



## ~ Chapter 4 ~

# HIV Transmission

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### GLOBAL EPIDEMIOLOGY OF HIV

The HIV epidemic was initially identified among men who have sex with men (MSM) in the United States in 1981, leading to the epidemiologic connection between unprotected anal intercourse and HIV infection. As the epidemic progressed, it became apparent that other modes of transmission were also possible. HIV transmission occurs through percutaneous or mucous membrane exposure to infected blood, genital secretions, and breast milk, with the efficiency of HIV transmission varying based on the type of exposure (Table 1). HIV transmission occurs through sexual contact, vertical transmission from mothers to infants, and among injection drug users sharing infected needles, as well as through transfusion of infected blood products. Nonsexual casual contact has not been associated with HIV transmission.

**Table 1. Estimated per act risk of acquisition of HIV.** Source: Centers for Disease Control and Prevention, 2005. *MMWR*. January 21, 2005 / 54(RR02), 1-20.

Exposure route	Risk per 10,000 exposures
Blood transfusion	9,000
Needle-sharing injection drug use	67
Percutaneous needle stick	30
Receptive penile vaginal intercourse	10
Insertive penile vaginal intercourse	5
Receptive anal intercourse	50
Insertive anal intercourse	6.5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

Globally, the HIV incidence is believed to have peaked in the late 1990s, and to have stabilized thereafter. In 2007, the WHO estimated that 33.2 million individuals were living with HIV world-wide, with 2.5 million people newly infected in 2007. Women are estimated to account for approximately half of infected adults, and approximately 2.1 million children under the age of 15 years are thought to be living with HIV. Sub-Saharan Africa is disproportionately affected, with approximately two thirds of the global persons (approximately 22.5 million individuals) living with HIV residing in sub-Saharan Africa. HIV epidemics in sub-Saharan Africa are highly diverse and still expanding in some parts of the region, with

a female to male ratio of 3:1 among 15–24 year olds. In some regions of southern Africa, the leveling off of the epidemic reflects realities where the number of persons newly infected with HIV roughly match the number of people dying of HIV-related illnesses. Structural interventions will need to address gender inequalities, the necessary continuum between HIV transmission prevention and treatment and reducing stigma and discrimination. In addition to biological factors to be discussed in this chapter, social and contextual factors such as global migration patterns, violence against women and commercial sex work clearly influence and drive HIV transmission within and between different global regions.

In this chapter, we will review the biology of HIV transmission, the risk of transmission via the various known modes of HIV transmission, and cofactors which can modulate the risk of HIV transmission.

## PRINCIPLES OF TRANSMISSION

The different interactions between host and pathogen dynamics, reflected in the equation  $R_0 = B \times D \times C$ , will determine whether an epidemic will grow or slow, where  $R_0$  (or the reproductive ratio) is the number of secondary cases produced by a single index case in a population of susceptible persons,  $B$  is the transmission efficiency of the pathogen or infectiousness,  $D$  is the duration of infectiousness and  $C$  is the rate of partner change. When the  $R_0$  is less than one, each infected individual will infect less than one person, and the infection is expected to die out. When  $R_0$  is greater than one, the infection will continue to be propagated through the population. HIV is a pathogen of low infectiousness, but has a long duration of infectiousness. Co-factors, such as genital ulcer disease and high HIV viremia, increase the transmission efficiency of the pathogen.

Sexually transmitted epidemics can also be classified as early or late and concentrated or generalized. Early in an epidemic, sexually transmitted infections (STIs) are transmitted between high risk persons with high rates of infection and frequent partner change (core groups). Examples of core groups are sex workers and their clients, mobile populations such as long distance truck drivers, MSM with multiple sex partners who engage in unprotected anal intercourse, MSM who have sex with women, members of the uniformed services, recreational sex tourists, substance users, incarcerated persons especially juveniles, persons who experience sexual or gender based violence, and children and young people who are living on the street. In a generalized epidemic, pathogens spread into lower risk populations often through bridge populations which can serve as important links between core groups and the general population. In countries with concentrated epidemics in specific high risk groups, interventions that interrupt high transmission networks will have the greatest impact. In countries with generalized epidemics, reducing partner number is key in reducing HIV prevalence.

