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Prevention of Sexually Transmitted HIV Infection

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1. Introduction

Bio-medical prevention of sexually transmitted HIV infection is an evolving area in the field of HIV. In recent years, multiple studies have demonstrated the efficacy of diverse biomedical interventions to prevent the sexual acquisition of HIV infection in specific populations. The major developments in the field of prevention of sexual transmission of HIV include male circumcision, HIV viral suppression of HIV infected individuals (Treatment of positives), use of antiretrovirals before exposure to HIV (Pre-exposure prophylaxis), and use of microbicides. Some of these highly controlled studies demonstrated high levels of protection ranging from 55 to more than 90% when a single intervention has been studied. However, in real world situations, it is foreseeable that individuals will have the opportunity and option to choose, and ideally to combine, appropriate interventions according to their background, attitudes, preferences and availability of methods.

Male circumcision: Male circumcision effectively decreases rates of heterosexual transmission of HIV: There is now ample scientific evidence that male circumcision reduces the risk of acquiring HIV through heterosexual intercourse in males by approximately 51 to 60%, thus exceeding the 30 percent risk reduction set as a target for an AIDS vaccine. This level of protection is similar to the 67.5% relative reduction in the risk of maternal-infant transmission of HIV with the use of zidovudine in HIV infected pregnant women; currently one of the most successful strategies to prevent HIV infection in a selected population, newborns. The evidence of the effectiveness of male circumcision in decreasing the risk of HIV infection in males is so compelling that in March 2007, the World Health Organization and the Joint United Nations Programme on HIV/AIDS held a technical consultation on male circumcision and produced a document that stated that male circumcision should be recognized as an efficacious intervention for the prevention of heterosexually acquired HIV infection in men. Male circumcision (MC) has been proven to be a potent HIV prevention strategy, reducing risk of HIV acquisition in heterosexual men by 50-60%. One of the most successful interventions to prevent the

acquisition of HIV infection in heterosexual men is circumcision, which has reduced HIV risk by 50-60% among heterosexual men in sub-Saharan Africa. The uptake of male circumcision in traditionally non-circumcision communities have been varied and influenced by different factor. In the US males from racial and ethnic minorities are less likely to be circumcised and also more likely to become infected with HIV so a recently published analyses showed that newborn circumcision resulted in lower expected HIV-related treatment costs and a slight increase in quality-adjusted life years.

Treatment of Positives: Since the early years of the epidemic, it was demonstrated that the use of antiretrovirals in infected pregnant women decreased the likelihood of HIV infection in the new born. Additional studies demonstrated that the key factor in the transmission of the infection from the mother to the newborn was the maternal HIV viral load; and then the suppression of HIV by the administration of antiretrovirals became the standard of care in the management of HIV infected pregnant women. This practice led to the almost eradication of congenital HIV infection in communities with access to medications. Circumstantial evidence suggested that the same principle could be applied to the sexual transmission of HIV as in general there is correlation between the HIV viral load in blood and genital secretions. In 2011 a breakthrough study proved that treatment of HIV positive decreased the likelihood of sexual transmission in more than 96% in discordant heterosexual couples.

Pre-exposure prophylaxis (PrEP) in MSM and heterosexual men and women: PrEP involves the use of antiretroviral medications before potential HIV exposure to prevent infection. In recent years several studies suggested the possible efficacy of the use of TDF/FTC as PrEP; but in the last six months, several controlled studies have provided definitive proof of its efficacy in certain populations: iPrEx was a study that randomized 2499 HIV-negative MSM or transgender women who have sex with men to take oral daily tenofovir and emtricitabine (FTC/TDF) or placebo. Overall, 100 subjects became infected during the study (36 in the FTC/TDF group and 64 in the placebo group), indicating a 44% reduction in the HIV incidence. The Partners PrEP Study was a phase III, randomized, double blind, placebo-controlled, three arm trial of oral daily (FTC/TDF) PrEP for the prevention of HIV acquisition by HIV seronegative partner in HIV serodiscordant partnerships. The independent DSMB recommended that the results of the study be publically reported, nearly 2 years earlier than expected, and the placebo arm discontinued, because clear demonstration of HIV protection due to PrEP. The TDF2A was a double-blind, randomized, trial of daily oral FTC/TDF or placebo for prevention of HIV acquisition in young (18-39) women and men in Bostwana. A total of 1219 individuals were randomized, about 30% of the study population did not complete follow up. Adherence to PrEP overall was estimated to be approximately 84%. Overall 9 HIV infections occurred among those assigned to FTC/TDF compared to 24 among those assigned to placebo, translating to an efficacy for HIV protection of 63%. All these studies shown that PrEP is a viable biomedical intervention that can be use for the prevention of sexually transmitted HIV infection in both heterosexual and male who have sex with men populations but is highly dependent of the adherence to the medications. There are few promising agents that could be use over extended periods of time decreasing the need for daily medication.

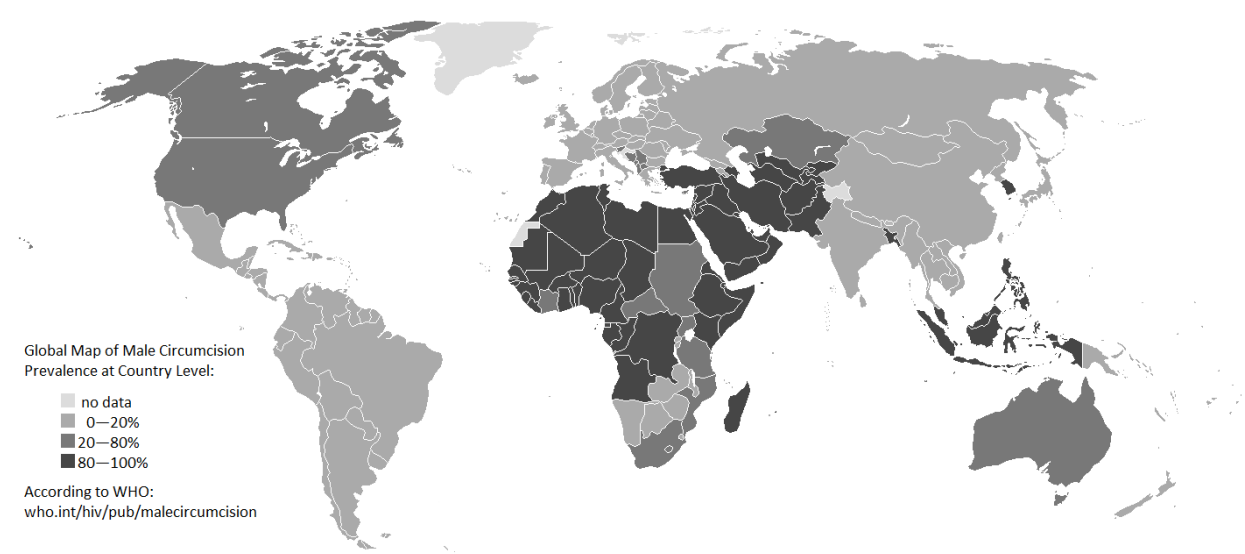
Microbicides: Given the theoretical advantages of a microbicide (controlled by women, no need for male cooperation) the search for an effective product was elusive until investigators from CAPRISA 004 study reported at the World AIDS conference in 2010 in Vienna, that 1% tenofovir gel used with coitus reduced HIV risk by 39% among 889 South African women. Sub-analyses of the data showed that protection was more pronounced (54%) in women with higher adherence to the gel. Several studies are under way with other products and with alternative delivery systems that will alleviate the need for strict adherence to its use before and after sex.

