Efficacy of HIV Pre exposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies

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This is to certify that the senior paper prepared by Jemal Washo entitled " Efficacy of HIV Pre exposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies" and submitted in partial fulfillment of the requirements for the degree of Master of Science in Pharmacology complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

The emergence of new prevention methods has increased the optimism towards achieving a more effective control over the AIDS epidemic, as these methods have shown the potential to promote significant reductions in the number of new infections. An important part of this optimism relates to the development of methods based on using antiretrovirals (ARV-based prevention), which may avoid acquisition of infection when used before or after exposure to HIV, and also avoid transmission of the virus in sexual intercourse among serologically discordant couples (treatment as prevention). The pre-exposure chemoprophylaxis (now commonly referred to as PrEP) of HIV infection has gained increased momentum, concomitantly with the successful use of combination drug regimens for the treatment of AIDS. Many studies among animals showed better results of this prophylaxis method. Tenofovir disproxil fumarate and Tenofovir disproxil fumarate /emtricitibine has proven effective, if orally administered daily or intermittently, in the prevention of rectal simian human immunodeficiency virus (SHIV) infection in macaques. However, the combined preventive efficacy of this method is not conducted/ published to date.

The aim of this study is to review and analyze the published literatures and un published literatures evaluating HIV transmission prevention efficacies of these drugs (Tenofovir disproxil fumarate and Tenofovir disproxil fumarate /emtricitibine), to reveal the combined outcomes of individual literatures, in non human primate models.

Keywords: HIV/AIDS prevention, HIV transmission, pre exposure prophylaxis, HIV prophylaxis, non human primate models, antiretroviral agents, treatment as prevention

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LIST OF ABBREVIATIONS

HIV----------human immunodeficiency virus
PrEP---------- Pre-exposure prophylaxis
PEP ----------Post-exposure prophylaxis
SIV ----------simian immunodeficiency virus
ARV ----------antiretroviral
HCW----------health care workers
IDUs---------- injecting drug users
CDC----------centre for disease control
CBC----------complete blood count
STIs----------sexually transmitted infections
ADR----------adverse drug reaction
PIs----------Protease Inhibitors
NRTIs----------nucleoside reverse transcriptase inhibitors
NNRTI----------non-nucleoside reverse transcriptase inhibitor
LFTs----------liver function tests
SIV----------simian immunodeficiency virus
PLWHA----------people living with HIV/AIDS
UNAIDS----------United Nations Programme on HIV/AIDS
PRISMA----------Preferred Reporting Items for Systematic Review and Meta-Analyses
ORs----------odds ratios
CIs----------confidence intervals
MSM----------men who have sex with men
WSW---------- Women who have sex with women
NPTs---------- New prevention technologies
FMoH----------Federal Ministry of Health
HTC----------HIV testing and counseling
IMAI----------Integrated Management of Adolescent and Adulthood Illness
TDF----------Tenofovir disproxil fumarate
FTC----------Emtricitibine
MTCT----------Mother To Child Transmission
FTC-TP----------Emtricitibine tri phosphate
TFV-DP----------Tenofovir di phosphate

BACKGROUND

Worldwide, approximately 60 million people have been infected with HIV since the beginning of the pandemic, and over 20 million have died. In 2003, there were an estimated 38 million people living with HIV; in that same year, nearly 5 million people became newly infected.1 As in many countries, HIV infections in the United States are on the rise—an estimated 950,000 people were living with HIV in 2003, up from 900,000 in 2001 (1).

Although behavioral interventions (including abstinence, reducing number of sexual partners, partner selection, use of male and female condoms, and needle hygiene) have shown efficacy in preventing HIV infection in diverse populations and settings, they are not always consistently implemented by individuals, are not universally effective, and have not ultimately been able to contain the pandemic (9). It is widely believed that, in addition to effective behavioral interventions, biomedical approaches to HIV prevention will be required to adequately curb the spread of the virus. The two most prominent technology-based HIV prevention strategies, however—HIV vaccines and vaginal and rectal microbicides—lack candidate agents that are likely to prove successful in the near- to midterm. Other practical options are desperately needed in the meantime (3).

It is likely that successful HIV prevention efforts will rely on multiple techniques and strategies used in combination. Just as the success of combination antiretroviral therapy relies on multiple drugs that may target more than one step in the viral life cycle, so too might prevention be enhanced by the synergistic use of social, behavioral, biomedical, and barrier methods (5).

Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention that has recently generated considerable interest. PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection. PrEP should be distinguished from post exposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection. It has been hypothesized that, in various international settings, PrEP could be a viable prevention strategy for certain people at high risk of HIV infection, such as commercial sex workers, those in serodiscordant relationships, and members of high-risk groups who choose not to use condoms or for whom consistent condom use has proved difficult (4,5). It is not yet known whether PrEP is a safe or effective approach to HIV prevention, however, as studies for its evaluation in several populations are just preparing to begin. These planned studies and future, yet-to-be-planned clinical trials will determine whether and to what degree PrEP is safe and effective. If safety and efficacy are demonstrated, post-marketing (Phase IV) studies will be needed to assess how PrEP gets used in clinical practice (4).

Post-exposure prophylaxis (PEP) on the other hand, is a medical response given to prevent the transmission of pathogens after potential exposure. The PEP for HIV refers to a set of comprehensive services to prevent HIV infection in exposed individuals where the exposure can be occupational or non-occupational (nPEP).

These services include first aid care, counselling and risk assessment, HIV testing and depending on risk assessment, the provision of short-term (28 days) antiretroviral (ARV) drugs, with follow-up.

From the emergence of more powerful and better accepted treatment regimens for HIV infection, added to the increase in the number of individuals treated, there was a substantial reduction in morbidity and mortality associated with AIDS. This reduction is estimated at 4 million deaths among people living with HIV/AIDS (PLWHA) undergoing treatment (12).The Joint United Nations Programme on HIV/AIDS (UNAIDS) set goals for the disease: by 2020, 90% of the PLWHA should know about their diagnosis; 90% of all PLWHA should receive antiretroviral therapy; 90% of people undergoing treatment should achieve durable viral suppression, representing effective treatment. These targets include a purpose: mathematical models suggest that, if these goals are met, they will allow eradication of the AIDS epidemic by 2030 (2).
Biomedical interventions include those that require the use of medications or other technologies involving continuous self-administration in order to be effective (5), as is the case of antiretroviral pre- and post-exposure prophylaxis, treatment strategies for HIV infection as a form of prevention of transmission, among others.The efficacy of antiretroviral as PrEP to prevent viral attainment was verified in nonhuman primate models of human immunodeficiency virus in the early 1990s (3). To complement the evidence base for efficacy of HIV PrEP in humans, the published data on PrEP efficacy across animal studies systematically reviewed and analyzed to evaluate HIV transmission prevention efficacies through the use of pre exposure prophylaxis (PrEP) interventions. One of the great tragedies of our times is the extent to which HIV prevention efforts are falling short. In 2004, more new HIV infections occurred than in any previous year: close to 14,000 a day, 570 per hour, almost ten per minute. The greater part of new infections occurs in young people, over half in persons between 15 and 24 years of age, and over half in women. The increasing feminization of the HIV/AIDS epidemic reflects the vulnerable position of women in many societies. HIV is a virus, but inequity is at the roots of most of its spread. Condoms are highly effective at preventing sexual transmission of HIV, but only if they are available and used (2). Even if the former is the case, women are often in a difficult position to negotiate use by their male partners (3); this applies to female as well as male condoms. In the absence of an effective preventive HIV vaccine (4), which is felt to be the only tool that can definitively break the epidemic, there is thus great need for alternative prevention technologies, especially those that can be “female-controlled”, i.e., use of which does not require consent of the male partner. Other vulnerable populations might equally profit from the availability of such interventions. The urgent need to develop female controlled prevention methods explains the thrust to develop vaginal microbicides (5,6), and the more recent interest in using an antiretroviral oral pre-exposure prophylaxis (PrEP), for which proof of concept has come from preventing mother-to-child transmission via breastfeeding (7)

EPIDEMIOLOGY OF HIV

HIV, the virus that causes AIDS, "acquired immunodeficiency syndrome (2) has become one of the world's most serious health and development challenges. The first cases were reported in 1981 and today, more than 30 years later; there are approximately 35 million people currently living with HIV and tens of millions of people have died of AIDS-related causes since the beginning of the epidemic. While new cases have been reported in all regions of the world, 95% of new infections occur in individuals that reside in low- and middle-income countries, particularly in sub-Saharan Africa (3).

Most people living with HIV or at risk for HIV do not have access to prevention, care, and treatment, and there is still no cure (6). HIV primarily affects those in their most productive years; about half of new infections are among those under age 25years. HIV not only affects the health of individuals, it impacts households, communities, and the development and economic growth of nations. Many of the countries hardest hit by HIV also suffer from other infectious diseases, food insecurity, and other serious problems (5). Despite these challenges, new global efforts have been mounted to address the epidemic, particularly in the last decade, and there are signs that the epidemic may be changing course. The number of people newly infected with HIV and the number of AIDS-related deaths have declined, contributing to the stabilization of the epidemic. In addition, the number of people with HIV receiving treatment in resource poor countries has increased from 400,000 in 2003 to 9.7 million in 2012 (3,6).