## MECHANISM OF HIV TRANSMISSION

Successful HIV transmission requires contact between infectious viral particles and susceptible host immune cells. The primary target of HIV is  $CD4^+$  T-lymphocytes. HIV enters the host cell by binding to the CD4 receptor and either the CCR5 or CXCR4 chemokine co-receptors. With mucosal introduction of HIV,  $CD4^+$  dendritic cells in the mucosa are infected and fuse with local  $CD4^+$  T-lymphocytes which transport HIV to the lymphatic system. Activated  $CD4^+$  T-lymphocytes are infected by the virus, with ensuing viral replication. Systemic dissemination of HIV through the blood stream follows within a few days, and infection becomes disseminated and established within the host.

## BIOLOGY OF HIV TRANSMISSION

Successful HIV transmission requires contact between infectious viral particles and susceptible host immune cells. The primary target of HIV is  $CD4^+$  T-lymphocytes. HIV enters the host cell by binding to the CD4 receptor and either the CCR5 or CXCR4 chemokine co-receptors. CXCR4 viruses become more abundant after several years of infection and are associated with accelerated disease. There is some evidence viruses that use CXCR4 receptors may be less transmissible than viruses using CCR5 receptors to enter target cells. Layers of stratified squamous epithelium that line female and male genital mucosa serve as a physical barrier to incoming virus. With cervical ectopy in women aged 15–24, endocervical columnar

epithelium grows onto the exocervical surface at the top of the vaginal vault. Endocervical cells express high levels of CXCR4 and CCR5 co-receptors; cervical ectopy has been associated as a risk factor for HIV acquisition. The thin rectal epithelium provides little protection to trauma. In addition, the rectum has organized lymphoid tissue with cells that can bind and present HIV. With mucosal introduction of HIV, CD4<sup>+</sup> dendritic cells in the mucosa are infected and fuse with local CD4<sup>+</sup> T-lymphocytes which transport HIV to the lymphatic system. HIV-1 can stay infectious in dendritic cells for up to 5 days without infecting the cell. Dendritic cells interact with and activate CD4<sup>+</sup> cells in T cell rich regions of lymph nodes. Activated CD4<sup>+</sup> T-lymphocytes are infected by the virus, with ensuing viral replication. Systemic dissemination of HIV through the blood stream follows within a few days, and infection becomes disseminated and established within the host.

Infection with more than one strain of HIV is possible, and several scenarios have been described. Dual infection is defined as infection with two HIV strains at or near the time of seroconversion. In a study of 31 female sex workers, 19% were dually infected. Dual infection is associated with a higher viral set point and more rapid AIDS progression. Superinfection, defined as infection with a second HIV strain after initial infection has occurred, is rare and documented in a few published case reports during early HIV infection. The relative infrequency of documented superinfection may be due to the inability of viral strains to compete given existing immune responses or to competitive pressure from existing viruses. Among 78 persons with new HIV infection, followed from primary infection, 3/78 (3.8%) became superinfected. In this cohort, superinfection was associated with an increase in plasma HIV RNA and rapid decline in CD4<sup>+</sup> cells.