2. Bio-medical interventions to prevent hiv sexually transmitted infection

2.1. Male circumcision

Male circumcision is the surgical procedure that consists in the removal of some or all the foreskin of the penis [1]. The word "circumcision" comes from the Latin *circum* (meaning "around") and *caedere* (meaning "to cut") [2]. The foreskin is a continuation of the skin from the shaft of the penis, which covers the glans penis and the urethral meatus. The foreskin is attached to the glans by the frenulum, a highly vascularized tissue of the penis. Male circumcision is one of the oldest surgical procedures known, traditionally undertaken as a mark of cultural identity or religious importance [3]. Rates of male circumcision are different around the world and related to cultural and religious beliefs [4]. Historically, male circumcision has been associated with religious practice and ethnic identity. Circumcision was practiced among ancient Semitic peoples including Egyptians and Jews, with the earliest records depicting the practice coming from Egyptian tomb artwork (from the Sixth Dynasty, 2345-2181 B.C.) and wall paintings dating from around 2300 BC [3]. Muslims are the largest religious group to practice male circumcision. As an Abrahamic faith, Muslims practice circumcision, as a confirmation of their relationship with God, and the practice is also known as *tahera*, meaning purification [3]. With the global spread of Islam from the 7th century AD, circumcision was widely adopted among previously non-circumcising peoples. In some regions, male circumcision was already a cultural tradition prior to the arrival of Islam (for example among the Poro in West Africa, and in Timor in SE Asia). [5-7] Circumcision has also been practiced for non-religious reasons for many thousand of years in sub-Saharan Africa, and in many ethnic groups around the world, including aboriginal Australasians, the Aztecs and Mayans in the Americas, inhabitants of the Philippines and eastern Indonesia and various Pacific Islands, including Fiji and the Polynesian islands [3]. In the majority of these cultures, circumcision is an integral part of a rite of passage to manhood, although originally it may have been a test of bravery and endurance. Male circumcision traditionally has been done for medical and non-medical reasons (including religious or cultural reasons). When it is practiced for non-medical reasons it is typically performed in the neonatal period or just before the adolescence. The practice of circumcision, in particular of neonatal circumcision remains highly controversial despite recent evidence of the medical benefits, including decreased risk of heterosexual acquisition of HIV infection by men, decreased risk of acquisition of several sexually transmitted infections, decreased risk of urinary tract infection and recent evidence of decreased

risk of prostate cancer [8-10]. There are no reliable data of the rate of circumcision in many areas of the world in particular in regions where is not commonly practiced; but in general it is believed that rates of circumcision are very low in Latin-America including the Caribbean region, China, India and Europe [2], Fig 1.



Global map of male circumcision prevalence at country level, as of December 2006.

Figure 1. Worldwide prevalence of Male Circumcision.

2.1.1. Studies addressing MC in the field of HIV prevention

2.1.1.1. Cohort studies

The first paper suggesting a protective effect of MC against HIV infection was published in 1986 [11]. Since then, many observational studies have been published, some of which have observed that most men living in East and southern Africa, the regions with the highest prevalence of HIV are not circumcised [12-14]. More than 30 cross-sectional studies found the prevalence of HIV to be significantly higher in uncircumcised men than in those who are circumcised [15] and 14 prospective studies all showed a protective effect, ranging from 48% to 88% [16-18]. A systematic review and meta analyses of studies from sub-Saharan Africa reported an adjusted relative risk of 0.42 (95% CI 0.34-0.54) in all circumcised men, with a stronger adjusted relative risk of 0.29 (0.20 – 0.41) in circumcised men who were at higher risk of acquiring HIV [19].

2.1.1.2. Randomized studies

Given the compelling observational data of the potential protective role of male circumcision in the acquisition of heterosexually transmitted HIV infection and the growing crisis of HIV infection in sub-Saharan Africa; it was clear that only randomized studies could provide unequivocally evidence of this protection. Under the sponsorship of the National Institutes of

Health (NIH) and the ARNS (French National Research Agency), three independent but similar randomized control trials were launched in three different communities in South Africa in 2002-2003 to address this question. The studies were performed in South Africa, Kenya, and Uganda, within peri-urban, urban, and rural communities respectively [20-22]. The study conducted in South Africa (Orange farm, bordering Johannesburg) included 3,128 men 18 to 24 years old. Eligible men were randomly allocated to undergo immediate or delayed (offered at the end of the follow up period) circumcision. Men were assessed at 3, 12 and 24 months for HIV acquisition, sexually transmitted infections, and changes in sexual behaviors. Interim analysis in 2004 revealed a 0.4 relative risk of HIV acquisition (95% CI, 0.24%-0.68%.; $P < 0.001$) among the circumcised compared to uncircumcised participants. This finding corresponds to a protective effect of circumcision of 60%, which is a level of protection similar many used vaccines. Given these striking results, the safety and monitoring board discontinued the trial early, and circumcision was offered to the control arm. The Orange Farm study results prompted ethical concerns about continuation of the two remaining studies. The World Health Organization (WHO) recommended continuation but mandated a previously unplanned, earlier interim evaluation. At the interim evaluation, the studies in Kenya and Uganda provided evidence of protection against HIV infection of 50% to 60%, remarkably similar to the results from the Orange Farm trial. These two trials were discontinued prematurely on December 12, 2006. Together, the three studies demonstrated a 50% to 60% reduction in HIV acquisition by medicalized circumcision. [20-22] In total, 10,908 uncircumcised, HIV-negative adult men were randomly assigned to intervention or control arms, and followed for up to 2 years. Overall retention rates were high (86-92% at the end of follow up, when men in the control arm were offered circumcision). Recent findings support the long-term benefit conveyed by MC, with the Kisumu, Kenya cohort maintaining/modestly increasing the earlier level of protection (60% to 64%) at 54 month follow up [23]. These studies, among others, provide "unequivocal evidence that circumcision plays a causal role in reducing the risk of HIV infection among men" [24].

On the basis of the findings from the three clinical trials, a WHO and UNAIDS consultation in March 2007, recommended that circumcision should be recognized as an effective intervention for HIV prevention of heterosexual HIV acquisition in men [24]. WHO and UNAIDS also recommended that male circumcision should be offered HIV-negative men in addition, but not as a substitute, to other HIV risk-reduction strategies. The public-health effect of male circumcision will be largest in generalized epidemics. As such, WHO and UNAIDS recommend that countries with hyperendemic and generalized epidemics and low prevalence of male circumcision expand access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support. [25]

2.2. Acceptability of MC as a tool for HIV prevention

The public health benefit of MC as a tool for HIV prevention, will depend of many factors. One of the most important is the acceptability and uptake of circumcision in traditionally non-circumcising societies. It can be expected that the benefit can spread beyond circumcised men because if sufficient number of males are circumcised, circumcision in the long range will also

protect women; effect similar to herd immunity [26]. In addition to the proportion of males who will become circumcised, the age at circumcision will be also a determinant of how rapidly the intervention results in reduction of HIV prevalence in the population. For example, if boys and young men before sexual debut are targeted, the measurable impact it is not likely to be realized for over 10 years; if older boys and men up to 30 years are prioritized a more rapid effect can be expected. On the other hand, circumcision of neonates, in whom the procedure is simpler and less risky, the impact of the strategy on HIV incidence would not be expected for at least 20 years. [25] Because acceptance of male circumcision by men and by parents of males in traditionally non-circumcising communities will be crucial to the success of a MC intervention for reducing HIV prevalence a significant number of studies have been conducted in different non-circumcising communities with high or increasing rates of HIV infection across the globe [26-29]. Across most of these studies, the most common barriers to the acceptability of male circumcision include the following factors: pain (apprehension about pain during and after the procedure has been reported to be the major barrier to MC acceptability; culture and religion have also factors that have been consistently brought up in the discussions about acceptability of MC in diverse groups; cost of the procedure has been named as a significant barrier to MC acceptability and safety (potential for complications and adverse effects). Other potential barriers named in some but not in all studies include: lack of access to health care, required time away from work, the concern about loss of penile sensitivity, reduction in penis size, decreased ability to satisfy women, excessive sexual desire, increased promiscuity and the perception of circumcision as old-fashioned [28-29]. On the other hand, the most consistently named facilitators of MC include the following factors: hygiene, which has universally been recognized as a major benefit of MC; protection from sexually transmitted diseases and HIV (linked through hygiene) and improved sexual pleasure.