According to the latest estimates from UNAIDS; there were 35.3 million people living with HIV in 2016, up from 29.4 million in 2001, the result of continuing new infections, people living longer with HIV, and general population growth. The global prevalence rate (the percent of people ages 15-49 who are infected) has leveled since 2001 and was 0.8% in 2012. 1.6 million people died of AIDS in 2012, a 30% decrease since 2005. Deaths have declined due in part to antiretroviral treatment (ART) scale-up. HIV is a leading cause of death worldwide and the number one cause of death in Africa.

New HIV infections overall have declined by 33% since 2001 and, in 26 low- and middle-income countries, new infections have declined by 50% or more. Still, there were about 2.3 million new infections in 2012 or more than 6,300 new infections per day. Most infections are transmitted heterosexually, although risk factors vary. In some countries, men who have sex with men, injecting drug users, and sex workers are at significant risk. Although HIV testing capacity has increased over time, enabling more people to learn their HIV status, the majority of people with HIV are still unaware they are infected (6).

Women represent about half (52%) of all people living with HIV worldwide. HIV is the leading cause of death among women of reproductive age.

Gender inequalities, differential access to service, and sexual violence increase women's vulnerability to HIV, and women, especially younger women, are biologically more susceptible to HIV. Young people, ages 15-24, account for approximately 39% of new HIV infections (among those 15 and over). Globally, young women are twice as likely to become infected with HIV than their male counterparts.
In some areas, young women are more heavily impacted than young men. Globally, there were 3.3 million children living with HIV in 2012, 260,000 new infections among children, 210,000 AIDS deaths, and in 2011, approximately 17.3 million AIDS orphans (children who have lost one or both parents to HIV), most of whom live in sub-Saharan Africa (88%) (4).

According to the 2016 HIV estimates, the national HIV prevalence in Ethiopia is 1.14%, indicating the country has more than achieved the Millennium Development Goal 6 target of 2.5%. Annual new HIV infections have also declined by 90% and AIDS-related deaths by 53% in the last decade (between 2000 and 2011). Across all the regions, urban areas are more affected than rural ones, and females are more affected than males by the HIV epidemic. The 2014 estimated number of people living with HIV (PLHIV) was 769 600 with 15 700 new HIV infections and 35 600 AIDS-related deaths. Ethiopia has made significant progress to ensure universal access to treatment of HIV/AIDS and HIV testing and counseling (HTC) services have also expanded with about 9.6 million tests done in 2013/14 alone. Almost 2,500 health facilities are providing prevention of mother-to-child transmission of HIV (PMTCT) services with a national level coverage of 61%.

Table 1: HIV Prevalence & Incidence by Region, 2016

Region	**Total No. (%) Living with HIV**	**Newly Infected**	**Adult Prevalence Rate**
Global Total	35.3 million (100%)	2.3 million	0.8%
Sub-Saharan Africa	25.0 million (71%)	1.6 million	4.7%
South/South-East Asia	4.0 million (11%)	270,000	0.3%
Latin America	1.5 million (4%)	86,000	0.4%
Eastern Europe/Central Asia	1.3 million (4%)	130,000	0.7%
North America	1.3 million (4%)	48,000	0.5%
East Asia	880,000 (2%)	81,000	<0.1%
Western/Central Europe	860,000 (2%)	29,000	0.2%
Middle East/North Africa	260,000 (0.7%)	32,000	0.1%
Caribbean	250,000 (0.7%)	12,000	1.0%
Oceania	51,000 (0.1%)	2,100	0.2%

Table 2: HIV epidemic and response estimates, global and by region, 2010 and 2015

	People living with HIV/AIDS (all ages)		New HIV infections (all ages)	
	2010	2015	2010	2015
Global	33.3 million [30.9 million–36.1 million]	36.7 million [34.0 million–39.8 million]	2.2 million [2.0 million–2.5 million]	2.1 million [1.8 million–2.4 million]
Asia and Pacific	4.7 million [4.1 million–5.5 million]	5.1 million [4.4 million–5.9 million]	310 000 [270 000–360 000]	300 000 [240 000–380 000]
Eastern and southern Africa	17.2 million [16.1 million–18.5 million]	19.0 million [17.7 million–20.5 million]	1.1 million [1.0 million–1.2 million]	960 000 [830 000–1.1 million]
Eastern Europe and central Asia	1.0 million [950 000–1.1 million]	1.5 million [1.4 million–1.7 million]	120 000 [110 000–130 000]	190 000 [170 000–200 000]
Latin America and the Caribbean	1.8 million [1.5 million–2.1 million]	2.0 million [1.7 million–2.3 million]	100 000 86 000–120 000]	100 000 [86 000–120 000]
Middle East and North Africa	190 000 [150 000–240 000]	230 000 [160 000–330 000]	20 000 [15 000–29 000]	21 000 [12 000–37 000]
Western and central Africa	6.3 million [5.2 million–7.7 million]	6.5 million [5.3 million–7.8 million]	450 000 [350 000–560 000]	410 000 [310 000–530 000]
Western and central Europe and North America	2.1 million [1.9 million–2.3 million]	2.4 million [2.2 million–2.7 million]	92 000 [89 000–97 000]	91 000 [89 000–97 000]

Sources: GARPR 2016; UNAIDS 2016 estimates.

Table 3: Antiretroviral therapy coverage among people living with HIV by region and AIDS related deaths, 2010 and 2015

	People living with HIV/AIDS on ART treatment (all ages)		AIDS related deaths (all ages)	
	2010	2015	2010	2015
Global	7 501 100	17 025 900	1.5 million [1.3 million–1.7 million]	1.1 million [940 000–1.3 million]
Asia and Pacific	907 600	2 071 900	240 000 [200 000–270 000]	180 000 [150 000–220 000]
Eastern and southern Africa	4 087 500	10 252 400	760 000 [670 000–860 000]	470 000 [390 000–560 000]
Eastern Europe and central Asia	112 100	321 800	38 000 [33 000–45 000]	47 000 [39 000–55 000]
Latin America and the Caribbean	568 400	1 091 900	60 000 [51 000–70 000]	50 000 [41 000–59 000]
Middle East and North Africa	13 600	38 200	9500 [7400–12 000]	12 000 [8700–16 000]
Western and central Africa	905 700	1 830 700	370 000 [290 000–470 000]	330 000 [250 000–430 000]
Western and central Europe and North America	906 200	1 418 900	29 000 [27 000–31 000]	22 000 [20 000–24 000]

Sources: GARPR 2016; UNAIDS 2016 estimates.

The latest UNAIDS data, covering 160 countries, demonstrate both the enormous gains already made and what can be achieved in the coming years through a Fast-Track approach. In just the last two years the number of people living with HIV on antiretroviral therapy has increased by about a third, reaching 17.0 million people—2 million more than the 15 million by 2015 target set by the United Nations General Assembly in 2011. Since the first global treatment target was set in 2003, annual AIDS-related deaths have decreased by 43%. In the world's most affected region, eastern and southern Africa, the number of people on treatment has more than doubled since 2010, reaching nearly 10.3 million people. AIDS related deaths in the region have decreased by 36% since 2010. However, huge challenges lie ahead. In 2015 there were 2.1 million [1.8 million–2.4 million] new HIV infections worldwide, adding up to a total of 36.7 million [34.0 million–39.8 million] people living with HIV.

Treatment coverage in Latin American and the Caribbean reached 55% [47–64%] in 2015. In the Asia and Pacific region, coverage more than doubled, from 19% [17–22%] in 2010 to 41% [35–47%] in 2015. Western and central Africa and the Middle East and North Africa also made important gains but achieved lower levels of coverage in 2015, 28% [23–34%] and 17% [12–24%], respectively. In Eastern Europe and central Asia, coverage increased by just a few percentage points in recent years to 21% [20–23%]—about one in five people living with HIV in the region. The gains in treatment are largely responsible for a 26% decline in AIDS-related deaths globally since 2010, from an estimated 1.5 million [1.3 million–1.7 million] in 2010 to 1.1 million [940 000 –1.3 million] in 2015. The reduction in deaths since 2010 has been greater among adult women (33% decrease) compared with adult men (15% decrease), reflecting higher treatment coverage among women than men, 52% [48–57%] and 41% [33–49%], respectively.

The gender gap for treatment among adults highlights the impact of gender norms that delay initiation of treatment among men, reduce treatment adherence, blunt the preventive effects of treatment, and lead to men accounting for 58% of adult AIDS related deaths.

WHO supports the Federal Ministry of Health (FMoH) of Ethiopia in leading and coordinating the national health sector response against the HIV epidemic. WHO is a key player in HIV forums both at national and regional levels in close collaboration with CDC and USAID and their implementing partners. A central area of support to the FMoH is the development, adoption and revision of HIV strategies and guidelines, training manuals and tools. Since 2005, WHO has particularly intensified its technical support to the adaptation and national roll out of IMAI (Integrated Management of Adolescent and Adulthood Illness) guidelines and training tools. Moreover, the Country Office has been a pioneer in promoting the application of task shifting and a public health approach in delivering HIV care and treatment services in Ethiopia. In the post-2015 context, WHO continues to support Ethiopia to strengthen the public health approach to scaling up of HIV/AIDS services through community empowerment. Intensified efforts are targeted at HIV prevention, care and treatment among key and vulnerable populations (5).