### **HIV TRANSMISSION THROUGH INFECTED BLOOD PRODUCTS**

Direct inoculation of HIV-infected blood through the transfusion of infected bodily fluids is the most effective mode of HIV transmission, with one Swedish study demonstrating HIV infection among 50 of 51 infected blood product recipients. HIV antibody testing of blood donors significantly decreases the risk of transfusion associated HIV transmission, but the potential for HIV transmission from HIV-infected individuals who are HIV antibody negative but RNA positive still exists. Screening of blood products using HIV antigen (p24) or RNA (viral load) testing will detect HIV infection among individuals still in the “window-period” prior to HIV antibody seroconversion, further increasing the safety of blood products. However, this can be an expensive undertaking, with variable yield with regards to the proportion of infections detected and transmission averted; such an undertaking would be more beneficial in areas with higher HIV prevalence. In theory, measures such as establishment of a “safe”, voluntary blood donor pool, and release of blood products after multiple HIV antibody-negative donations from any one individual can also decrease the likelihood of transfusion of HIV sero-negative but RNA positive blood products without incurring the higher cost of HIV RNA screening of all blood donations.

### **OCCUPATIONAL AND NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS**

HIV transmission to a health care worker after a needlestick exposure was documented early in the HIV epidemic. Studies indicate that the risk of seroconversion after needle stick exposure to HIV infected blood is between 0.1–0.5%. Factors associated with an increased risk of seroconversion after an occupational exposure include injury with a device visibly contaminated with a patient’s blood, injury involving the needle being placed directly in a vein or artery, deep injuries and source patients with high viremia.

To date, post exposure prophylaxis (PEP) which by definition includes mother-to-child transmission (MTCT), remains the only way to decrease the risk of developing HIV infection in a person exposed to the virus. In the only retrospective case control study, after controlling for other risk factors for HIV transmission, AZT monotherapy for PEP was associated with an 80% reduction in the risk of acquiring HIV infection. Data from prospective studies with currently used 2 and 3 drug PEP regimens are not available, but expert opinion recommendations advocate for their use in the setting of higher risk exposures. PEP is always voluntary, necessitates informed consent (which can be verbal) that emphasizes the importance of adherence to a 4 week course, and should occur in the context of rapid HIV testing for exposed and source persons.

PEP is also advocated after non-occupational exposures, such as sexual contact or injection drug use. The estimated risk of acquiring HIV infection from a single episode of consensual receptive vaginal intercourse is between 0.1% and less than 1%, and from a single episode of consensual receptive anal sex, is between 1% and 5%. These risks may be higher in the context of sexual assault. Among 700 non-occupational PEP recipients in San Francisco, 1% PEP failures were reported. PEP failures were associated with commencement of drugs after 72 hours, poor adherence, or further HIV exposures before or after PEP. Eligibility criteria for PEP include an exposure that has the potential for HIV transmission, defined as one involving non-intact skin or mucous membrane exposure through sexual exposure or splash to eyes, nose or oral cavity to potentially infected body fluid from a source that is HIV infected or with unknown HIV status. Body fluids that may transmit HIV include blood, genital secretions, cerebrospinal fluid, amniotic, peritoneal or pleural fluids. Fluids regarded as non-infectious include feces, saliva, urine and sweat. PEP should be initiated as soon as possible after potential exposure, and no later than 72 hours after exposure. Animal studies support improved efficacy at earlier commencement of PEP. An overview of current recommendations for PEP use based on type of exposure, baseline prevalence of community resistance and HIV status of source person can be found at: <http://www.who.int/hiv/pub/guidelines/PEP/en/index.html> (Annex 6 of document). NRTIs used for PEP should be part of WHO ARV treatment regimens. WHO calls for PEP provision to be integrated into existing national prevention and service frameworks for occupational health and for persons who have been sexually assaulted.