In summary, the protective effect of adult male circumcision on HIV acquisition has been reported in a review of epidemiological studies and demonstrated by three randomized controlled trials conducted in Southern and Eastern Africa, which found that the risk of HIV acquisition among circumcised men was reduced by about 60%. Based on this evidence, in 2007 WHO/UNAIDS recommended adult male circumcision as an important, additional intervention which should be delivered as part of a comprehensive HIV prevention package in communities with generalized HIV epidemics and low male circumcision rates. Since then, a number of initiatives have taken place in different countries to role out adult male circumcision services as an additional scientifically proven biomedical strategy to prevent HIV acquisition.

3. Treatment of positives

The idea to use antiretrovirals to prevent the acquisition and transmission of the Human Immunodeficiency virus was tested early in the 90's after animal models of retroviral infection demonstrated that zidovudine could prevent or alter the course of maternally transmitted HIV infection [30 – 33]. The results of this initial US Pediatric AIDS Clinical Trials Group Protocol (PACTG) 076 clinical trial were announced in 1994, which showed that giving pregnant women

infected with HIV oral zidovudine from 14 weeks, intravenously at labor and delivery, and followed by six weeks of zidovudine prophylaxis to their newborns, could reduce transmission by 67.5% (95 percent confidence interval, 40.7 to 82.1 percent) [30]. Since this pivotal study proved the concept that antiretrovirals could be used to prevent HIV infection, significant progress has been accomplished in the prevention of mother to child transmission, to the point that current transmission rates are estimated at less than 2 percent with the use of triple antiretroviral drugs during pregnancy. [34, 35], Figure 2. Despite these major advances in the prevention of mother to child transmission of HIV-1, it was not until several years later that these ideas were extrapolated to the prevention of sexual transmission of HIV-1. A central idea was that the quantity of HIV-1 in plasma was a primary determinant of the risk of HIV-1 transmission [36]. By then it was already clear that antiretroviral therapy could reduce plasma HIV-1 to undetectable concentrations within 6 months of initiation in most patients [37, 38] and seminal and cervicovaginal HIV-1 concentrations could also be reduced to undetectable levels in most people on ART [39 – 41]. A meta-analysis of data from five studies reported only five cases of HIV-1 transmission from patients receiving antiretroviral therapy to sexual partners during 1098 person-years of follow up, which is consistent with an infection rate of 0.19 – 1.09 per 100 person-years [42]. Additional evidence was obtained from a pos-hoc analysis of the Partners in Prevention HSV/HIV Transmission study of acyclovir HSV-2 suppressive therapy versus placebo [43]. In this analysis of almost 3,400 HIV-1 serodiscordant heterosexual couples from seven African countries, ART use by the infected person was accompanied by a 92% reduction in the risk of HIV-1 transmission to their partner. Several other observational and some ecological studies added to the evidence and set the need for a randomized study to test the hypothesis if index individuals taking ART are less likely to transmit HIV infection than individuals not on ART. In 2007 the HIV Prevention Trials Network (HPTN) started to enroll participants in a multi-continent, randomized, controlled trial, called HPTN 052, to compare early versus delayed antiretroviral therapy for patients with HIV-1 infection who had CD4 counts between 350 and 550 cells per cubic millimeter and who were in a stable heterosexual relationship with a partner who was not infected [44]. A total of 1763 HIV-1 serodiscordant couples were enrolled (886 couples were randomly assigned to the early therapy group and 877 to the delayed-therapy group). The study was slated to end in 2015, but an interim data review on April 26 2011, by an independent data and safety monitoring board (DSMB) found that of the total 28 cases of HIV infection among the previously uninfected partners, only one case occurred among those couples where the HIV-infected partner began immediate antiretroviral therapy. The DSMB, therefore, called for immediate public release of the study's findings on the basis of data collection through February 21, 2011. At that time, 90% of couples remained enrolled in the study, with a median follow up of 1.7 years. This study demonstrated the power of early antiretroviral treatment (ART) for almost completely preventing onward sexual HIV transmission in the clinical trial setting. This study offered proof of the concept that reduction of viral load through treatment could prevent HIV transmission, a concept that has served as the foundation for multiple modeling studies on treatment-as-prevention and one which was already held to be true by many. The data are incontrovertible, and although they resolve the question of whether this approach can prevent HIV transmission, they also lead to a more fully informed discussion of how ART might actually be used to prevent

transmission in communities. The magnitude of protection against HIV infection demonstrated in HPTN 052 has made the successful strategy of the clinical trial a key component of public health policies recently discussed by federal officials and others saying that achieving an end to the HIV/AIDS pandemic is now feasible with additional research and implementation efforts. Given the profound implications of HPTN 052's for the future response to the AIDS epidemic, the journal *Science* chose this study as its Breakthrough of the Year [45].

In summary, in 2011 it was scientifically demonstrated that treating individuals with HIV infection will prevent the transmission of HIV infection. However, the use of this strategy to the population level it is still not ready to fully achieve its potential because there are resource constraints and logistical hurdles, that limit its implementation.

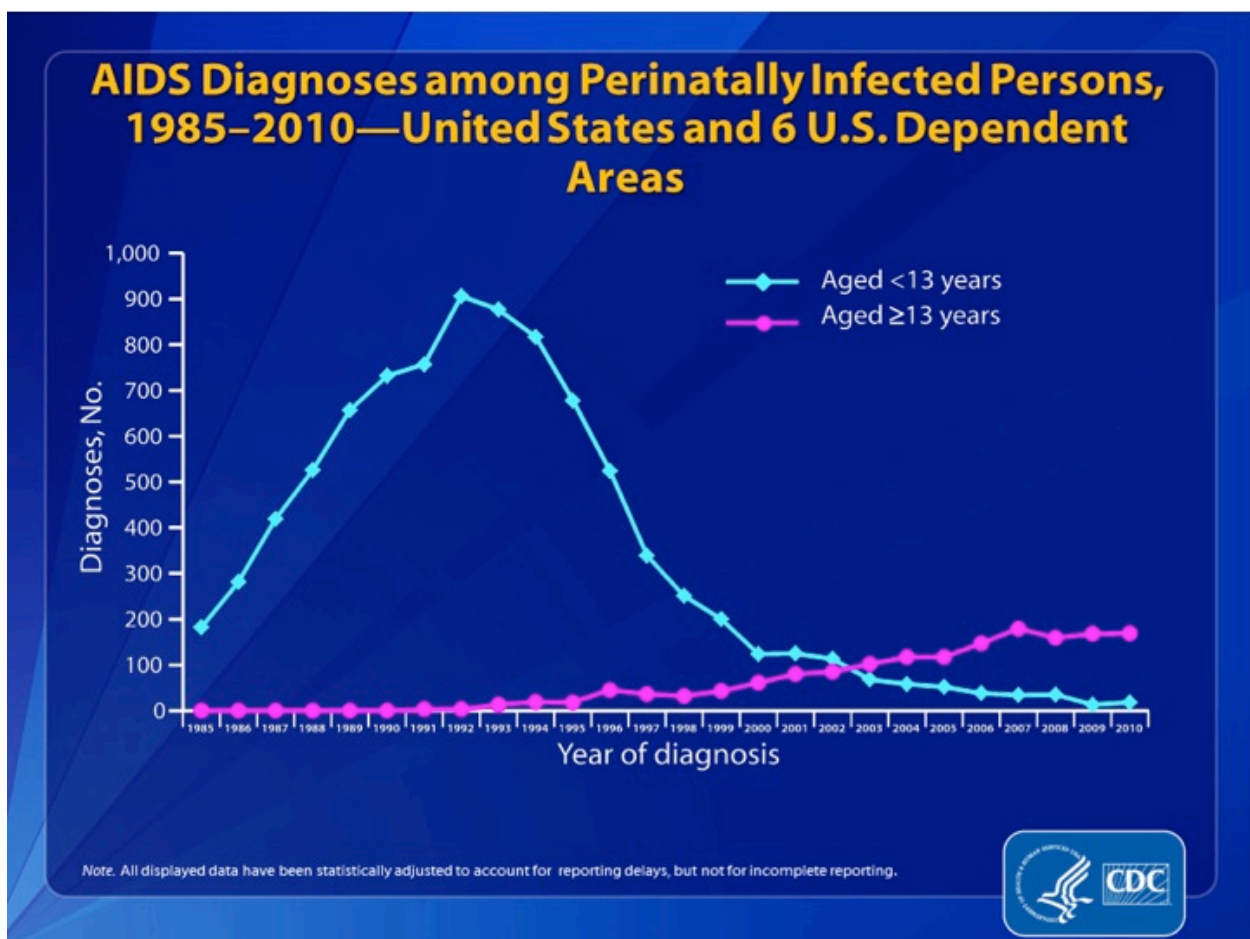


Figure 2. AIDS Diagnoses among perinatally infected persons, 1985–2010. United States and 6 U.S. dependent areas.

