Comparison of the effectiveness of different HIV-1 prevention methods, and their mechanisms.

Akihiko Sawanobori *

Shanghai High School International Division, Shanghai, China

* Corresponding Author Email: 631301070232@mails.cqjtu.edu.cn

Abstract. HIV is an incurable disease that destroys the body's immune system, resulting in acquired immune deficiencies, or AIDs. The United States, responding to UNAIDS' 90-90-90 project, is greatly focused on reducing the number of HIV-infected patients, and the deaths caused by AIDS. Over the past decade, the number of new HIV cases per year decreased by approximately 11.4% from 2010 to 2018, due to the implementation of new prevention methods. According to the study, US was committed to providing interventions to increase public awareness of HIV, reduce death caused by HIV/AIDS, and retain those diagnosed with HIV in medical care. To achieve such a goal, the prevention of HIV plays a key role. The relevant treatment plan is mainly to control the viral load by intervening in the transcription and replication of the virus through drugs. to maintain the relative number of CD4+ cells. This research, therefore, analyses the mechanism and discusses the effectiveness of the prevailing prevention strategies through availability, effectiveness, efficacy, side effects, and percent of correct usage.

Keywords: HIV, AIDS, Prevention Methods, Mechanism.

1. Introduction

Following the 2010-2015, and the later 2015-2020 NHAS [1], progress in stigmatizing and changing the public understanding of HIV/AIDS was accomplished in the US. The implementation of NHAS over the past decade resulted in the US HIV-infected population with suppressed viral load to increase from 27.9% to 56.0% in seven years; from 43,806 new cases in 2010 to 38,789 new cases in 2018, there was an 11.4% decrease in the annual number of new HIV cases [1].

In response to the innovations and advancements of the past decade's development of new options for the virus prevention, the new HIV National Strategic Plan: 2021-2025 mentions the need for investigating new methods of prevention. It established the need to inform the public of the latest information on the options and effectiveness of HIV treatments.

This paper examines the mechanism and effectiveness of the different prevention methods through the analysis of research papers, CDC reports, and databases. The objective is to provide needed information on prevention methods and call into action for further detailed research. The paper searched for randomized trials that reported the effectiveness of different preventions applicable to HIV-1 preventions on PubMed. Only English language and Human studies were included. Mechanisms of drugs are acquired through accessdata.fda.gov. The data were then compiled and analyzed.

2. The different prevention methods

2.1. PrEP

PrEP is a drug that should be taken before possible exposure to HIV through sex or through drug injection. PrEP is a newly developed prevention method that has emerged in the past decade. As of 2019, there was only one approved PrEP medication, and there are only 2 different PrEP medications approved by the World Health Organization (WHO) by now (2022); in form of pills or injections.

2.2. PrEP tablets

The pill medications are provided by two companies: Truvada® and Descovy®. The discussion will be focused on Truvada, for its more common use in the market. The PrEP pills provided by Truvada are composed of emtricitabine and tenofovir disoproxil fumarate (TDF/FTC) compounds. Since HIV is a retrovirus that replicates itself with the aid of the reverse transcriptase enzyme, Truvada can halt the process of HIV replication, thus reducing one's risk of HIV infection.

Emtricitabine is similar to the compound of cytidine but with fluorine in the 5-position. Emtricitabine can be metabolized to add a phosphate group to it, a substance that inhibits the virus reverse transcriptase by taking the place of deoxycytidine 5'-triphosphate, which can also bind with the viral DNA, resulting in the termination of the DNA strand.

Tenofovir disoproxil fumarate is metabolized into tenofovir. It is further phosphorylated to form a compound containing a phosphate group, which occupies the position of deoxyadenosine 5'-triphosphate to inhibit HIV-1 reverse transcriptase. Like emtricitabine 5’-triphosphate when tenofovir diphosphate binds with Viral DNA, it can terminate the DNA strand.

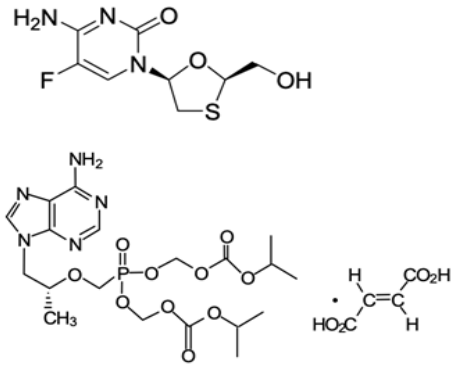

Figure 1. Chemical structure of emtricitabine (top) and Tenofovir disoproxil fumarate (bottom)

A 2-year follow-up study (McCormack 2015) was conducted to examine the effectiveness of oral Truvada on the prevention of HIV transmission in gay and bisexual men. 554 men of the MSM population that had anal intercourse without condoms recently (90 days) were selected. The population was randomly separated into two groups, the immediate group (a group that was given PrEP immediately after being randomly assigned to groups, n=275) and the deferred group (a group that was provided with PrEP after a year of assigning randomly, n=269). A total of 3 reported HIV cases were present in former group and 20 in delayed group. All the 3 HIV cases reported in the immediate group underwent seroconversion before taking PrEP. There were adverse events over the course of the conducted study, with one case being fatal, but there was no association between the fatal case with the PrEP intake. At the same time, all 28 participants (considering the death case) that showed severe adverse events had no correlation to the examined drug. However, symptoms of nausea, headaches, and arthralgia were considered to be related to the test drug [2].