### **INJECTION DRUG USE**

Individuals who use drugs are at increased risk of HIV acquisition. Drug use increases HIV risk through sexual disinhibition and risk taking as a direct effect of drug use, or in association with drug-seeking (for example engaging in transactional sexual intercourse in exchange for drugs/money). Injection drug use can result in HIV transmission through sharing of infected drug paraphernalia such as needles and syringes. With an estimated 13 million injecting drug users worldwide, 5–10% of HIV cases are attributable to injection drug use. Drug use is the primary driver of the HIV epidemic in some regions of the world, including eastern Europe and central Asia, and contributes to HIV infection within many regions of the world. The risk of HIV transmission through shared needles is approximately 1% per contact act, with varied inoculum based on the method of drug injection. As drug use is illicit in most nations, drug using populations are often marginalized and may not be easy populations to reach. Comprehensive approaches to increase HIV counseling and testing and treatment, safer-sex practices, access to clean needles and syringes, as well as drug rehabilitation programs with appropriate drug substitution (methadone or buprenorphine in the case of opiate addiction), have been shown to decrease HIV transmission related to drug use and should be incorporated into HIV transmission prevention, care, and treatment programs.

### **SEXUAL TRANSMISSION OF HIV**

Sexual transmission of HIV is the predominant mode of HIV transmission worldwide. Heterosexual transmission accounts for the majority of global HIV infections, with concentrated epidemics related to sexual activity among MSM. Epidemiologic studies have been conducted to quantify the risk associated with various exposures, and provide a general probability of infection based on sexual exposure. Anal receptive intercourse carries the higher risk of HIV acquisition compared to insertive anal intercourse. In general, male to female through penile-vaginal transmission is greater than female to male transmission of HIV. Oral intercourse is less likely to result in HIV transmission, though there are documented cases in which transmission has been related to oral sexual exposure. The expected range of per-contact act is shown in Table 1.

These estimates of risk of HIV transmission provide a conceptual framework and are of use for epidemiologic and research studies, but counseling services that provide risk estimates of HIV infection based on exposure should always keep in mind that despite the seemingly low probabilities of infection per coital act, there is variability in transmissibility, and HIV infection has been documented after just a single exposure.

## Cofactors in HIV sexual transmission

### *HIV RNA levels*

Sexual transmission of HIV is the predominant mode of HIV transmission worldwide. The probability of sexual transmission of HIV has been shown to vary based on the clinical stage of infection, correlated with HIV RNA levels. Acute HIV infection may be highly infectious and efforts should focus on early diagnosis, ideally using HIV RNA testing, prevention counseling and partner services. Clinically, symptoms of acute HIV are non-specific and resemble other viral syndromes, with fewer than 1,000 persons worldwide being diagnosed within the first month of infection. The time period between acute HIV infection (with viral loads peaking at 4 weeks) and development of measurable antibodies represents a period of high infectiousness that increases in the presence of an STI. A study in Rakai, Uganda among discordant heterosexual couples prior to initiation of antiretroviral therapy demonstrated that the highest risk of HIV transmission was during incident (recent) infection, followed by late stage disease, with the lowest transmission among those with prevalent disease. No transmission events occurred when HIV RNA levels were below 1,500 copies/mL in the HIV-infected partner. Incremental increases in transmission were noted with 5.6% transmissions among those with HIV RNA levels ranging from 400 to 3,499 copies/mL; 17.7% with HIV RNA levels 3,500 to 9,999 copies/mL; 40% in 10,000–49,999 copies/mL; and 36.7% in those with greater than 50,000 copies/mL. Studies evaluating the risk of heterosexual transmission among hemophiliacs infected with HIV through blood products similarly showed a relationship between HIV-1 RNA levels and risk of transmission to an uninfected sexual partner. HIV-1 RNA levels in semen were found to be higher among men with acute HIV infection compared with those with chronic infection, a factor which may explain the above observations of increased HIV transmission risk during acute infection.