HIV TRANSMISSION

One can become infected with HIV if he/she does certain things that allow enough of the virus to get into their bloodstream. There are only four body fluids of an infected person that have enough HIV in them to pass this virus on:

- Semen
- Vaginal Fluids
- Blood
- Breast Milk

More than 70% of HIV infections worldwide are estimated to result from sexual contacts between men and women. 10% can be traced to sexual transmission between men, and 5% of infections are due to sharing needles, syringes and drug preparation equipment by people who inject drugs. Four out of five injecting drug users are men (9).

Sexual Transmission

Penetrative sex is when a man's penis penetrates the vagina or anus (of a woman or a man). HIV can be transmitted through unprotected (i.e. without the protection of a condom) penetrative sex. It is difficult to calculate the odds of becoming infected through sexual intercourse; however it is known that the risk of infection through vaginal sex is high (5). Transmission through anal sex has been reported to be 10 times higher than by vaginal sex(This is because rectal mucosa differs from vaginal mucosa. There is a higher density of lymphoid follicles (i.e., HIV target cells) in rectal mucosa and it is more susceptible to abrasions than vaginal mucosa) (3). A person with an untreated sexually transmitted infection, particularly involving ulcers or discharge, is, on average, 6-10 times more likely to pass on or acquire HIV during sex (21). Oral Sex (using the mouth to stimulate a person's sexual organ) is regarded as a low-risk sexual activity in terms of HIV transmission. The risk can increase if there are cuts or sores around or in the mouth and if ejaculation occurs in the mouth (6).

Women who have sex with women (WSW)

Woman-to-woman sex carries a low risk of HIV transmission. Some sexual practices such as oral sex have a low risk of HIV transmission. However, some women who have sex with women have unsafe sex with men and some women who have sex with women inject drugs and share needles (6).

Transmission through Injecting Drug Use

Re-using or sharing needles, syringes and drug preparation equipment represents a highly efficient way of transmitting HIV and other infections such as hepatitis. The risk of transmission can be lowered substantially among injecting drug users by using new needles and syringes and not sharing them, by properly sterilizing reusable needles and syringes before reuse, and not sharing drug preparation equipment (7).

Transmission through Blood and Blood Products

There is a high risk (greater than 90%) of acquiring HIV through transfusion of infected blood and blood products. However, the implementation of blood safety standards ensures the provision of safe, adequate and good-quality blood and blood products for all patients requiring transfusion. Blood safety includes appropriate donor selection as well as screening of all donated blood for blood borne viruses including HIV (6).

Mother to Child Transmission

HIV can be transmitted to an infant during pregnancy, labour, and delivery as well as by breastfeeding. A pregnant woman or a woman planning to get pregnant should consider being tested for HIV. If she tests positive, antiretroviral drugs can be provided to help prevent the spread of HIV to the baby during birth (8).

THE HIV LIFE CYCLE

Binding and Fusion

HIV begins its life cycle when it binds to a CD4 receptor and one of two co-receptors on the surface of a CD4+ T- lymphocyte. The virus then fuses with the host cell. After fusion, the virus releases RNA, its genetic material, into the host cell.

Reverse Transcription

An HIV enzyme called reverse transcriptase converts the single-stranded HIV RNA to double-stranded HIV DNA.

Integration

The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called integrase "hides" the HIV DNA within the host cell's own DNA. The integrated HIV DNA is called provirus. The provirus may remain inactive for several years, producing few or no new copies of HIV.

Transcription:

When the host cell receives a signal to become active, the provirus uses a host enzyme called RNA polymerase to create copies of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). The mRNA is used as a blueprint to make long chains of HIV proteins.

Assembly:

An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.

Budding:

The newly assembled virus pushes out ("buds") from the host cell. During budding, the new virus steals part of the cell's outer envelope. This envelope, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co- receptors. The new copies of HIV can now move on to infect other cells.

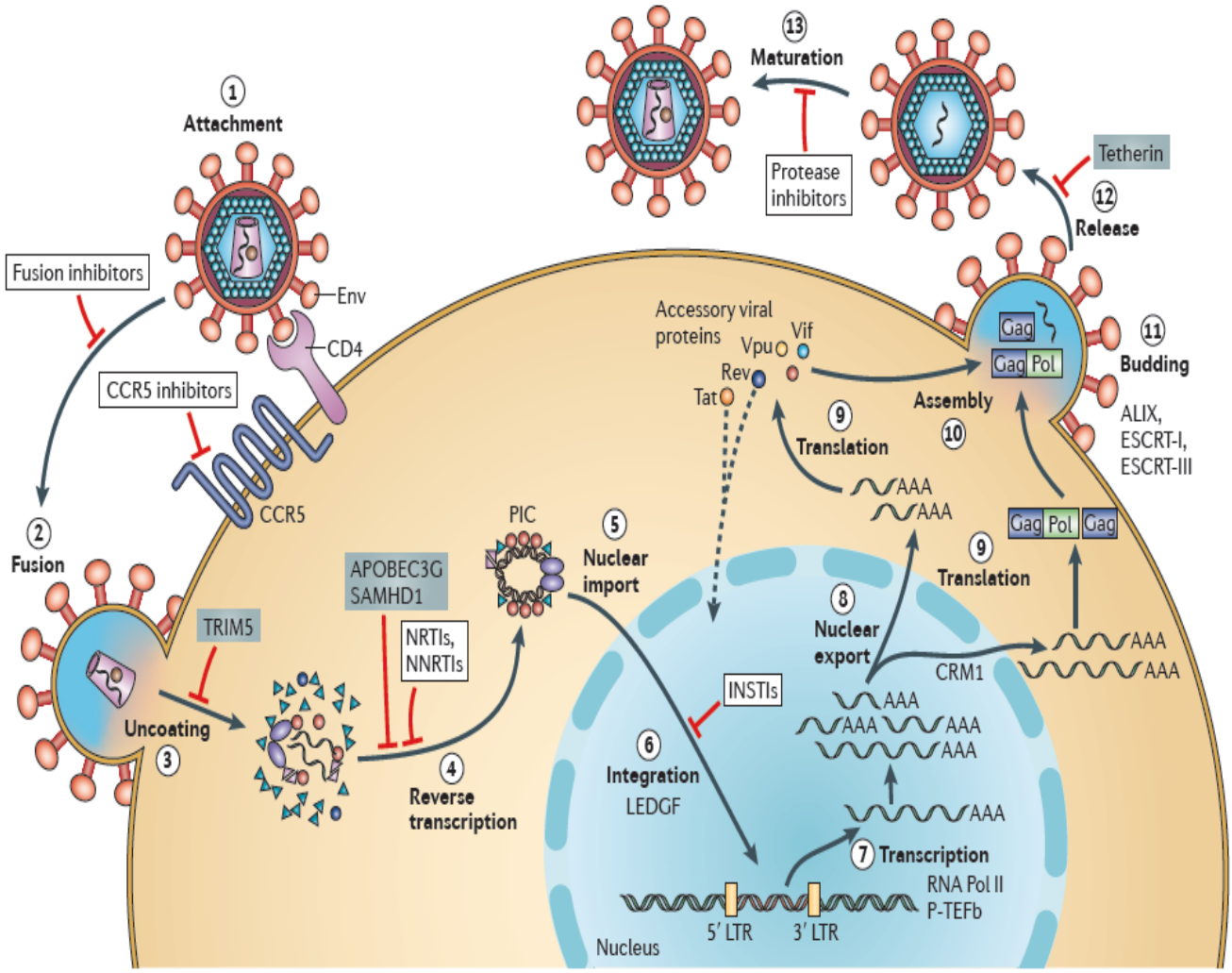


Figure 1: The HIV life cycle *(Alan E et al, 2009)*

STAGES OF HIV DESEASE PROGRESSION TO AIDS

HIV disease progression occurs along a continuum. There are three major stages.

The 1st stage is the acute infection period. In this stage, which can last for several weeks; the virus is establishing itself in the body. Up to 70% of people newly infected experience "flu-like" symptoms (fevers, chills, night sweats, rashes). After experiencing these initial flu-like symptoms, people resume feeling and looking normal. During this initial stage the virus makes it way to the lymph nodes where it actively replicates itself. This burst of rapid HIV replication usually lasts two months. At this stage, the person has a very high viral load. Detection and formation of antibodies take roughly 6 to 12 weeks and the person will not test positive for HIV antibodies. During the period of early infection, a person has the greatest chance of passing HIV infection to others.

The 2ndstage is the clinical latency period. This stage has two phases: (1) the asymptomatic stage and (2) the early-and medium-stage of HIV symptomatic disease. During the asymptomatic stage, people feel normal and can feel well for many years. During this time the only indication of HIV infection is through testing or the presence of swollen lymph glands. During this time, even though, the person feels great –the virus is slowly dismantling their immune system and this can go on for longer than 10 years.

Early and Medium Stage HIV Symptomatic Disease is when people being experiencing mild HIV disease symptoms such as skin rashes, fatigue, night sweats, slight weight loss, mouth ulcers, and fungal skin and nail infections. It can take 5 to 7 years for the mild symptoms to appear. As the disease progresses, typical problems include chronic oral or vaginal thrush, recurrent herpes blisters, ongoing fevers, persistent diarrhea, and significant weight loss.

