises and pitfalls. Clin Infect Dis **2006**; 43(7): 904–910.
23. Thio CL, Sulkowski MS, Thomas DL. Treatment of chronic hepatitis B in HIV-infected persons: thinking outside the black box. Clin Infect Dis **2005**; 41(7):1035–1040.
24. Mayer KH, Mimiaga MJ, Cohen D, et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston Community Health Center. J Acquir Immune Defic Syndr **2008**; 47(4):494–499.
25. Trial finds tenofovir gel safe for daily use and most women adhered to study regimens: results of phase II study of ARV-based microbicide presented at international meeting in India bolster interest in latest approach. http://www.mtnstopshiv.org/node/359. 28 July 2009.
26. Marx PA, Spira AI, Gettie A, et al. Progesterone implants enhance SIV vaginal transmission and early virus load. Nat Med **1996**; 2(10): 1084–1089.
27. Sun Z, Denton PW, Estes JD, et al. Intrarectal transmission, systemic infection, and CD4+ T cell depletion in humanized mice infected with HIV-1. J Exp Med **2007**; 204(4):705–714.
28. Denton PW, Estes JD, Sun Z, et al. Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice. PLoS Med **2008**; 5(1):e16.
29. Tsai C-C, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science **1995**; 270:1197–1199.
30. Van Rompay KKA, Miller MD, Marthas ML, et al. Prophylactic and therapeutic benefits of short-term 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) administration to newborn macaques following oral inoculation with simian immunodeficiency virus with reduced susceptibility to PMPA. J Virol **2000**; 74(4):1767–1774.
31. Van Rompay KKA, McChesney MB, Aguirre NL, Schmidt KA, Bischofberger N, Marthas ML. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. J Infect Dis **2001**; 184(4):429–438.
32. 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 Med **2008**; 5(2):e28.
33. Garcia-Lerma G, Cong M-E, Mitchell J, et al. Prevention of rectal simian HIV transmission in macaques by intermittent pre-exposure prophylaxis with oral truvada. In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 47.
34. Van Rompay KK, Miller MD, Marthas ML, et al. Prophylactic and therapeutic benefits of short-term 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) administration to newborn macaques following oral inoculation with simian immunodeficiency virus with reduced susceptibility to PMPA. J Virol **2000**; 74(4):1767–1774.
35. Grant RM, Buchbinder S, Cates W Jr, et al. Promote HIV chemoprophylaxis research, don't prevent it. Science **2005**; 309(5744):2170–2171.
36. Mills EJ, Rachlis B, Wu P, et al. Media reporting of tenofovir trials in Cambodia and Cameroon. BMC Int Health Hum Rights **2005**; 5(1):6.
37. Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? PLoS Med **2005**; 2(9):e234.
38. Liu AY, Kittredge PV, Vittinghoff E, et al. Limited knowledge and use of HIV post- and pre-exposure prophylaxis among gay and bisexual men. J Acquir Immune Defic Syndr **2008**; 47(2):241–247.
39. Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. J Acquir Immune Defic Syndr **2009**; 50(1):77–83.
40. Kahn JO, Martin JN, Roland ME, et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP study. J Infect Dis **2001**; 183(5):707–714.
41. Skoler-Karpoff S, Ramjee G, Ahmed K, et al., Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. Lancet **2008**; 372(9654): 1977–1987.
42. Karim S, Coletti A, Richardson B, et al., Safety and effectiveness of vaginal microbicides buffergel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in women: results of the HPTN 035 trial (48LB). In: Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections (Montreal). **2009**. Abstract 48LB.
43. Moss AR, Hahn JA, Perry S, et al. Adherence to highly active antiretroviral therapy in the homeless population in San Francisco: a prospective study. Clin Infect Dis **2004**; 39(8):1190–1198.
44. Kalichman SC, Amaral CM, Stearns H, et al. Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone. J Gen Intern Med **2007**; 22(7):1003–1006.
45. De Lalla F. Perioperative antibiotic prophylaxis: a critical review. Surg Infect (Larchmt) **2006**; 7(Suppl 2):S37–S39.
46. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? BMJ **2006**; 332(7541):605–607.
47. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med **2005**; 2(11):e298.
48. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet **2007**; 369(9562):657–666.
49. Bailey RC, Moses S, Parker CB, et al., Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet **2007**; 369(9562):643–656.
50. Bartholow BN, Buchbinder S, Celum C, et al. HIV sexual risk behavior over 36 months of follow-up in the world's first HIV vaccine efficacy trial. J Acquir Immune Defic Syndr **2005**; 39(1):90–101.
51. Martin JN, Roland ME, Neilands TB, et al. Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. AIDS **2004**; 18(5):787–792.
52. Celum C, Wald A, Hughes J, et al., Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet **2008**; 371(9630):2109–2119.
53. Chesney MA, Chambers DB, Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. J Acquir Immune Defic Syndr Hum Retrovirol **1997**; 16(4):266–271.
54. Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis **2009**; 48(6):806–815.
55. 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.