This slide from the CDC presents trends from 1985 through 2010 in the estimated numbers of AIDS diagnoses among persons who were perinatally infected in the U.S. The blue line shows the annual numbers of perinatally infected children who were diagnosed with AIDS when they were less than 13 years of age; the pink line shows the annual numbers of persons who were infected with HIV perinatally and were diagnosed with AIDS at the age of 13 or older.

This graphic provides evidence of the impact at the population of an effective bio-medical intervention to prevent HIV infection.

4. Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) involves the use of antiretroviral medications by HIV negative individuals before exposure to the HIV virus, to prevent HIV acquisition. The principle behind the use of antiretrovirals (ART) to prevent sexual acquisition of HIV lies on the success of HIV prevention in mother to Child transmission (PMTCT) and accidental exposure in healthcare workers. Early in the HIV epidemics, two large prevention trials (HIV Prevention Network Trial, HPTN 076 and HIVNET 012) showed that providing ART to infants born to HIV positive mothers significantly decreased the rates of HIV infection in newborns [30,46]. This is one of the greatest accomplishments in the field of HIV prevention, has been incorporated to PMTCT guidelines, and provided a starting ground for PrEP [30,46, 47]. In the area of health care related exposure to HIV, primarily needle sticks, the use of ART by the negative individual during the weeks after exposure reduces HIV acquisition by 80% [48, 49].

Following the human studies assessing PMTCT and prevention in the healthcare setting, animal studies to address PrEP demonstrated that the administration of ART to macaque monkeys exposed to HIV prevented HIV infection [50,51]. All this data provided basis for designing clinical trials to test PrEP in humans.

In recent years, tremendous advances in the field of PrEP in individuals at risk for HIV acquisition have led to landmark large randomized controlled studies using oral or topical agents. Results of the initial major studies addressing PrEP were somehow controversial, but recent data provides evidence that PrEP is an effective and safe alternative to prevent HIV infection.

A major benefit of PrEP is its use by the individual at risk without involvement of sexual partners. Men who have sex with men (MSM) and women are especially vulnerable to HIV infection due to cultural, social and biological factors. Stigma associated with homosexuality, gender disparities, inability for women to negotiate condom use and fidelity, as well as fragility of vaginal and rectal mucosa, predispose these populations to HIV infection and make them ideal candidates for such preventive method. PrEP is therefore emerging as a new powerful prevention method of especial importance in those populations at higher risk.

To date, most studies regarding PrEP have focused on two main modes of delivery: oral agents or topical microbicides. The two delivery modes will be presented separate in this chapter. Other forms of delivery such as subcutaneous or vaginal implants are under investigation and will be briefly mentioned.

While some studies addressing PrEP yielded important and relevant results, other studies are still undergoing and some are in the early stages of development. PrEP is therefore an evolving area in the field of HIV prevention and emerging data is likely to change the way we prevent sexually acquired HIV infection in the near future.

Table 1 summarizes the results of clinical trials on oral and topical agents addressing PrEP.

Study name	Sponsor	Country	Participants	Design	Results
iPREX (Grant 2010)	NIAID Gates Foundation	South America Thailand USA	2,499 MSM	FTC/TDF vs placebo	42% reduction (CI=6-60)
TDF2 (Thigpen 2012)	CDC NIH	Bostwana	1,219 heterosexual men and women	FTC/TDF vs placebo	62% reduction (CI=21-83)
Partners PrEP (Baeten 2012)	Gates Foundation	Sub Saharan African countries	4,758 serodiscordant couples	TDF vs placebo FTC/TDF vs placebo	TDF: 76% reduction (CI=42-81) FTC/TDF: 75% reduction (55-87)
FemPrEP (van Damme 2012)	US Agency for International Development	Kenia, Tanzania South Africa	2,210 women	FTC/TDF vs placebo	Study discontinued due to futility (2011)
VOICE	Microbicides Trial Network NIH	South Africa Uganda, Zambia Zimbabwe	5,000 women	TDF vs placebo FTC vs placebo TDF gel vs placebo	TDF oral and gel discontinued due to futility (2011) FTC/TDF ongoing
CAPRISA (Abdoul Karim 2010)	Multiple agencies	South Africa	1,341 women	TDF gel vs placebo	39% reduction

Table 1. Summary of randomized controlled studies addressing the use of PrEP to prevent sexually transmitted HIV infection.

4.1. PrEP using oral agents to prevent HIV infection in MSM and heterosexual men and women

The oral agents evaluated or under evaluation for PrEP include anti HIV drugs currently approved for treatment of HIV infection. Such drugs are tenofovir (TDF) and a combination of emtricitabine/tenofovir FTC/ TDF.

Tenofovir is a nucleoside analog approved in combination with other ART for the treatment of HIV infection. As a nucleoside analog, the mechanism of action of TDF is to blocking HIV reverse transcriptase, which prevents HIV virus from replicating. In HIV infected individuals, as a result, TDF lowers HIV viral load in the blood. Tenofovir is a drug that achieves good drug levels in plasma as well as in female lower genital tract mucosa and rectal mucosa [52]. TDF is used orally and once a day, and is normally well tolerated, but as most drugs, could have potential side effects. The most common side effects of TDF are gastrointestinal (nausea and vomiting), rash or headaches, and occur in about 10% of the patients. The most serious risk factors of TDF are acute liver and kidney toxicity. Chronic risk factors of TDF, relevant to

the chronic use of TDF for PrEP, include decline in kidney function and decrease in bone density [52].

Emtricitabine/tenofovir is a combination of nucleoside analogs approved for treatment of HIV. FTC/TDF is formulated as single day pill and is taken in combination with other agents for the treatment of HIV infection. Orally administered emtricitabine achieves good levels in plasma, lower female genital tract, and especially in the rectum making this combination a promise for PrEP [52]. The combination of FTC/TDF can cause those side effects listed above as well as those associated with FTC. Emtricitabine common side effects include nausea, vomiting, headaches, rash, abdominal pain, dizziness or abnormal dreams and occur in about 10% of the cases. Emtricitabine can also be associated with fatal lactic acidosis, liver or kidney toxicity.

4.1.1. Studies addressing oral PrEP

Five studies have evaluated the use of oral agents to prevent HIV infection and will be described in this section. One study included only MSM (iPrEX), 2 included men and women (TDF2, PIP), and 2 included exclusively women (FEM-PrEP and VOICE). Two of these studies have validated the use of PrEP for HIV prevention, two have been prematurely stopped due to futility, and others are undergoing. Important to say is that all of these studies have addressed the use of PrEP in combination with intensive safer sex practices counseling.