Increased availability of effective combination antiretroviral therapy (ART) may have an impact on HIV transmission, by decreasing the infectiousness of HIV-infected individuals. However, ART is not 100% effective, and viremia despite ART can result in the development of drug resistance. In high-income countries where ART has been available for over a decade, there is strong evidence for transmitted drug resistance. Transmitted or primary drug resistance is defined as resistance against antiretroviral drugs among previously antiretroviral naïve (untreated) HIV-infected individuals. Studies from Western Europe and the US have identified primary drug resistance in 9–12% of HIV-1 infected individuals. Increasing prevalence of primary drug resistance will have an implication both on the effectiveness of public health approaches to antiretroviral therapy espoused by WHO and implemented in many resource-constrained countries, as may limit the effectiveness of antiretroviral therapy to prevent HIV transmission. Active surveillance to evaluate for primary drug resistance is therefore an important aspect of HIV care and prevention.

### *Genital ulcer disease*

The presence of genital ulcer disease has been associated with increased risk of HIV transmission and acquisition. Proposed mechanisms whereby HIV infection is facilitated include the presence of mucosal disruption which decreases the physical boundary between HIV particles and susceptible cells. Increased inflammation associated with genital ulcer disease can further enrich the immune components in the region, increasing the number of HIV target cells. Recent studies have demonstrated an increase in CCR5 in the cellular milieu both within genital ulcers among women with ulcerative disease secondary to syphilis or herpes infection. An increase in monocytes expressing CCR5 were also noted on non-ulcerated vulvar tissue contralateral to the lesion, as well as in peripheral blood mononuclear cells among women with primary or secondary syphilis, which further exemplifies the potential distal effects which can further modulate HIV transmission and acquisition. HIV acquisition has also been associated with non-ulcerative sexually transmitted infections.

Clinically, HSV-2 is the main STI associated with higher risk of HIV acquisition. However, a recent study in which acyclovir was administered with a goal to decrease the presence of genital ulcer disease among women HSV-2 seropositive and HIV-uninfected at entry into the study did not result in a decrease in HIV acquisition. There was no difference in the rates of genital ulcer disease between the acyclovir and placebo group, and questions remain as to whether higher dosages of

acyclovir or agents with higher bioavailability would result in improved suppression of genital ulcer disease and provide protection from HIV acquisition.

### **Male circumcision status**

Observational studies had demonstrated a potential relationship between HIV prevalence and the prevalence of male circumcision within populations. In the four city study, two cities with high rates of circumcision (>99%) in Benin and Cameroon, were found to have much lower HIV prevalence than two cities in Kenya and Zambia. In the Kenyan and Zambian study sites, circumcised men were found to have a lower prevalence of HIV infection than their non-circumcised counterparts. Removal of the male foreskin increases keratinization, and is thought to decrease the available target cells and surface area thereby decreasing the susceptibility of the circumcised male to HIV acquisition. Such epidemiologic associations with potential biologic plausibility led to the construction of randomized clinical trials to determine the impact of male circumcision on the risk of HIV-1 acquisition. Three randomized controlled trials were stopped early after significantly fewer men were found to acquire HIV after circumcision, with approximately 55–60% protection attributed to circumcision. There were very few serious complications among study participants in the three randomized controlled studies, and plans to implement this potentially valuable prevention tool are currently underway in many high HIV prevalence areas.

While the above randomized controlled trials demonstrated a clear benefit to the men undergoing circumcision, the impact of this intervention on female partners is still under investigation. Observational studies in Uganda and Zimbabwe have not shown decreased rates of HIV-1 acquisition among female partners of circumcised HIV-1 infected males. Studies have also begun to explore the potential impact of circumcision of HIV-infected men to decrease potential transmission to their HIV negative partners. Circumcision among HIV-infected males decreased the incidence of genital ulcer disease among the men, but did not have an impact on HIV incidence among their female partners, with higher transmission seen among couples who re-initiated sexual intercourse prior to full healing of the surgical wound. Circumcision in the absence of concurrent HIV-testing may thus be problematic in the event that sexual transmission is re-initiated prior to full wound healing. Programs seeking to implement male circumcision as a prevention tool will need to provide comprehensive counseling and provide an opportunity for HIV testing in order to maximize the potential benefit of this prevention tool.