The 3rdstage is late-stage HIV disease also known as AIDS. With AIDS, the T-cell count drops down to 200 or less, and opportunistic infections develop. These are infections and illnesses that the normal immune system can suppress or present. According to the CDC, an AIDS diagnosis includes an HIV infection, a T-cell CD4 count under 200 cells/mm3of blood, and 1 or more OIs. Having AIDS is not an imminent death sentence. With treatment it may be possible to keep HIV from progressing to AIDS.

HIV-RELATED TESTING

The diagnosis of HIV-1 infection is based on the detection of specifi c antibodies, antigens, or both, and many commercial kits are available. Serological tests are generally used for screening. A major advance has been the availability of rapid HIV-1 antibody tests. These assays are easy to do and provide results in as little as 20 minutes enabling specimen collection and proper diagnosis at the same visit (15). Rapid tests are important tools for surveillance, screening, and diagnosis, and can be reliably done on plasma, serum, whole blood, or saliva by health-care providers with little laboratory expertise. The two limitations of these serological tests are detection of infection during primary infection when antibodies are absent, and in infants younger than 18 months who might bear maternal HIV-1 antibodies. In these instances direct virus detection is the only option (eg, quantification of viral RNA [standard] or p24 antigen in heat denatured serum [less expensive]).

For staging purposes, measurement of CD4+ cells and viraemia is required. Plasma viral load is widely used to monitor therapeutic success on antiretroviral treatment. Several commercially available tests provide sensitive quantification of plasma HIV-1 RNA copies (17). While the viral load determines the rate of destruction of the immune system, the number of CD4+ cells reveals the degree of immunodeficiency and is, therefore, used to assess the stage of infection. CD4+ cell counts together with clinical manifestations (eg, occurrence of opportunistic infections) are key criteria for HIV-1 disease classification. Flow cytometry analysis is the standard method for CD4+ cells quantification. Standard methods for quantifying viral load and CD4+ cell counts need advanced laboratory infrastructures, and assays require a specimen to be tested within a short time of collection. These requirements pose challenges for resource-constrained settings. The use of dried blood spot specimen has resolved some of the difficulties associated with transportation of samples needed for virological assessments. Measurement of reverse transcriptase activity in plasma samples, simplification of gene amplification methods (eg, Taqman technology), and paper-strip quantification (dipstick assays) might provide cost-eff ective alternatives for the future. Similarly microcapilliary flow-based systems, CD4+ chips, or total white counts (panleucocyte gating) provide alternatives for establishment of the level of immunodeficiency in resource-limited settings (16). HIV serological testing (typically an enzyme-linked immunosorbent assay (ELISA) or rapid blood test), followed by confirmatory test (typically western blot) (12). CD4 cell count to determine the severity of immune deficiency. Viral load testing by polymerase chain reaction (PCR), to determine level of viral replication (14).

ANTIRETROVIRAL TREATMENT

Antiretroviral treatment is the best option for long lasting viral suppression and, subsequently, for reduction of morbidity and mortality. However, current drugs do not eradicate HIV-1 infection and lifelong treatment might be needed. Development of new anti retro virals focuses on molecules that target entry, reverse transcription, integration, or maturation. Compounds that have been designed to inhibit resistant viruses are urgently needed since many patients treated during the past decades harbor viral strains with reduced susceptibilities to many if not all available drugs. The goal of antiretroviral treatment is to decrease the morbidity and mortality that is generally associated with HIV-1 infection. A combination of three or more active drugs is needed to achieve this aim in most patients. Effective treatment returns to near normal the turnover rates of both CD4+ and CD8+ T-cell populations. Potent but well tolerated drugs with long half-lives and simplified regimens improve the options for first-line and second-line chemotherapeutic interventions (41).

Combination antiretroviral treatment

High rate of viral replication, low fidelity of reverse transcription, and the ability to recombine are the viral characteristics that lead to the diversity of HIV-1 species (quasi-species) in chronically infected individuals. This high genetic variability provided the rationale for highly active antiretroviral treatments (HAART). By combination of several potent antiretroviral agents, viral replication is suppressed to such low levels that emergence of drug resistant HIV-1 variants was, if not prevented, at least delayed. By doing so, CD4+ T-lymphocyte numbers increase, leading to a degree of immune reconstitution that is sufficient to reverse clinically apparent immunodeficiency. Widespread introduction of HAART in industrialized countries resulted in a striking decrease in morbidity and mortality, putting forward the hope that HIV-1 infection can be transformed into a treatable chronic disease (15).

In resource-limited settings the decision to initiate ART in adults and adolescents relies on clinical and immunological assessment. In order to facilitate the rapid scale-up of ART programmes with a view to achieving universal access to this therapy, WHO emphasizes the importance of using clinical parameters in deciding when to initiate it. However, it is recognized that the value of clinical staging in deciding when to initiate and monitor ART is improved by additional information on baseline and subsequent (longitudinal) CD4 cell counts. While WHO continues to advocate wider availability of affordable point-of-care CD4 cell count testing, the lack of a CD4 count should not delay the initiation of ART if the patient in question is clinically eligible. WHO encourages national programmes to increase access to CD4 measurement technologies (12).

The process of initiating ART involves assessing patient readiness to commence therapy and an understanding of its implications (lifelong therapy, adherence, toxicities). Access to nutritional and psychosocial support and to family and peer support groups is important when decisions

are being made about the initiation of ART (17).
A set of criteria composed of plasma viraemia concentration, absolute or relative CD4+ cell counts, and clinical manifestations, is used to recommend initiation of HAART. The benefits of treatment clearly outweigh the potential side-effects in patients with clinical signs of immunodeficiency (eg, AIDS defining illnesses) or with CD4+ numbers less than 200 per μL (recommendation of US Department of Health and Human Services, October, 2005). However, the best time point to begin treatment remains controversial in asymptomatic patients with modest depletion of CD4+ T cells (eg, more than 350 per μL) and modest levels of viraemia (eg, less than 100 000 copies per mL) (27).

The best point at which to start ART is under discussion. A review of several cohort studies and guidelines shows a widespread view that clinical staging (stage 3 or 4) and CD4 counts are the best primary markers and viral load the secondary marker for this decision. Prior to starting ART, support to ensure adherence should be initiated (20). The decision to initiate ART should be based on two different CD4 counts, ideally at least 7 days apart because of variability in the CD4 count itself and to rule out laboratory mistakes and other variances (for example, concurrent illnesses). In case of a concurrent acute illness, CD4 cell count should be repeated only after the illness is cured. Therapy should not however be delayed if a patient is unwell or if the second count cannot readily be performed. If the CD4 count is not available, the decision to initiate ART can still be made on clinical grounds alone – with clinical stage 3 or 4 illness (9).

Baseline CD4 count at the onset of ART (ideally determined when the patient is free from any active major opportunistic infection) is a critical value in determining prognosis, response to ART and for monitoring the subsequent immunological response to ART (21).

Viral load is associated with loss of CD4 cells. Though on its own it is not a marker for initiating ART, in case of viral load >100 000 copies/ml (this can go as high as 1 million copies), the probability of rapid CD4 cell count decline is very high. Therefore, it is recommended to consider initiation of ART at CD4 cell count of 350/mm3 if the viral load is higher than 100 000 copies/ml. While viral load testing is more expensive and may be less accessible, it is important to have a baseline viral load if at all possible, as this value is relevant for monitoring ART. The absence of viral load data should not be a criterion for delaying the start of treatment, or used as a reason for treatment exclusion. Prevalence of HIV drug resistance varies in different countries and is linked to several factors, including the duration of ART availability, history of treatment (mono- and dual therapy) and adherence. In Western Europe, multicentric studies showed a 10% overall prevalence of resistance in newly diagnosed HIV-infected individuals between 1996 and 2002 (32). A study of 40 cities in the United States revealed a resistance rate of 14% (33). The highest results from these studies were 26% in Spain (34) and 19% in San Francisco (35). In countries with a short or no history of ART, risk of HIV drug resistant virus transmission is significantly lower, and the first-line highly active antiretroviral treatment (HAART) regimen

recommended below is effective for treatment of naïve patients. It is important to have population-based HIV drug resistance strategies in place to monitor for the appearance and spread of HIV drug resistance; and to act on the early warning indicators for drug resistance emergence in order to minimize its appearance and onward spread (102).
WHO does not recommend individual drug resistance testing prior to initiation of ART in settings where only one first-line regimen is provided in the public sector because any results will not influence ART. Instead, sentinel surveys that demonstrate resistance at population level above the threshold of 5% (36, 37) should be taken into consideration in adapting national recommendations for first-line ART. Where resources permit, and the public sector provides more than one first-line regimen, then drug resistance testing at baseline may help determine the choice of optimal ART; cost and availability will likely limit the widespread use of this in many settings (38–40).

First-line HAART regimen
It is recommended that two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) be combined in the first-line HAART regimen (24).

Table 4: First-line HAART regimens

Table	Recommended first-line HAART
ARV drug classes	HAART regimens
2 NRTIs + 1 NNRTI	ZDV + 3TC + (EFV or NVP) Or
	TDF + FTC + (EFV or NVP) Or
	ABC + 3TC + (EFV or NVP)

Abbreviations
HAART----------Highly active antiretroviral treatment
ZDV----------Zidovudine
3TC----------Lamivudine
EFV----------Efavarenz
NVP----------Nevirapine
TDF----------Tenofovir
FTC----------Emricitibine
ABC----------Abacavir

PREVENTION OF HIV AND AIDS

There is no preventive vaccine or cure yet. The only option available today is to prevent it by observing practices that are safe (2).