4.1.1.1. iPREX (pre exposure prophylaxis initiative)

iPREX was a randomized controlled study to evaluate the efficacy in reduction of new HIV infections using a daily tablet of fixed dose of FTC/TDF when compared to placebo. iPREX was funded by the National Institute of Allergy and Infectious Diseases and by the Bill and Melinda Gates Foundation. The study included 2499 young high-risk MSM in South America, Thailand and the US. The preliminary results of this study were released in 2010 and the study was the landmark for the use of oral PrEP. Results suggested for the first time that oral ART in combination with safe sex and condom use counseling could be used to reduce new HIV infections in MSM. The use of oral FTC/TDF was associated with a 42% reduction in HIV acquisition over 3 years (CI: 6%-60%). The study also analyzed the results according to self-reported adherence and reveal the importance of adhere to the prescribed drug. The incidence of new HIV cases was reduced to 68% when adherence was high (more than 90% of pills taken), to 50% if adherence was between 50% and 90%, and to 32% if adherence was low (less than 50%). In order to clarify if detectable drug levels were associated with protection against HIV infection a case control design was used to compare rates of infection in individuals with detectable blood levels with those without detectable levels. A relative risk reduction of 92% (CI: 40%-99%) in individuals with detectable study drug levels was found. This finding provided evidence that protection was directly related with drug levels, an indirect measurement of adherence. In addition, this study showed that FTC/TDF had a good safety profile with minimal gastrointestinal side effects. A minimal decrease in bone density in individuals taking the drug was also observed. Among the individuals that seroconvert, most of them were in the process of HIV seroconversion at enrollment and some developed a virus with resistant mutations. This finding reinforced the importance of excluding HIV infection when using FTC/

TDF for PrEP. The study results were published in the *New England Journal of Medicine* in 2010 [53]

4.1.1.2. TDF2

TDF2 was a randomized controlled study to evaluate the efficacy to reduce new HIV infection of a daily fixed dose of an oral combination pill of TDF/FTC when compared to placebo. This study was funded by the Centers for Disease Control and Prevention (CDC) and the division of AIDS at the National Institutes of Health. The study was conducted in Botswana and included 1219 males and females, unmarried adults. This study had high rates of loss of follow up (30%) and due to low retention, enrollment was prematurely stopped and study closed. Enrolled participants were followed as planned and the last participant was followed until 2011. The results offered 62% (CI: 21%-83%) protection against HIV infection overall. This study also evaluated drug levels in individuals receiving the drug and revealed that plasma concentration were lower among the participants who seroconverted to HIV. Reported adherence was high and similar in the two groups (above 80%), although detectable drug levels in the drug arm suggested that adherence was lower than reported. Risky sexual behaviors were similar and did not change in the two groups during the study. Among the participants receiving the study drugs, there was an increase in number of gastrointestinal side effects (nausea and vomiting) and dizziness as well as a significant decline in bone density. One participant was enrolled with unrecognized acute HIV infection and developed a resistant virus [54].

4.1.1.3. Partners PrEP (*partners in prevention*)

Partners in Prevention study is the largest trial evaluating PrEP in heterosexual discordant couples. It is an ongoing study with 3 study arms: daily TDF, daily TDF/FTC, and placebo. This study is supported by the Bill and Melinda Gates Foundation. The study enrolled 4758 serodiscordant couples in which the HIV infected partner was not eligible for ART according to country guidelines. This study is being conducted in sub-Saharan Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia). Extensive counseling in safe sex and condom use was additionally provided to enrolled participants. TDF conferred a 67% (CI: 44%-81%) and FTC/TDF a 75% (CI: 55%-87%) reduction in new HIV infections. The difference in rates of HIV seroconversion among the two treatment groups was not statistically different. In July 2011 the DSMB recommended that the placebo group be discontinued since the predetermined criteria for stopping had already been met and a benefit in the treatment arms was achieved [55]. The study results followed iPREX in supporting the use of PrEP in high risk individuals.

4.1.1.4. FEM-PrEP

The FEM-PrEP study was a randomized controlled trial that included women in sub-Saharan Africa (Kenya, South Africa and Tanzania). This study was supported by US Agency for International Development. Women were randomized to receive either oral daily FTC/TDF or placebo. This study evaluated 2120 women and was the first one designed

to address the effectiveness and safety of PrEP by gender. Incidence of new HIV infections was 4.7% person-years in the treatment group and 5% person-years in the placebo group and this difference was not statistically significant. This study was the first large study discontinued based on recommendations from the Data Safety Monitoring Board after interim results were unable to demonstrate efficacy of PrEP. In April of 2011 the study was stopped. As in prior studies, gastrointestinal side effects occurred more commonly in the treatment arm (nausea, vomiting and elevation of ALT) as well as renal laboratory abnormalities. Despite extensive counseling on adherence, less than 40% of the women in the treatment arm enrolled in the study had detectable drug levels raising once again the importance of adherence to the prescribed regimen, perhaps lower in women [56].

4.1.1.5. VOICE (*vaginal and oral interventions to control the epidemic*)

VOICE is the largest clinical trial being conducted evaluating efficacy of PrEP in women. The study is sponsored by the Microbicide Trials Network and the National Institutes of Health. It enrolled over 5000 women in South Africa, Uganda, Zambia and Zimbabwe. Women were randomized to 3 arms: daily oral TDF, daily oral TDF/FTC, or topical TDF. Results of this trial resulted in the discontinuation of the oral TDF arm in September 2011 and the topical TDF arm in November 2011 because of inability to demonstrate efficacy. The topical arm of the study will be discussed under the microbicide section below and results of the TDF/FTC arm are expected to be reported in 2013 [57].

4.1.1.6. Bangkok TDF trial

The Bangkok tenofovir study is an ongoing trial evaluating the efficacy of oral TDF in male injection drug users receiving direct observation therapy. Enrollment for this study is complete but no results are available at the time of this publication.

Studies addressing oral PrEP have yielded conflicting results and although the use of oral PrEP appears to be beneficial in high risk MSM, the use in women still is under debate. Partners PrEP, TDF2 and iPrEx provided a proof of concepts for the use of oral antiretrovirals for HIV prevention. However, the results from VOICE and Fem-PrEP and other ongoing studies will provide further information on the efficacy and safety of oral PrEP, especially in women.

Efficacy of PrEP seems to be directly related to adherence, and detectable blood levels is a better marker of protection than self-reported adherence or pill count. Although in most studies, adherence measured by self reporting or by pill count was high, detectable blood drug levels were found only in 50% of participants in the treatment arm of iPREX [53].

The highest levels of adherence were reported in Partner PrEP, where serodiscordant couples were enrolled and received extensive counseling. Tenofovir was detected in over 80% of participants in the treatment group and PrEP reduced by 70% new HIV infections. The results of Partner PrEP suggest that partner involvement is important, especially when addressing HIV prevention in women [58,59].

In regards to decrease efficacy of PrEP in women the question of availability of drug at the exposure site has been raised. However, high drug levels are found in cervicovaginal lavages,

and even higher than in plasma or rectal mucosa, what would dispute this hypothesis [52,60]. Another possibility is a decrease of drug levels in women receiving hormonal contraceptives and it is under evaluation by the study team.

Nevertheless, the possibility of low efficacy of oral PrEP in women suggest that microbicides or other delivery methods may be a better option in this population.

Following the positive results of daily ART use for HIV prevention, especially in MSM, newer studies are undergoing to evaluate the use of intermittent PrEP. These intermittent regimens could be more feasible in certain setting such as in non stable relationships. A large study in Kenia (ADAPT, Alternative Dosing to Augment PrEP Pill-Taking) is evaluating the safety and adherence to daily oral TDF/FTC versus intermittent TDF/FTC (Monday, Friday and within 2 hours after sex) or placebo. Another study (HPTN 067) is a study including MSM and heterosexual women aiming to identify dosing regimens in people at high risk for HIV infection. Preliminary data demonstrated that although adherence may be decreased in intermittent dosing, it may still be appropriate for PrEP.

4.1.2. Potential problems associated with oral PrEP

In July 2012, and based on the results of the mentioned trials, especially iPREX and Partners PrEP, the United States Food and Drug administration (US FDA) approved the use of daily TDF/FTC or Truvada® for prevention of sexually acquired HIV in individuals at risk for HIV infection. However, even if approval was granted, serious concerns have been raised by experts in the field of HIV prevention. The issues that need to be addressed before recommending PrEP as a generalized HIV prevention strategy are: development of drug resistance viruses, long term side effects, increase in sexual risk behaviors, cost, and incorporating PrEP as part of primary care prevention.