### **Hormonal contraceptive use**

Several observational studies have analyzed the relationship between sexual transmission of HIV infection among women and use of hormonal contraceptives. Use of hormonal contraceptives had been associated with cervical ectopy, irregular uterine bleeding, altered bacterial flora, and alterations in the local target immune cells, all of which are postulated to potentially modulate the risk of HIV acquisition. One study evaluated the potential role of hormonal contraceptive use among women seeking reproductive general medical care in Uganda and Zimbabwe. No relationship was found between hormonal contraceptive use and HIV acquisition overall, but identified an increased incidence of HIV among the subset of women exposed to hormonal contraceptives who were HSV-2 uninfected. In a cohort of Kenyan female commercial sex-workers, a significant association was identified between hormonal contraceptive use and HIV incidence, independent of HSV-2 serostatus. Randomized clinical trials are being planned to further investigate the possible relationship between hormonal contraceptive use and HIV.

## **STRATEGIES FOR PREVENTING THE SEXUAL TRANSMISSION OF HIV**

World Health Organization (WHO) strategies for preventing the sexual transmission of HIV have focused on three main areas: 1) condom use promotion, 2) sexually transmitted infection (STI) treatment and 3) reduction in unsafe sexual behavior. The US Centers for Disease Control and Prevention recommends all providers incorporate HIV testing into routine medical care and employ rapid HIV tests in primary care and field based settings.

### **Condom use promotion**

Male latex condoms provide an impermeable barrier to viruses even smaller than HIV under conditions more stringent than those during intercourse. In addition, epidemiological studies in HIV serodiscordant couples conclusively show that consistent use of latex condoms provide a high degree of protection. Male condoms can significantly decrease the risk of HIV acquisition, and a systematic review of condom effectiveness to prevent HIV transmission estimated a median effectiveness of 86.6%, but with effectiveness as high as 95.8% with optimal use. Several studies have shown that condoms can protect against the transmission of discharge diseases (Chlamydia, gonorrhea and trichomonas) and protects against genital ulcer diseases when the infected area is covered by the condom (genital herpes and syphilis). For patients with latex allergy, polyurethane condoms are available. Oil based lubricants should be avoided with latex condoms, as should nonoxynol-9, a spermicide that has been shown to increase the risk of HIV acquisition.

The female condom is built to fit inside the vagina with rubber rings to keep it in place. The female condom is more expensive, difficult to use and has had limited distribution in countries hardest hit by the HIV epidemic. Studies are underway to evaluate whether the female condom can be used more than once.

### **STI treatment for index cases and partners**

Over 80% of the global burden of STIs occurs in developing countries where access to diagnostic testing is limited. WHO recommends syndromic treatment based on local epidemiologic patterns where diagnostic testing is not available while highlighting the need for the development of rapid diagnostic tests to improve the quality of diagnosis and care in resource limited settings.

### **Reduction in unsafe sexual behavior**

Examples include decreasing concurrency, or using condoms consistently during the first three months of a new relationship to reduce transmission during the acute infection period.

### **ABSTINENCE AND ABSTINENCE-PLUS PROGRAMS**

There has been much publicity regarding the role of abstinence or abstinence-plus strategies for the prevention of HIV transmission. Abstinence programs contend that only abstinence will effectively prevent HIV infection. Limitations of these programs include their lack of proven effectiveness, and lack of incorporation of alternative approaches in the event abstinence is not feasible. Programs which have advocated for abstinence-only have been shown to have no impact on episodes of unprotected intercourse, number of sexual partners, initiation of sexual activity, or reported condom use, and in one study, was shown to increase the risk of sexually transmitted infections and pregnancy. Abstinence-plus programs, which advocate for abstinence as the most effective preventive tool, but also disseminate information on safer sex information (including proper use of condoms, advocating for limiting the number of sexual partners, decreasing frequency of unsafe sexual intercourse, information about sexually transmitted infections, pregnancy, contraception and HIV) showed an overall protective effect on at least one biologic or behavioral outcome in 62% of programs evaluated, with no overall increase risk identified. While the above two studies were not performed in the resource-constrained settings, there are valuable lessons learned that should instruct the direction taken in planning prevention programs globally.