Responsible Sexual Behaviors:

Reduction of heterosexual transmission is crucial for control of the epidemic in many parts of the world (13). Prevention is achieved through reduction in the number of discordant sexual acts or reduction of the probability of HIV-1 transmission in discordant sexual acts. The first can be achieved through abstinence and sex between concordantly seronegative individuals. Abstinence and lifelong monogamous relationships might not be adequate solutions for many people and therefore several interventions aimed at lowering the risk of transmission per discordant sexual act are in the process of clinical testing. Male and female condoms provide a proven and affordable prevention option (15).

In combination, these options are also more commonly referred to as the ABC (abstinence, be faithful, condom use) approach. The basic approach that has been promoted in the context of HIV prevention is:

• Abstinence: The person does not have sex. It is the only 100% safe way of protection against pregnancy, STIs and HIV

• Be faithful: Sex with only one uninfected partner, i.e. monogamous relationships

• Correct and consistent use of condoms provides protection against pregnancy, HIV and STIs

Use of Safe Blood and instruments:

• Use of only sterilized instruments:

Instruments which are used to draw blood and are used in activities such as circumcision, tattooing or ear piercing can be cleaned by leaving them in a solution of bleach (Bleach contains chemicals with oxidizing bleaching action such as sodium hydrochloride and chlorine). These chemicals are also good disinfectants and instruments can be kept immersed in these chemicals (powder or liquid) in the ratio of 1 part chemical to 9 parts of water for 30 minutes or boiled in water for 20 minutes.

• Use of Sterilized syringes and needles:

If an injection is needed, one must ensure that the syringe and the needle are disposable or are properly sterilized. There should never be any sharing of needles and syringes while taking an Injection.

• Blood safety:

The Blood Safety Programme in the country is an integral part of the National AIDS Control Programme. There are a large number of Blood Banks, both government and non-government, which collect and supply safe blood. HIV Zonal Blood Testing Centres have been set up in a number of cities and towns of the country. The centres receive samples of blood from Blood Banks for HIV testing (8).

Under the Drugs and Cosmetics Act 1940 (amended till 1995), it is mandatory to test every unit of blood for HIV.

The Zonal Blood Testing centers/district level Blood Banks have been provided with testing kits and the necessary equipment for conducting tests. The blood of a donor is discarded, if it is tested HIV positive. In order to know the prevalence and progression of HIV in the community and in the country as a whole, the mechanism of sentinel surveillance has been established. This is being done through screening of the blood samples, collected from sentinel sites including STD clinics, antenatal clinics, drug de-addiction clinics, etc. The surveillance data from different States is compiled at the national level. Efforts are also being made to augment voluntary blood donations and to phase out professional blood donors. There is need to promote voluntary blood donation, as it is safer and less likely to be infected with HIV (9).

Mother-to-Child:

Termination of pregnancy was probably the only solution to prevent vertical transmission. Although this option is relevant even today, most HIV positive mothers in our country opt to continue pregnancy due to social pressures and longing for motherhood. Also, registration for antenatal care and subsequent diagnosis of seropositivity takes place late in pregnancy, well beyond the safe limit of 20 weeks for a voluntary termination of pregnancy. Antiretroviral treatment remains the main backbone strategy for preventing mother to child transmission all through pregnancy (26).

As part of a comprehensive approach to addressing HIV and AIDS, the international community has been calling for sustained investments and increased efforts towards universal access to prevention, care, treatment and support. This includes significantly improving access to existing proven means of preventing HIV transmission. At the same time, the world desperately needs new prevention tools in the fight against HIV/AIDS – tools and new technologies that will work with and complement existing prevention methods (11).

Until medical male circumcision trial results were released in late 2006, there had been no significant new biomedical HIV prevention strategy in more than a decade. The US Food and Drug Administration approved the female condom for sale in the US in 1993; in 1994 zidovudine was identified as an effective means of preventing mother-to-child transmission of HIV. These prevention methods were added to those that had already been identified—male condoms, clean needles, blood bank screening, post-exposure prophylaxis and universal precautions for health care workers (11).

There are a number of global efforts underway to develop new technologies to prevent HIV. Currently, there is research being conducted on vaginal and rectal microbicides, vaccines, pre-exposure prophylaxis (PrEP) and HIV treatment as prevention. Research into new prevention technologies (NPTs) is a lengthy process that takes 12 years or more to go through laboratory and animal testing, safety and efficacy studies, regulatory approval and post marketing studies (14).

Medical Male Circumcision

The male foreskin contains a concentration of immune cells that are targeted by HIV during the earliest stages of infection. In particular, the inner side of the foreskin of the penis is highly susceptible to HIV infection; the skin that remains after circumcision is thought to be less, so.

It is possible that circumcision helps protect men from HIV infection by removing these targets for HIV. Since the 1980s, observational studies have found that countries with higher rates of male circumcision have lower rates of HIV infection. In 2006, the first randomized efficacy trial of male circumcision for HIV prevention, conducted in South Africa, showed that circumcision reduced the men's risk of becoming infected by 60% in settings in which transmission risk is largely between men and women. This result was confirmed in two subsequent trials in Kenya and Uganda. Overall, the three studies suggest that safe, sterile male circumcision performed by a trained professional can reduce HIV-negative men's risk of acquiring HIV through vaginal sex by at least 50%. There are no conclusive data on the impact on transmission to female partners. One study found an insignificant trend towards increased risk of male-to-female transmission; this could be related to resuming sexual activity before complete wound healing, and more research is needed (17).

Microbicides

Microbicides are substances that could be applied vaginally or rectally to prevent the sexual transmission of HIV. Microbicides could take the form of a gel, foam, cream or film, be contained in a vaginal ring that releases the active ingredient gradually or in a rectal enema or douche. Microbicides can be contraceptive or non-contraceptive in functionality (9).

A number of vaginal microbicides have been tested in clinical trials. Six vaginal microbicide candidates— nonoxynol-9, Savvy, cellulose sulfate, Carraguard, BufferGel and PRO 2000— have been tested in latest age trials and have been found to be ineffective for HIV prevention. A number of next generation candidates, based on antiretroviral (ARV) drugs, are in earlier stages of clinical trials (19).

Vaccines

A vaccine is a substance that teaches the body to recognize and defend itself against bacteria and viruses that cause disease. A vaccine causes a response from the immune system—the body's defense system preparing it to fight, and also to remember how to fight, if exposed to a specific infection. A vaccine is not a cure, but prevents infection or slows disease progression.

Currently, there are close to 30 clinical trials of experimental HIV vaccines underway in over 20 different countries around the world. The majority of these trials are small Phase I and II safety studies. Two efficacy trials of a vaccine candidate called AIDSVAX ended in 2003. Both of these studies found that the candidate did not protect against infection. One of the trials was among men having a sex with men (MSM) in the US, Canada and the Netherlands. The other trial was among injection drug users (IDUs) in Thailand (17).

In late 2007, vaccinations in two large-scale Phase IIB proofs of efficacy trials (the STEP study) were halted after a planned initial analysis showed lack of efficacy (11).

In September 2009, results from a large-scale Phase III efficacy trial in Thailand, RV144, were released. This prime-boost trial tested a combination of two vaccines called ALVAC and AIDSVAX, and found that the vaccine lowered the rate of HIV infection by 26.2 to 31.2 percent compared to the placebo. The trial results did not show evidence that the vaccine reduced the viral load of those who became infected. Some analyses indicate that the reduction in infections was statistically significant, meaning that the possibility of the result being due to chance is low. However, other analyses indicate that the results were not statistically significant. The results of the trial are undergoing continued analysis and will be important in guiding future vaccine research and provide important evidence that an effective HIV vaccine is possible (9).

Another recent and positive finding in the field of vaccine research was the discovery of two broadly neutralizing antibodies to HIV that reveal a previously unknown site on the virus that could prove to be a good target for vaccine design (21).

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP), is a medical response given to prevent the transmission of pathogens after potential exposure. The PEP for HIV refers to a set of comprehensive services to prevent HIV infection in exposed individuals where the exposure can be occupational or non-occupational (nPEP). These services include first aid care, counseling and risk assessment, HIV testing and depending on risk assessment, the provision of short-term (28 days) antiretroviral (ARV) drugs, with follow-up (4).

The efficacy of antiretroviral drugs as post exposure prophylaxis (PEP) to prevent viral infection was first demonstrated in nonhuman primate models in the early 1990s (2), and subsequently shown in humans by a case-control study in 1997 (3). Because of the ethical difficulties involved in carrying out further studies in humans, subsequent controlled studies of PEP efficacy have been conducted in primate models, especially simian immunodeficiency virus (SIV) infection of macaques. A systematic review of PEP for human occupational human immunodeficiency virus (HIV) exposure concluded that a formal systematic review of all relevant animal studies was warranted because the rationale for PEP is partly based on results from individual primary animal studies (5).

Pre-Exposure Prophylaxis

Pre-exposure Prophylaxis or “PrEP” refers to HIV prevention strategy that would use antiretrovirals to reduce the risk of HIV infection among HIV-negative people. In the strategies that are currently being tested, HIV-negative people would take a daily dose of a single drug or a combination of drugs (30).