4.1.2.1. Development of drug resistant viruses

Development of drug resistance was identified in some of the participants who seroconvert in the mentioned studies but in most cases, occurred in individuals that enrolled with a new non identified HIV infection. Addressing this potential problem is difficult, since individuals at risk may have an early infection missed by routine antibody testing and routine viral load may not be easily available in high risk settings.

4.1.2.2. Long term side toxicity

As both TDF and FTC have potential serious long term side effects, it is important to determine if long use of FTC/TDF in HIV negative individuals will increase the risk of kidney failure or osteoporosis. In order to evaluate long term side effects, long term follow up is necessary to address if decline in renal function or bone density are clinically significant. However, as in HIV positive individuals using those agents, side effects may take many years to develop.

4.1.2.3. Increased of high risk sexual behavior

In regards to increase of risky sexual risk behaviors, both iPREX and Partners PrEP revealed that all participants increased condom use, decrease number in sexual partners, unprotected anal intercourse, and reduced rates for syphilis. This was likely due to the extensive counseling that both drug and placebo groups received and sustainability of sexual risk behavior needs to be further examined.

4.1.2.4. Cost

The cost of providing PrEP to individuals at risk is of course under great debate due to both economical and ethical issues. ART are expensive medications and not available for all HIV infected patients in need for their own health. PrEP is an expensive approach and cost effectiveness will need to be justified prior to generalization to the population at risk. A cost-effectiveness analysis of PrEP for HIV prevention in MSM published in 2012 in *Annals of Internal Medicine* revealed that although PrEP could have an important impact in the HIV epidemics, it will be an extremely expensive approach [63]. In a modeling analysis, Juusola recently showed that providing PrEP to all high-risk MSM for 20 years will cost \$75 billion in health care related cost, a non-insignificant amount [61]. An ethical concern is whether providing them to those HIV uninfected individuals will interfere with the treatment of HIV infected patient in need for treatment, especially in poor resource settings.

4.1.3. Feasibility of generalizing the use of oral PrEP to the population at risk.

The use of PrEP includes identification of high risk individuals, extensive risk counseling, provision of a drug and follow up risk assessments, HIV and laboratory tests. If PrEP is incorporated as part of primary care prevention activities, the primary care physician will need to become familiar with drugs normally prescribed for highly specialized physicians and will need to be aware of new research data and changes in the recommendations as they become available [63].

As summary, oral PrEP has demonstrated efficacy in certain populations at risk for HIV infection, especially in MSM. Studies assessing acceptability, long term efficacy, toxicity, risk of HIV resistance, cost and use in women are needed before including oral PrEP as part of HIV prevention tools in the population at risk.

4.2. Microbicides to prevent HIV infection in women and MSM

Women are more vulnerable than men to acquire HIV during sex due to biological factors as well as difficulties in negotiating barrier methods and fidelity. Women can rarely negotiate condom use or faithfulness with their sexual partners and could greatly benefit of controlling their own risk of HIV infection without involvement of male partners. Studies addressing oral PrEP suggested lower efficacy of oral agents in women, which make microbicides an attractive alternative for HIV prevention in women at risk.

Microbicides are topical products applied to the rectum or the vagina to prevent HIV infection in HIV negative individuals. Research on microbicides has included primarily women but

studies addressing several rectal formulations in MSM are currently undergoing. Unfortunately, results on microbicide research have been conflicting and further research is needed. Topical vaginally applied TDF showed promising results in the CAPRISA trial. However, other agents have not been efficacious and research in this area is ongoing.

In order for a microbicide to be successful it must fulfill the following characteristics: be biologically active, safe, and acceptable by the individual at risk. The principals mechanisms of action evaluated in microbicide development are: buffer agents, surfactants, blockers and antiretrovirals.

4.2.1. Buffers

Buffers are supplements to the natural immune defenses of the vagina. Buffers maintain the vaginal pH favoring the persistence of the naturally protective vaginal lactobacilli. Alterations of the vaginal pH due to exposure to semen or vaginal infections such as bacterial vaginosis damage the vaginal microbiota and facilitate HIV infection. Buffergel[®], a buffer designed to maintain vaginal pH was tested in animals and in a phase III effectiveness trial; but unfortunately, did not prevent new HIV infections [63].

4.2.2. Surfactants

Surfactants act by inactivating infectious agents. Noxynol-9, a wide available microbicide with known activity against several infectious agents has been tested in multiple forms (film, sponge and gel) and was not effective in preventing new HIV infections [64]. SAVVY[®] (C31G) was a surfactant in a gel form tested in Ghana and Nigeria between 2004-2006 and not found to be effective [65]. Surfactants are no longer being considered as potential agents for microbicide use.

4.2.3. Blockers

Blockers inhibit the fusion of the HIV virus to the cell membrane. Four compounds in this category have been tested to date: PRO2000[®], Carrguard[®], cellulose sulfate and dextrin 2-sulfate and have not demonstrated activity in clinical trials [66].

4.2.4. Drugs with anti HIV activity

Antiretroviral agents act by inhibiting the HIV replication cycle in the vaginal mucosa have been tested in two major clinical trials (CAPRISA and VOICE). Other agents acting as co-receptor blockers binding to chemokine co-receptors such as VVR5 or CxCR4 are also under investigation.

4.2.4.1. CAPRISA

The landmark study suggesting that the potential of microbicides as HIV prevention tools is CAPRISA, a two-arm randomized double blind placebo controlled trial conducted in South Africa between 2007 and 2010. The study evaluated the efficacy in HIV reduction of

a coitally (before and after sex) related application of TDF vaginal gel when compared to placebo. 1341 women were enrolled. The incidence of HIV infections in the tenofovir arm was 5.6 (CI: 4.0-7.7) per 100 women-years and 9.1 (CI: 6.9-11.7) in the placebo arm. (IRR: 0.61; CI:0.4-0.94,p=0.017). Tenofovir gel reduced HIV acquisition by an estimate of 39% overall and by 54% in women with high adherence to the gel. This study did not find major side effects associated with the use of TDF and no TDF resistant virus were found in women who seroconverted. The results of this study were released in the International AIDS conference in Vienna in 2010 and provided a potential armamentum for women unable to negotiate fidelity and condom use. Caprisa also provided a reduction in HSV acquisition [67].

4.2.4.2. VOICE

VOICE as described in the oral PrEP section included one arm evaluating daily use of vaginal TDF gel. The gel arm enrolled approximately 1000 women. In September of 2011 this arm was discontinued as a recommendation from the DSMB due to no efficacy. No safety issues were identified [68]. In order to clarify if the differences between CAPRISA (39% reduction on new HIV infections) was found and VOICE (no effect of TDF gel), a new study will replicate CAPRISA (FACTS 001) and its results will help to clarify if TDF gel is useful and can be incorporated to the field of HIV prevention.

4.2.5. Agents under development

4.2.5.1. Vaginal rings

The use of vaginal rings for prevention of HIV acquisition is under evaluation in several studies. Vaginal rings with antivirals could potentially be used in combination with contraceptives, and will release antiviral agent long term and independent of sexual intercourse. Dapivirine (TMC120) vaginal ring is currently evaluated under phase III studies as ASPIRE – A Study to Prevent Infection with a Ring for Extended study [69]. A combination of Dapivirine and Maraviroc is currently undergoing a phase 1 safety and pharmacokinetic study [70]. Other vaginal rings with maraviroc alone or in combination with tenofovir are also being developed.

4.2.5.2. Long acting injectables

The use of a long acting injectable agent that will provide protection for 3-9 months is a potential method that will increase adherence. Rilpivirine is under development for this purpose [71].