### **MOTHER-TO-CHILD TRANSMISSION OF HIV**

HIV-1 is a leading cause of infant mortality in resource-limited countries in sub-Saharan Africa. An estimated 420,000 children were newly infected with the virus in 2007, primarily through mother to child transmission. In the absence of an intervention, the majority of mother-to child transmission (MTCT) occurs during pregnancy and delivery, with transmission occurring in approximately 25% of infants born to HIV-1 infected mothers; there is further risk of transmission to the infant through breast feeding, with up to a third of infections due to breast-feeding. Factors associated with higher

probabilities of vertical transmission include higher maternal HIV RNA levels, lower CD4<sup>+</sup> counts, infant prematurity, chorioamnionitis, and duration of rupture of membranes.

Use of combination antiretroviral therapy, with or without cesarean section to further diminish risk of transmission intrapartum has resulted in transmission risk of less than 2% among infants born to HIV-1 infected mothers in resource rich areas. Due to the lack of health infrastructure, personnel and resources, delivery of combination antiretroviral therapy is not yet standard practice in many resource-limited countries. Several strategies have been studied to prevent vertical transmission of HIV. In the Pediatrics AIDS Clinical Trials Group 076, initiation of zidovudine (AZT) monotherapy starting at approximately 14 weeks of gestation decreased vertical transmission to 8.3% compared to 25.5%. Single dose nevirapine (SD NVP) prophylaxis administered to the mother during labor and the infant post-delivery has been shown to decrease perinatal transmission. HIVNET 012 was a study that evaluated the impact of SD NVP on HIV transmission among HIV infected pregnant women in Uganda. In this study, transmission at birth was 8.2% in the SD NVP arm, and by 14–16 weeks post-partum, transmission rates remained at 13.1%, 47% below the expected transmission rate in the absence of an intervention. The early gains seen in transmission prevention are mitigated by the ongoing exposure of the infant to HIV through breast-milk, and by 18 months post-partum, transmission rates were 15.7%, with an overall decrease in transmission of 41%. Concerns have been raised about the use of SD NVP not only because of the lower effectiveness of this intervention among breast-feeding populations, but as studies have identified an increased risk of drug resistance associated with the administration of SD NVP. Nevirapine is lipophilic and has a long half-life, qualities that are useful in its use for prevention of MTCT, but these same attributes result in prolonged monotherapy when women receive SD NVP for vertical transmission prevention. An estimated 20–76% of women develop non-nucleoside reverse transcriptase associated drug resistance mutations following the administration of SD NPV. This has been shown to impact women's responses to combination antiretroviral therapy for their own health when treatment is initiated within 6 months of exposure to SD NVP.