PrEP can be compared to birth control pills: whereas a contraceptive pill is taken once daily to prevent pregnancy, PrEP could be taken once daily to prevent HIV infection in case of exposure. Current PrEP trials are testing tenofovir (Viread) or Truvada™ (tenofovir with emitricitabine), two antiretroviral drugs currently used as treatment for HIV infection (39).

According to World Health Organization data (December 2008), 33.4 million of people are HIV infected all over the world. AIDS was the reason of 2.0 million deaths in 2008 (91).
Deaths of children under 15 years old accounted for 280000. There were over 7000 new daily HIV infections. Apart of present HIV prophylaxis programs, such as condome use, prescribing of sterile injection equipment and post exposure prophylaxis (PEP), 2.7 million newly infected were encountered in 2008 (1). Till now, no effective HIV vaccine was developed and knowledge concerning modern vaccine prevention is being challenged (2). All those facts underline need of more effective strategies to reduce incidental infections. Pre exposure prophylaxis (PrEP) is a new HIV prophylaxis program. This method could be used by HIV-negative people in advance of hazardous contacts. Many studies among animals showed better results of this prophylaxis method than those given after HIV exposure (3). It is discussed, that it could be a promising strategy to reduce new infections and further deaths related to HIV/AIDS (4).

PrEP Researches In Primate Models

The potential use of antiretroviral drugs for HIV prophylaxis has been studied extensively in nonhuman primate models of mucosal and parenteral SIV or SHIV transmission and, more recently, in humanized mouse models. Early work with subcutaneous TFV in macaques showed the first proof-of-concept data on the efficacy of ARV prophylaxis against intravenous virus inoculation. Subsequent work showed that post exposure prophylaxis with TFV can protect against intravenous SIV inoculation and helped define the optimal timing for initiating ARV therapy and the need for a 4 wk treatment to achieve protection (6). Indications that ARV drugs administered before exposure could also prevent oral SIV infection came from studies that used different doses of TFV (8). More recently, repeat low-dose macaque models of mucosal transmission have been developed and used to assess PrEP efficacy of different ARV regimens and modalities. These models closely mimic human transmission of HIV in many aspects, including the use of a lower and more physiologic virus inoculum than that used in conventional single high-dose challenge models (17).

In addition, the SHIV challenge contains an R5-tropic HIV-1SF162 envelope similar to naturally transmitted viruses. Virus exposures are repeated to mimic high-risk human exposures, thereby providing the opportunity to measure protection against multiple transmission events in each animal. Using such a model of rectal infection to assess the efficacy of TDF, FTC, or TDF/FTC combination at human equivalent dosing, it was found that daily TDF provided little protection, whereas FTC reduced risk by 3.8-fold. In contrast, TDF/FTC combination was more protective and provided a nearly eightfold lower risk of infection; a higher FTC/TFV dose afforded full

protection (20). These experiments showed a dose-response relationship and suggested that TDF/FTC may be more effective than either TDF or FTC alone against rectal infection (51).
Data on PrEP efficacy against vaginal challenges in macaques are not available. These studies are important because similar to what is observed in humans, oral Truvada in macaques achieves different drug exposures in vaginal tissues than in rectal tissues. However, data from a humanized mouse model showed that a high dose of TDF/FTC combination administered intraperitoneally protected mice against a vaginal HIV infection. Recent findings also showed that oral PrEP with either raltegravir or maraviroc protected humanized mice from vaginal HIV infection, although drug concentrations were not measured (21).

Several important observations of potential relevance to humans have been made from the analysis of PrEP breakthrough infections in macaques. First, drug resistance can emerge if ARV therapy continues after PrEP fails. In one macaque study, two of six animals infected during daily PrEP with FTC or Truvada showed selection for drug-resistant viruses. In both macaques, the M184V mutation associated with FTC resistance was selected, thus reiterating the importance of closely monitoring PrEP failures to minimize drug-resistance emergence (26).

Second, PrEP breakthroughs during FTC and Truvada treatment had lower acute viremias than control animals. A reduction in viremia during PrEP might conceivably contribute to a decrease in HIV-1 transmissibility at the population level and could add to the overall effectiveness of PrEP. Attenuated acute viremia might also reduce early $CD4^+$ T cell depletion, help to preserve immune function, and attenuate the course of HIV infection (30). Animal models have also been used to explore the efficacy of intermittent drug dosing with TFV or Truvada. Intermittent PrEP can reduce the risks of drug toxicities, increase adherence, minimize drug-resistance emergence, and be more cost effective. Both FTC-TP and TFV-DP have long (40 to .100 h) intracellular half-lives in humans and can potentially achieve extended prophylactic activity when administered intermittently. Intermittent PrEP regimens of TDF or Truvada can be designed to be exposure driven or to follow a fixed schedule. Studies in macaques showing protection from oral or rectal SIV/SHIV exposures by a two-dose subcutaneous regimen containing TFV or TFV/FTC have provided the first proof-of-concept evidence for intermittent PrEP. However, the high drug doses and subcutaneous drug delivery might have overestimated efficacy in both studies. More recent work using human equivalent doses of Truvada showed that macaques can be protected from rectal SHIV infection by several PrEP modalities, including a single oral dose given 1–7 d before exposure, followed by a second dose 2 h after exposure. Exposure-driven prophylactic modalities initiated around the time of exposure also maintained protection. These studies showed that intermittent PrEP, particularly with long-acting ARV drugs, can be highly effective and have a wide window of protection. They strengthen the possibility of developing feasible, cost-effective strategies to prevent HIV transmission in humans (14).

Antiretroviral drugs for PrEP

Drug candidates for oral PrEP have largely been selected from currently approved drugs for treatment of individuals infected with HIV-1 because development of drugs exclusively for HIV prevention has not been pursued. Nevertheless, there are currently >30 drugs or drug combinations that are approved for treatment that target key steps in the HIV replication cycle, including inhibitors of virus entry, reverse transcription, integration and maturation (28).

Many desirable drug characteristics for PrEP overlap with those for treatment. These properties include good tolerability and safety, low pill burden, once-daily dosing, long half-life, high potency, and good resistance profiles that do not allow rapid emergence of resistance or broad cross-resistance with other drugs. Pre-integration drugs that prevent the establishment of infected cells are thought to be more suitable than post-integration drugs like protease inhibitors (although evidence to support this assumption is lacking). Additional pharmacokinetic properties that might be important for PrEP drugs targeting sexual transmission include the ability to rapidly reach and accumulate in genital and rectal tissues. In general, non-nucleoside RT inhibitors (e.g., nevirapine and efavirenz) or protease inhibitors (e.g., amprenavir, saquinavir and ritonavir) consistently achieve lower drug concentrations in the genital tract of males and females than in blood plasma (29).

High drug exposure in the female genital tract makes the entry inhibitor maraviroc a potentially attractive drug for PrEP (32). Nucleoside and nucleotide RT inhibitors, including FTC, TDF, zidovudine (AZT) and lamivudine (3TC), also achieve concentrations in the genital tract that are 2–6-fold higher than in blood plasma (35). However, the active drug of nucleoside and nucleotide analogs is the phosphorylated intracellular form and not the extracellular drug measured in plasma or genital secretions. Limited data with TDF have shown that the high extracellular tenofovir (TFV) concentration seen in seminal plasma is also associated with high intracellular levels of TFV-diphosphate (TFV-DP) in seminal mononuclear cells. Intracellular FTC-triphosphate (FTC-TP) concentrations in seminal mononuclear cells were comparable with those seen in peripheral blood mononuclear cells (38). Among the available candidate drugs for PrEP, only TDF and FTC are currently being evaluated in humans. They are administered as TDF alone or in combination with FTC (Truvada).

There are many arguments for selecting FTC and TDF for human clinical trials. In contrast to other nucleoside RT inhibitors such as AZT and stavudine (d4T), both drugs are active in resting and activated T cells. The intracellular half-life of FTC-TP and TFV-DP is also very long (40 h to >100 h) thereby potentially extending their prophylactic activity if administered intermittent (38). FTC and TDF are very potent, have a synergistic to additive effect in vitro, and a favorable safety and drug resistance profile (40). FTC-resistant viruses containing the M184V mutation have a unique resistance pattern not shared by most RT inhibitors; if PrEP fails the antiviral activity of other nucleoside RT inhibitors may be maintained even in the presence of M184V.

When combined with TDF, M184V and not the TDF-associated K65R mutation is the most frequent pathway of resistance to Truvada (41). Both drugs are conveniently co-formulated in a once-daily pill.

Evidence of need for additional HIV prevention methods (eg.PrEP)

Approximately 50,000 people in the United States are infected with HIV each year (17). From 2008 through 2010, HIV incidence remained stable or declined among IDU and heterosexuals of all races and Hispanic/Latino ethnicity, but incidence increased among MSM (12% increase), especially among adolescent and young adult MSM (aged 13-24 years) (22% increase) (12). The greatest number of new HIV infections among MSM occurred in young African American MSM (4,800). In 2010, 63% of the estimated 47,500 new infections were attributed to male-male sexual activity without injection drug use, 4% to male-male sexual activity with injection drug use, 25% to male-female sexual contact without injection drug use, and 8% to injection drug use. Among the 25% of persons newly infected through heterosexual activity, 66% were African-American women and men. These data indicate a need for additional methods of HIV prevention to further reduce new HIV infections, especially (but not exclusively) among young adult and adolescent MSM of all races and Hispanic/Latino ethnicity and for African American heterosexuals (populations with higher HIV prevalence and at higher risk of HIV infection among those without HIV infection) (27).