Two different studies were carried out on the effectiveness of oral Truvada PrEP in heterosexual serodiscordant couples. The Partners PrEP study concluded a 75% decrease in the risk of HIV infection in couples that took Truvada PrEP compared to the placebo group. According to the TDF2 study, using Truvada PrEP results in a 62% lower chance of contracting HIV (Thigpen, 2012) [3,4].

2.3. Injected PrEP

The injected PrEP is provided by Apretude®, the active molecule of this specific PrEP is cabotegravir. This mode of PrEP is an injection of 3 ml of 200mg/ml solution through the muscles of the butt. The injection is required for the first two months, and for the following months, injections are bimonthly. Cabotegravir injection can only be applied to those weighing 33kg or above.

Cabotegravir is an integrase strand transfer inhibitor. By binding with the HIV integrase, prohibiting viral DNA from transferring, it inhibits the process of HIV replication cycle.

The FDA conducted a blindfold experiment (HPTN 083 trial) on high-risk MSM and transgender women. A total of 4566 suspects were randomly assigned into two equal groups: one group received Apretude injections and placebo pills daily (2281 participants) the other group received daily oral Truvada with monthly placebo injections (2285 participants). The results revealed that the risk of getting HIV infection is 66% less in those taking Apretude than were those taking Truvada [5].

Another study compared the efficacy of cabotegravir injection PrEP and Truvada® PrEP in women. The study gathered 3224 participants in African countries randomly separating them into two groups; one group received cabotegravir with placebo for TDF/FTC (n=1614), and the other group received TDF/FTC with placebo for cabotegravir (n=1610). The results indicate 0.20 HIV cases/100 person-years in the cabotegravir group and 1.85 HIV cases/100 person-years in the TDF/FTC group. The absolute risk of cabotegravir reveals to be 1.6% (1.0% to 2.3 %) lower than tenofovir disoproxil fumarate and emtricitabine [6].

2.4. Post Exposure Prophylaxis (PEP)

PEP is a medication taken by those that may recently have had exposure to HIV (3 days). PEP would not be considered a typical prevention method, as it is taken after exposure in order to reduce the HIV from replicating. However, PEP medications will still be discussed as they can prevent HIV development. This form of medication usually consists of 3 different drugs a common combination is emtricitabine and tenofovir disoproxil from Truvada® combined with raltegravir from Isentress®.

Raltegravir is an integrase inhibitor that inhibit the virus integrase. With it inhibited, the HIV-1 virus will not be able to integrate the viral DNA into the somatic cells, preventing a viral infection to occur.

A medical trial was conducted to estimate the Raltegravir taken with TDF/FTC. Participants were selected from adults that have HIV-1 and never participated in ART programs. The population was randomly assigned (2:1) to a group that received 1200mg (once per day) raltegravir QD + Truvada (n=531) or a group that received 400mg (twice per day) raltegravir BID + Truvada (n=266). A 90% compliance is observed in 97.2% and 95.9% of the population in the 1200mg QD group and the 400mg BID respectively. At 96 weeks into the study, 81.5% of the 1200mg QD group had plasma HIV RNA concentration of fewer than 40 copies/ml, and 80.1% of the 400mg BID group showed less than 40 copies/ml [7].

2.5. Antiretroviral (ARV) Therapy (ART)

ART is a therapy that should be taken by those that are confirmed as HIV positive, where the antiretroviral drugs can reduce the development of AIDS.

Table 1. Types of ARV drugs, representative drugs of each type, and their general mechanism

Type	Examples of ARV drug	Function
NRTI	emtricitabine, lamivudine, tenofovirabacavir, stavudine, zidovudine, didanosine, zalcitabine	Alter HIV reverse transcriptase
NNRTI	efavirenz, nevirapine, rilpivirine, etravirine, delavirdine	Alter HIV reverse transcriptase
PI	amprenavir, fosamprenavir, tipranavir,	Alter protease
Fusion inhibitor	Fuzeon	Alter the receptors of cells
CCR5	Maraviroc	Alter the receptors of cells
HIV integrase inhibitor	Raltegravir	Alter HIV integrase

In the current market, there are a total of 6 different categories of ARVs: Nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 receptor antagonists, and HIV integrase inhibitors. The latter three are relatively new categories of ARVs. Despite the different categories of ARVs, the central mechanisms are to keep the number of the CD4+ cells high and to keep the viral load suppressed for as low and as long as possible.