Other studies have evaluated the potential role for short courses of antiretroviral medications. A Thai study showed that the addition of a single maternal dose of nevirapine at delivery following a short course of AZT initiated in the third trimester of pregnancy and formula replacement feeding further decreased transmission to 2.8%. Similar gains were seen in the Mashi study in Botswana, where initiation of AZT at 34 weeks gestation followed by SD NVP to the mothers, and 1 month of infant AZT prophylaxis and formula-feeding achieved transmission rates of 5.6% compared to a 9% transmission rate among infants who were breast-fed. In addition to increased effectiveness in preventing vertical transmission of HIV, the addition of a short course of AZT may also result in lower rates of drug resistance. Various other short courses of dual therapy antiretroviral therapy have also been studied. The Petra study was conducted in Tanzania, Uganda, and South Africa, in which AZT and lamivudine were administered starting at 36 weeks gestation with intrapartum oral dosing, followed by one week of infant prophylaxis with the same agents. This intervention led to 5.7% transmission rates at six weeks, but with infections attributable to breast-feeding transmission resulting in 15% transmission rates by 18 months post-partum. The most recent WHO guidelines recommend combination antiretroviral therapy for pregnant women with WHO clinical stage  $\geq 3$  and CD4<sup>+</sup> cell count of  $< 350$  cells/mm<sup>3</sup>. If women do not meet criteria for combination antiretroviral therapy for their own health, the WHO guidelines recommend administration of either: 1) AZT from 28 weeks gestation followed by SD NVP and lamivudine at the onset of labor, followed by 7 days of AZT and lamivudine post-partum, and infant prophylaxis including SD NVP at birth followed by 7 days of AZT, 2) AZT from 28 weeks gestation plus SD NVP for mother and infant, and 7 days of AZT for the infant, 3) SD NVP in addition to AZT and lamivudine during labor and for 7 days post-partum to the mother, and SD NVP to the infant or 4) SD NVP to the mother and infant. The administration of AZT in the antepartum period and lamivudine in the peri and post-partum period minimizes monotherapy with NVP, thus potentially limiting the development of drug resistance.



## APPROACHES TO HIV TRANSMISSION PREVENTION UNDER ACTIVE INVESTIGATION

### Microbicides

Microbicides are topical agents designed to block HIV infection by targeting either incoming virus or the mucosal cell it infects. Four types of microbicides are currently undergoing investigation in efficacy trials: 1) vaginal acidifying agents which promote a protective vaginal pH, 2) detergents or surfactants that inactivate viral particles, 3) polymers that block attachment of virus to target cells and 4) antiretrovirals such as tenofovir (TDF). As the HIV membrane is derived from host cells, concern exists that a compound which attacks the viral membrane non-specifically could also cause tissue damage. The detergent nonoxynol-9 was found to damage vaginal epithelium and increase the risk of acquiring HIV. Microbicides that target HIV envelope glycoproteins gp 120 and gp 41 are limited by the large sequence diversity of the envelope gene. Antiretroviral microbicides may offer the most promise. A recent study of 1% tenofovir (TDF) gel in HIV negative, sexually abstinent women found low but detectable serum TDF levels in 14 of 25 women. This permits local activity for prevention, while avoiding potential toxicities associated with high systemic levels. No new HIV RNA resistance mutations were detected after 2 weeks of TDF gel in 24 HIV infected participants. A Geneva Consensus conference in 2004 recommended microbicide studies should move ahead in HIV negative populations. Given the underappreciated risk of unprotected anal intercourse globally, efforts to test vaginal microbicides for rectal use should be encouraged.

### Pre-exposure Prophylaxis (PreP)

One of the most promising approaches for HIV transmission prevention currently being tested in a number of global trials employs daily oral PreP with tenofovir or tenofovir/emtricitabine (Truvada). Animal studies were encouraging and provided evidence for human trials. Human PreP trials were first proposed in 2001. TDF is a good candidate for a pre-exposure prophylactic antiretroviral for several reasons. TDF has a long intracellular half life permitting once daily and possibly longer dosing and lacks drug interactions with tuberculosis therapy, hormonal contraceptives or opiates. TDF also has a high barrier to ARV resistance and an established safety record. Current TDF PreP trials are ongoing in Thai injection drug users (n = 2,400), heterosexual men and women in Botswana (n = 1,200), MSM in Atlanta, San Francisco and Boston (n = 400), Peruvian MSM (n = 3,000), African women (n = 4,200), and Kenyan serodiscordant couples (n = 3,900). Safety is being closely followed in current trials with frequent laboratory monitoring especially for renal toxicity and lipid measures as well as bone densitometry measurements for osteopenia. In addition, frequent HIV testing allows study drug to be stopped before there is a substantial risk of drug resistance in the event of HIV acquisition during preventive chemoprophylaxis.

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