OBJECTIVES OF THE STUDY

General objective:

To determine the efficacy of HIV pre exposure prophylaxis in non human primate models.

Specific objectives:

To identify and describe the newly emerging HIV prevention methods

To describe the evidence for the needs of additional HIV prevention methods

To describe the ARV drugs which are being used as pre exposure prophylaxis for HIV infection and determine the efficacy of these drugs.

To compare and contrast the effectiveness of these ARV drugs which are being used as pre exposure prophylaxis for HIV, with groups receiving no drug or placebo

To promote the adoption of this HIV prevention method in to the Ethiopian guidelines

METHODS

Conduct of systematic review

The investigator developed a protocol for this systematic review and conducted it in accordance with the prisma (preferred reporting items for Systematic Review and Meta-Analyses) statement (6). A search was conducted to identify studies assessing the efficacy of ARV drugs used for pre exposure prophylaxis.

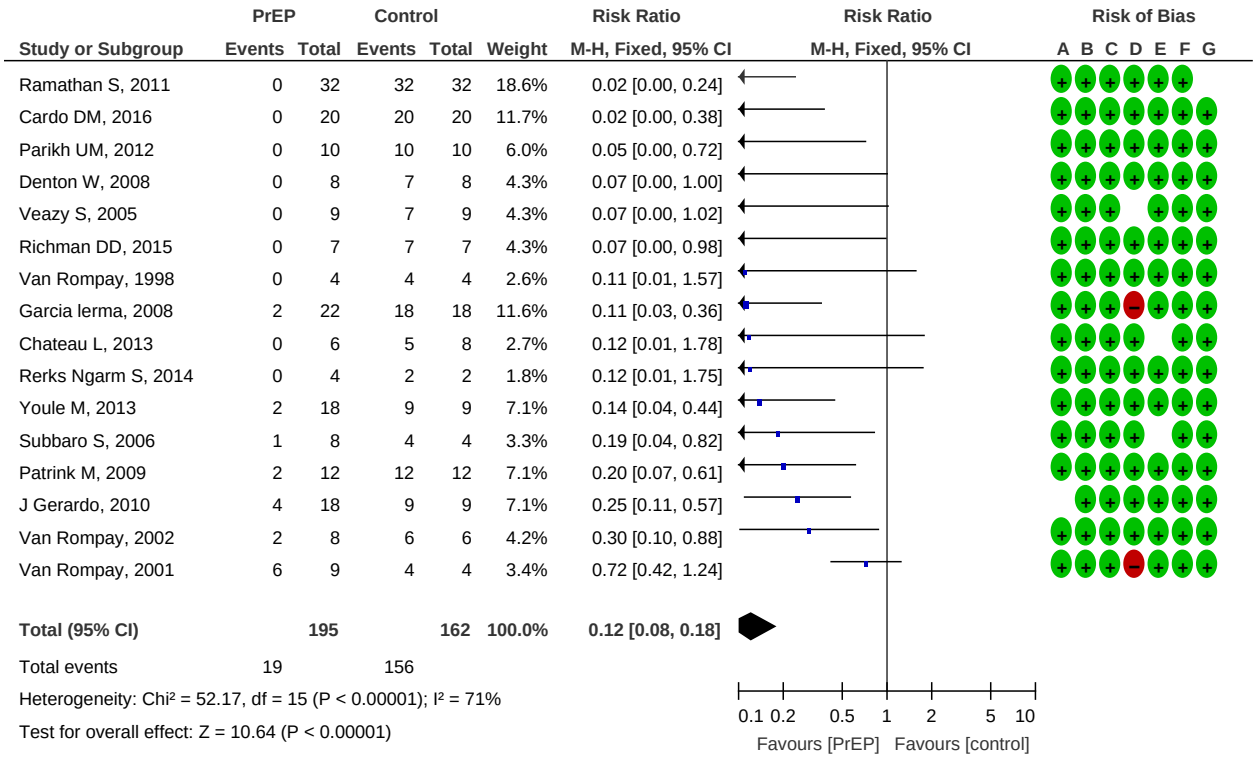
Search Strategy and Selection Process

PubMed, Google Scholar, Web of Science, ScienceDirect, Medscape and the Cochrane library were systematically searched. No date, geographic, or language restrictions were applied. Randomized and non randomized studies were included if they reported sero-conversions among uninfected animals exposed to HIV irrespective of route of exposure and at least 1 animal was earlier given one or more antiretroviral drugs as PrEP. Only nonhuman primate studies were included in the final review. Human studies, in vitro studies, and studies where outcomes were not reported were excluded. The last search was run on September 14, 2016.

Data were extracted independently and in duplicate by 2 scholars (J.W & D. D.) using a standardized data extraction form on key study variables including the following outcome variables: number of animals exposed to virus, type, timing and duration of intervention, and number sero converting. Study quality was assessed using an adapted version of the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies quality checklist, as follows: (1) publication in a peer reviewed journal, (2) allocation concealment, (3) randomization to treatment or control group, (4) blinded assessment of outcome, (5) sample size calculation, (6) statement of compliance with regulatory requirements, and (7) statement regarding possible conflicts of interest [12].

DATA ANALYSIS

To assess the efficacy of the antiretrovirals in preventing virus acquisition, risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated for each study comparing sero-conversion among animals in the intervention group (receiving antiretrovirals) with those who are in the control group (receiving placebo, or untreated controls). Estimates were pooled using the Mantel-Haenszel method to estimate the RR using a fixed-effects model (9). Cumulative meta-analysis was used in which the pooled estimates of each study is pooled each time the results of a new study are published to display the accumulation of evidence over time (10). Heterogeneity was assessed using the I^2 statistic (11). The potential difference of running a fixed effects model was explored in sensitivity analysis. Sources of potential study heterogeneity were explored through a preplanned subgroup analysis to assess the influence of number of drugs and duration of PrEP on risk ratios of sero conversion. The influence of timing of PrEP initiation and type of drug was evaluated through meta-regression. For those animals receiving the intervention, the proportion sero converting was estimated together with corresponding 95% CIs, and data were transformed to stabilize the variance in the raw proportions prior to meta-regression [12, 13]. Publication bias was assessed for the primary outcome of treatment discontinuation by funnel plot and the Egger's test for small study effects [14]. All analyses were conducted using RevMan software, version 5.3 (Cockrane Collaboration), with a P value <.05 considered to be statistically significant.



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias)

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Figure 2. Cumulative meta-analysis of the pooled risk ratios of sero conversion.

RESULTS

From a total of 545 titles screened, 16 studies were taken through for full review, providing data on 357 primates exposed to HIV or SIV (Figure 3). Studies were conducted across 5 countries (United States, France, Japan, Sweden, and China), between 1990 and 2016 (average, 2003). The main species used were rhesus macaques (10 studies) or cynomolgus monkeys (6 studies). The main route of virus exposure was intravenous exposure (12 studies). The main route of drug administration was subcutaneous administration (14 studies). Fifteen studies were randomized, but all reported allocation concealment, three studies didn't report blinded assessment of outcomes, or sample size calculations. Sixteen studies provided evaluable data for the assessment of PrEP efficacy comparing PrEP (195 primates) against controls (162 primates). The risk of sero conversion was 88% lower among animals exposed to PrEP compared with those that did not receive PrEP (RR, 0.12 [95% CI, 0.08–0.18]). Heterogeneity was low (I^2 = 0.0%). Individual study estimates and pooled results are shown in Figure 2. This result did not differ much if a random-effects model was used (RR, 0.14 [95% CI, 0.07–0.28]; I^2 = 0.0%).

Table 6. Efficacy of preexposure prophylaxis modalities in animal models

Reference	Animal	Drug & Dose	Route of drug Admn.	Virus exposure	Interventions	RR, 95% CI
Ramathan S, 2011	Rhesus Macaque	TDF 10mg/kg	SC	IV	TDF	0.02 [0.00-0.24]
Cardo DM, 2016	cynomolgus monkeys	TDF, 20mg/kg	SC	IV	TDF	0.02 [0.00-0.38]
Parikh UM, 2012	Rhesus Macaque	TDF 20mg/kg; FTC 20mg/kg	Oral	Atraumatic rectal	TDF	0.05 [0.00-0.72
Denton W, 2008	Rhesus Macaque	TDF 22mg/kg	SC	IV	TDF	0.07 [0.00-1.00]
Veazy S, 2005	cynomolgus monkeys	TDF 25mg/kg;	SC	Oral	TDF/FTC	0.07 [0.00-1.02]
Richman DD, 2015	Rhesus Macaque	22mg/kg	Oral	IV	TDF	0.07 [0.00-0.98]
Van Rompay, 1998	Rhesus Macaque	TDF, 22mg/kg; FTC 20mg/kg	SC	IV	TDF/FTC	0.11 [0.01-1.57]
Garcia Lerma, 2008	Rhesus Macaque	TDF, 31 kg/kg	SC	IV	TDF	0.11 [0.03-0.36]
Chateau L, 2013	cynomolgus monkeys	25 mg/kg	SC	IV	TDF	0.12 [0.01-1.78]
Rerks Ngam S, 2014	Rhesus Macaque	TDF 30 mg/kg	SC	Atraumatic rectal	TDF	0.12 [0.01-1.75]
Youle M, 2013	cynomolgus monkeys	TDF 27mg/kg	SC	IV	TDF	0.14 [0.04-0.44]
Subbaro S, 2006	cynomolgus monkeys	TDF 32mg/kg; FTC 28mg/kg	SC	IV	TDF/FTC	0.19 [0.04-0.82]
Patrikh M, 2009	Rhesus Macaque	TDF 20mg/kg	SC	IV	TDF	0.20 [0.07-0.61
J Gerardo, 2010	cynomolgus monkeys	TDF 22mg/kg	SC	Atraumatic rectal	TDF	0.25 [0.11-0.52]
Van Rompay, 2002	Rhesus Macaque	Raltegravair (164 mg/kg) or Maraviroc (62 mg/kg)	oral	IV	Raltegravair or Maraviroc	0.30 [0.10-0.88]
Van Rompay, 2001	Rhesus Macaque		SC	IV		0.72 [0.42-1.24]