PrEP using oral or topical agents is a promising strategy in the field of HIV prevention. However, as single intervention may not be successful in controlling the HIV epidemics and the results obtained in controlled clinical trials are unlikely to persist overtime. The CDC recently published interim guidance for clinicians considering the use of PrEP for the prevention of HIV infection in heterosexually active adults [72]. This report addresses the remaining gap in knowledge regarding PrEP but provides a comprehensive evaluation of

the available data and guidance to health care providers regarding the use of PrEP. However, HIV prevention guidelines are under development and 30 years of the history of HIV have shown the scientific community that a single intervention is unlikely to succeed.

In summary, the science of HIV prevention has seen significant progress in recent years. After decades of frustration and lagging behind the spectacular progress brought up in the control of HIV disease by the use of antiretrovirals, the field of biomedical prevention of HIV has been revolutionized and energized by the scientific evidence produced in the last few years that supports the use of the four strategies discussed above: adult male circumcision, treatment of HIV infected people, pre-exposure prophylaxis and microbicides (Figure 3). However, although the foundations for successful HIV prevention programs are being laid out, there are still significant challenges ahead that will need to be solved before all these strategies can be fully scaled up, combined and delivered to the at risk individuals and communities. The field is also confident that the still elusive vaccine to prevent HIV infection can be unveiled in a not distant future.

Figure 3 lists currently proven biomedical interventions that prevent sexually transmitted HIV infection by gender.

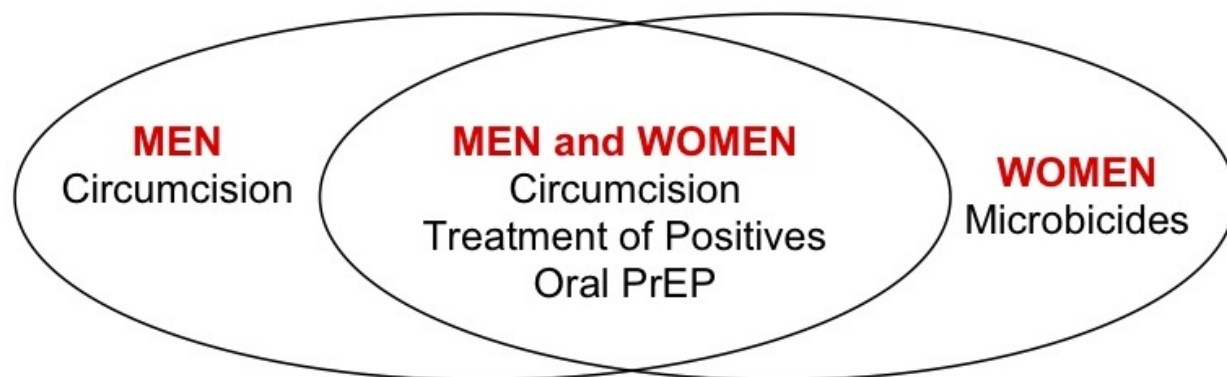


Figure 3. Interventions to Prevent Sexually Transmitted HIV Infection by Gender

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References

- [1] Alanis, M. C, & Lucidi, R. S. Neonatal circumcision: a review of the world's oldest and most controversial operation. *Obstet Gynecol Surv.* (2004). May; , 59(5), 379-95.
- [2] Johnson, P. Israelities, in *A History of the jews.* (1993). Phoenix Press. , 37.
- [3] Dunsmuir, W. D, & Gordon, E. M. The history of circumcision. *BJU International* ((1999). Suppl. , 1, 1-12.
- [4] UNAIDSMale circumcision: Global trends and determinants of prevalence, safety and acceptability. (2007).
- [5] Thomas, A. Circumcision: an ethnomedical study. (2003). The Gilgal Society.
- [6] Hull, T. H, & Budiharsana, M. Male circumcision and penis enhancement in Southeast Asia: matters of pain and pleasure. *Reprod Health Matters.* (2001). , 9(18), 60-7.
- [7] Mcwilliam, A. Case studies in dual classification as process: childbirth, headhunting and circumcision in West Timor, Oceania. (1994). , 65, 59-74.
- [8] Siegfried, N, Muller, M, & Volmink, J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane Database Sust Rev.* (2003). CD003362.
- [9] Benatar, M, & Benatar, D. Between prophylaxis and child abuse: the ethics of neonatal male circumcision. *Am J Bioeth.* (2003). Spring; , 3(2), 35-48.
- [10] Wright, J. L, Lin, D. W, & Stanford, J. L. Circumcision and the risk of prostate cancer. *Cancer,* (2012). published on line; doi:10.1182.26653.
- [11] Fink, A. J. A possible explanation for heterosexual male infection with AIDS. *N Engl J Med.* (1986).
- [12] Bongaarts, J, Reining, P, Way, P, & Conant, F. The relationship between male circumcision and HIV infection in Africa population. *AIDS* (1989). , 3, 373-377.
- [13] Caldwell, J. C, & Caldwell, P. The African AIDS epidemic. *1996 Sci Am* (1996).
- [14] Moses, S, Bradley, J. E, Nagelkerke, N. J, Ronald, A. R, et al. Geographical patterns of male circumcision practices in Africa: Association with HIV seroprevalence. *Int J Epidemiol* (1990). , 19, 693-697.
- [15] Bailey, R. C, Plummer, F. A, & Moses, S. Male circumcision and HIV prevention: current knowledge and future research directions. *Lancet Infect Dis* (2001). , 1, 223-31.
- [16] Buchbinder, S. P, Vittinghoff, E, & Heagerty, P. J. Sexual risk, nitrite inhalant use and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Def Syndr* (2005). , 39, 82-89.
- [17] MacDonald KSMalonza I, Chen DK. Vitamin A and risk of HIV-1 seroconversion among Kenyan men with genital ulcers. *AIDS* (2001). , 15, 635-39.

- [18] Reynolds, S. J, Shepherd, M. E, & Risbud, A. R. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet* (2004). , 363, 1039-40.
- [19] Weiss, H. A, Quigley, M. A, & Hayes, R. J. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* (2000). , 14, 2361-70.
- [20] Bailey, R. C, Moses, S, Parker, C. B, Agot, K, Maclean, I, Krieger, J. N, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet* (2007). , 369, 643-656.
- [21] Gray, R. H, Kigozi, G, Serwadda, D, Makumbi, F, Watya, S, Nalugoda, F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet* (2007). , 369, 657-666.
- [22] 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). e298.
- [23] Riess, T. H, Achieng, M. M, Otieno, S, Ndinya-achola, J. O, & Bailey, R. C. (2010). "When I Was Circumcised I Was Taught Certain Things": Risk Compensation and Protective Sexual Behavior among Circumcised Men in Kisumu, Kenya. *PLoS ONE* 5(8): e12366. doi:10.1371/journal.pone.0012366.
- [24] Byakika-TusiimeJayne. Circumcision and HIV Infection: Assessment of Causality. *AIDS and Behavior* (2008). DOI:s10461-008-9453-6., 12(6)
- [25] UNAIDS and WHONew data on male circumcision and HIV prevention: policy and programme implications; WHO/UNAIDS technical consultation male circumcision and HIV prevention: research implications for policy and programming Montreaux, Geneva: Joint United Nations Programme on HIV/AIDS and World Health Organization, (2007).
- [26] Westercamp, N, & Bailet, R. C. Acceptability of male circumcision for prevention of HIV/AIDS in sub-Saharan Africa: A review. *AIDS Behav* (2007). , 11, 341-355.
- [27] Castro, J. G, Jones, D. L, Lopez, M, Barradas, I, & Weiss, S. Making the case for circumcision as a public health strategy: opening the dialogue. *AIDS Patient Care and STDs*. (2010). , 24(6), 367-372.
- [28] Madhivanan, P, Krupp, K, & Chandrasekaran, V. Acceptability of male circumcision among mothers with male children in Mysore, India. *AIDS* (2008). , 22, 983-988.
- [29] Castro, J. G, Jones, D. L, Lopez, M, Deeb, K, Barradas, I, & Weiss, S. Acceptability of neonatal circumcision by Hispanics in southern Florida. *Journal of STD & AIDS* (2010). , 21, 591-4.

- [30] Connor, E. M, Sperling, R. S, Gelber, R, Kiselev, P, & Scott, W. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Eng J Med* (1994). , 331, 1173-1180.
- [31] Shih, C-C, Kaneshima, H, & Rabin, L. Post exposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. *J Infect Dis* (1991). , 163, 625-627.
- [32] Sharpe, A. H, Jaenisch, R, & Ruprecht, R. M. Retroviruses and mouse embryos: a rapid model for neurovirulence and transplacental antiviral therapy. *Science* (1987). , 236, 1671-4.
- [33] Sharpe, A. H, Hunter, J. J, Ruprecht, R. M, & Jaenisch, R. Maternal transmission of retroviral disease: transgenic mice as a rapid test system for evaluating perinatal and transplacental antiretroviral therapy. *Proc Natl Acad U S A* (1988). , 85, 9792-6.
- [34] Dorenbaum, A, Cunningham, C. K, & Gelber, R. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* (2002). , 288(2), 189-98.
- [35] Cooper, E. R, Charurat, M, & Mofenson, L. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr* (2002). , 29(5), 484-94.
- [36] Quinn, T. C, Wawer, M. J, & Sewankambo, N. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Eng J Med* (2000). , 342, 921-929.
- [37] Chaisson, R. E, Keruly, J. C, & Moore, R. D. Association of initial CD4 cell count and viral load with response to highly active antiretroviral therapy. *JAMA* (2000). , 284, 3128-29.
- [38] Phillips, A. N, Staszewski, S, & Weber, R. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA* (2001). , 286, 2560-67.
- [39] Graham, S. M, Holte, S. E, & Peshu, N. M. Initiation of antiretroviral therapy leads to a rapid decline in cervical and vaginal HIV-1 shedding. *AIDS* (2007). , 21, 501-07.
- [40] Gupta, P, Mellors, J, & Kingsley, L. High viral load in semen of human immunodeficiency virus type 1-infected men at all stages of disease and its reduction by therapy with protease and nonnucleoside reverse transcriptase inhibitors. *J Virol* (1997). , 71, 6271-75.
- [41] Marcelin, A. G, & Tubiana, R. Lambert-Niclot. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma. *AIDS* (2008).

- [42] Attia, S, Egger, M, & Muller, M. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* (2009). , 23, 1397-404.
- [43] Celum, C, Wald, A, & Lingappa, J. R. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* (2010). , 362, 427-39.
- [44] Cohen, M. S, Chen, Y. Q, & Mccauley, M. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* (2011). , 365, 493-505.
- [45] Cohen, J. Breakthrough of the year. HIV treatment as prevention, *Science* 23 December (2011). , 334(6063), 1628.
- [46] Guay, L. A, Musoke, P, Fleming, T, Bagenda, D, Allen, M, Nakabiito, C, 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). Sep 4; , 354(9181), 795-802.
- [47] World Health Organization Use of Antiretroviral Medication for Treating Pregnant Women and Preventing HIV infection in Infants (2012). Available from: http://www.who.int/hiv/PMTCT_update.pdf
- [48] Cardo, D, Culver, D. H, & Ciesielski, C. A. study of HIV seroconversion in health care worker after percutaneous exposure. *New Eng J Med.*, , 337, 1485-90.
- [49] Garcia-lerma, J. G, Otten, R. A, & Qari, S. H. (2008). Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLOS medicine*, e , 28, 0291-0299.
- [50] Van Rompay, K. K, Mchesney, M. B, & Aguirre, N. L. (2001). Two low doses of tenofovir protect new-born macaques against oral simian immunodeficiency virus infection. *J Infect Dis*. 2001; , 184, 429-438.
- [51] Anderson, P. L, Kiser, J. J, Gardner, E. M, Rower, J. E, Meditz, A, & Grant, R. M. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother*. (2011). , 66(2), 240-50.
- [52] Gilead laboratories Tenofovir disoproxil fumarate. Updated August (2012). Available from: http://www.gilead.com/pdf/viread_pi.pdf.
- [53] Gant, R, Lama, J, Anderson, P, McMahan, V, Liu, A, & Vargas, L. et al. IPrEX study team. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *N Engl J Med* (2010). , 363(27), 2587-2599.
- [54] Thigpen, M. C, Kebaabetswe, P. M, Paxton, L. A, Smith, D. K, Rose, C. E, Segolodi, T. M, et al. TDF2 Study Group. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. (2012). , 367(5), 423-34.

- [55] Baeten, J. M, Donnell, D, Ndase, P, Mugo, N. R, Campbell, J. D, Wangisi, J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* (2012). , 367(5), 399-410.
- [56] Van Damme, L, Corneli, A, Ahmed, K, Agot, K, Lombaard, J, Kapiga, S, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* (2012). Aug 2; , 367(5), 411-22.
- [57] Microbicide Trials NetworkVOICE (MTN-003) study. Available from:<http://www.mtnstopshiv.org/news/studies/mtn003>.
- [58] Montgomery, E. T, Van Der Straten, A, Chidanyika, A, Chipato, T, Jaffar, S, & Padian, N. The importance of male partner involvement for women's acceptability and adherence to female initiated HIV prevention methods in Zimbabwe. *AIDS Behav* (2011). , 15, 959-969.
- [59] Montgomrery, E. T, Van Der Straten, A, & Torjesen, K. Male involvement in womens and children's HIV prevention: challenges in definition and interpretation. *J Acqui Immune Defic Syndr* (2011). e , 114-116.
- [60] Patterson, K, Prince, H, Kraft, E, Jenkins, A, Shaheen, N. J, Rooney, J. F, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission, *Sci Transl Med* (2011).
- [61] Juusola, J, Brandeau, M, Owens, D, & Bendavid, E. The Cost-Effectiveness of Preexposure Prophylaxis for HIV Prevention in the United States in Men Who Have Sex With Men. *Ann Intern Med* (2012). , 156, 541-550.
- [62] Krakower, D, & Mayer, K. H. What Primary Care Providers Need to Know About Preexposure Prophylaxis for HIV Prevention: A Narrative Review. (2012). epub ahead of print].
- [63] Abdool Karim SSRichardson B, Ramjee G. Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women. *AIDS* (2010). , 25, 957-966.
- [64] Van Damme, L, Ramjee, G, & Alary, M. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomized controlled trial. *Lancet* (2002). , 360, 971-977.
- [65] Van Damme, L, Govinden, R, & Mirembe, F. M. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV TransmissionInternational Partnership for Microbicides (2012). Available from: <http://www.ipmglobal.org/our-work/ipm-product-pipeline/maraviroc>.
- [66] 66. Skoler-karpoff, S, Ramjee, G, & Ahmed, K. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet* (2008). , 372, 1977-1987.

- [67] Abdool Karim Q, Abdool Karim S, Frohlich J, Grobler A, Baxter C, Mansoor L et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*; , 329(5996), 1168-1174.
- [68] Microbicide Trials Network VOICE (MTN-003) study. Available from: <http://www.mtnstopshiv.org/node/3909>. Accessed September 10th (2012).
- [69] International Partnership for Microbicides (2012). Available from: <http://ipmglobal.org/node/532>
- [70] International Partnership for Microbicides (2012). Available from: <http://www.ipmglobal.org/our-work/ipm-product-pipeline/maraviroc>.
- [71] Van'Klooster, t, Hoeben, G, Borghys, E, Looszova, H, Bouche, A, Van Velsen, M, et al. Pharmacokinetics and disposition of rilpivirine (TMC 278) nanosuspension as a long-acting injectable antiretroviral formulation. *Antimicrob Agents Chemother* (2010). , 54, 2042-2050.
- [72] Smith, D, Thigpen, M, Nesheim, S, Lampe, M, Pazton, L, Fenton, M, et al. Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults. *MMWR* (2012). Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a2.htm?s_cid=mm6131a2_w , 586-589.