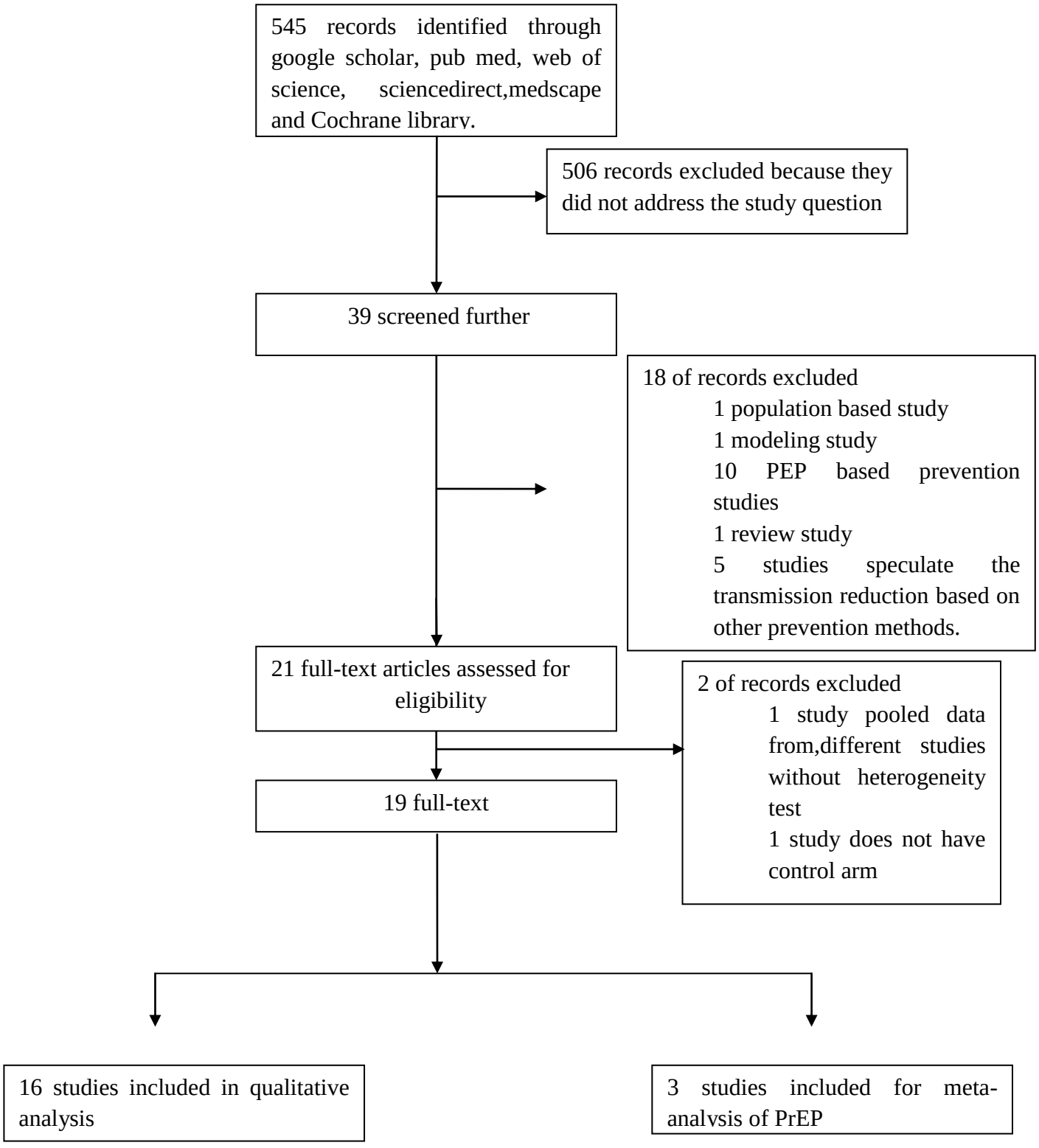


Figure 3. Study selection process. Abbreviations: PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis.

DISCUSSION

This work provides the first systematic review and meta-analysis of PrEP studies in nonhuman primate models of HIV. The investigator was able to pool data across 16 studies, increasing the confidence in the estimate of the effect of PrEP in preventing SIV or HIV acquisition.

Strengths of this review include a broad search strategy that evaluated >500 titles, and compliance with standard approaches to limit potential errors and biases that can be introduced in the conduct of systematic reviews. Although every attempt have been made to systematically and robustly explore these data, there are a number of limitations that should be considered. The overall quality of the included studies was relatively low and no study performed a sample size calculation, and as such, this review may include studies that are underpowered.

In addition, previous animal review work has suggested that an absence of blinding or randomization can have an impact on observed outcomes (38). The inconsistency in reporting of data across studies limited our ability to assess other outcomes that could potentially inform clinical practice, notably duration of treatment and number or class of antiretroviral. Although we would have liked to perform a sensitivity analysis for the impact of study quality, it was not possible in the described dataset. Finally, only studies in the public domain are included in this review and although our analyses did not suggest publication bias it is still feasible that reporting and publication bias exist within this literature.

The estimated protective benefit of PrEP in this meta-analysis (RR, 0.12 [95% CI, 0.08–0.18]) was greater and more precise than that reported in the case-control study in humans (RR, 0.36 [95% CI, 0.06–0.52]) (3). These differences may partly be the result of the larger sample size in our study, and may suggest a greater protective efficacy than previously reported, although any inferences derived from animal studies should be interpreted with caution.

Animal models can help to obtain critical patho physiological information that cannot always be gleaned from human studies. The strengths of the primate model in the case of HIV PrEP include (1) the window it provides on critical events that precede the earliest time clinical signs and symptoms of HIV type 1 (HIV-1) infection disease are manifest; (2) ability to control the virus strain and inoculum dose to achieve infection of a high proportion of animals within a known number of exposures; (3) access to relevant tissues in a relevant time frame, which increases chances to directly observe virus–host cell interactions and critical events; and (4) similarities in anatomy, physiology, and immunology of the rhesus macaques to humans, and the general similarities of pathogenic SIV infection to HIV-1 infection in CD4 T-cell depletion, pathology, and AIDS (40).

Beyond informing proof-of-concept of an intervention strategy that can be translated into clinical practice, the purpose of animal model studies can be to prove a hypothesis in a biological system, or to provide a platform for future research. Despite the many similarities of animals models, inherent differences in route of inoculation, virus titer, drug dose, and duration of intervention, as well as innate biological differences, all need caution against absolute inferences from animal to human studies. Previous studies have suggested that approximately one-third of highly cited animal research translates at the level of human clinical trials, but in some specific animal model fields there have been suggestions that there is too much noise in the animal data to extrapolate findings directly to clinical trials. Data from animal models—despite their limitations—can guide human clinical trials; however, the results of such trials must also feedback continuously into the animal model, so that the animal models can be further improved to increase their relevance and predictability for subsequent clinical trials.In conclusion, the findings of this review provide further evidence supporting the use of PrEP to reduce the risk of HIV infection prior exposure to HIV.

CONCLUSION

The available relevant studies were included in this meta-analysis. My findings support that PrEP has protective effect against HIV infection in high risk populations. If other on-going and large scale studies provide more data on the relationship between PrEP and HIV infection in coming years, it will help to further define the role of PrEP in the prevention of HIV transmission. However, as a strategy, PrEP should always be regarded as a component of prevention but not a replacement for existing methods, and should be integrated as much as possible into existing programs to bring us closer to our goal of full prevention.

By maximizing the potential of test, link, and treating strategies; developing other effective interventions and strategies; and combining them in an optimal manner with proven interventions, such as prevention of mother-to-child transmission and male circumcision, we have the opportunity to bring the HIV epidemic under control.

RECOMMENDATIONS

The investigator advocates well-conducted trials with the statistical power to answer questions about the value of PrEP in preventing HIV infection in various populations and risk groups.

Ongoing and future trials should evaluate other important issues, such as behavioural disinhibition and drug resistance, which are some of the major concerns about the use of chemoprophylaxis for HIV

A more comprehensive and coordinated prevention research strategy that includes basic research, clinical trials, and implementation science is urgently needed

Carefully designed outcome studies are urgently needed to answer questions regarding feasibility, acceptability, adherence, resistance, role of less expensive drugs, and behavioral change to guide implementation.

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