NRTIs are drugs that alter the HIV reverse transcriptase to prevent it from translating viral RNA into DNA. By doing so the drug can prevent HIV-1 viruses to be replicated in the cell body. NRTI drugs are usually nucleosides or nucleotides, they require some levels of phosphorylation to activate. Mutations may lead to resistance.

NNRTIs function similarly to NRTIs, however, they are more readily able to alter the function of HIV reverse transcriptase; NNRTIs do not require phosphorylation to come activated. Resistance can more easily be developed

PIs are usually used in combination with other forms of medication, due to the easy development of resistance. The drugs alter proteases' ability to separate large protein molecules into finer pieces which are later used in synthesizing viruses.

Fusion inhibitors are drugs that alter receptors on the host cells or prevent the fusion of the pathogen membrane and that of the host cell, with HIV specifically altering CD4+ cells.

CCR5 are similar to fusion inhibitors but bind and alter with CCR5 co-receptors.

HIV integrase inhibitor is a relatively new form of drug that inhibits the HIV integrase. The HIV intergrade is crucial in the formation of HIV. These types of drugs are provided for people with developed resistance to other forms of medications; resistance against these inhibitors may still develop.

Several studies were conducted to determine how well ART usage is in limiting the transmission of HIV. The studies involve heterosexual couples in whom the HIV-positive partner takes part in ART while decreasing HIV load.

A study from 2010 to 2014 (Roger 2016) was conducted to investigate the transmission rate of HIV-1 in heterosexual and gay couples with one partner being HIV-negative (not taking PEP or PrEP), and the other partner HIV-positive (using ART and HIV-1<200 copies/ml) that usually participated in condomless sex. Results indicate the rate of transmission through any form of condomless sex in these serodiscordant couples to be 0, with a 95% CL of 0.30/100 couple years. In term of male positive couples, the 95% CL is 0.97/100 couple years. As in female positive group, the CL is reported as 0.88 per 100 couple years. And in gay couples, the 95% CL is reported to be 0.71 per 100 couple years [8].

An extension to the previous study (Roger 2019) was conducted on 972 serodiscordant heterosexual or gay couples. In the two follow-up years, there were no associated transmissions in the couples over the course; no PrEP was used, and the HIV-positive partner had suppressed plasma viral load. The estimation of transmission is estimated to be 0 per 100 couple years with the 95% CL being 1.59 per 100 couple years [9].

2.6. Male Condoms

During sexual intercourse, the use of a condom can physically block HIV transmission, a rather convenient and available method to the public. Latex condoms are the most commonly found type of condom and the most effective in preventing STDs. A study was conducted to test the condoms. Results indicate 60 of 89 off-shelf purchasable condoms in the US show no signs of leakage, 21 condoms leaked at rates <1nl/s,7 condoms leaked at rates 1nl/s to 6nl/s, and only one item leaked at about 10nl/s [10].

Some aspects may affect the effectiveness of condoms in preventing HIV. As FDA regulates male condoms, however, the baseline effectiveness of condoms is 99.6% meaning a 1 in 250 chance of encountering a defective condom. Even that being said, the worst-case scenario tested in laboratories indicates that the worst product failure will still reduce 99.99% of volume leakage. [10]

The misuse of condoms is another factor that puts people at risk during every sex action. User error increases the chance of condoms slipping, ripping, and leaking and thus the chance of exposure to HIV. A cohort study (Weller 2002), screening for heterosexual couple population that self-reported as always or never using condoms (not including information about whether condom uses were proper or not,) reveals a homogeneous HIV infection of 1.14 cases per 100 person-years in populations that reported as always using condoms. It also concludes an estimated 80% decrease in the likely hood of HIV infection with the use of condoms among heterosexual couples [11].

Two other analyses were done on condom effectiveness in the MSM population. The first study (Smith 2015) conducted an analysis on two reports, VAX004 and EXPLORE trials. Classifying the screened population by two aspects: self-reported frequency of condom use, and mode of sex with an HIV-positive partner. The frequency is classified into always use, sometimes use, and never use; the mode of sex is classified into insertive anal sex, receptive anal sex, and a combination of insertive and receptive anal sex. In receptive anal sex, the report estimates a 72% reduction in HIV infection between always use a condom and never use a condom population, for insertive anal sex population the estimate is 63%, and for the population that participated in both insertive and receptive annal sex the estimate is 70% [12]. The second study (Johnson 2018) analyzed data from four reports Jumpstart, VPS VAX004 and project explore. An estimated 91% reduction in infection was reported in response to the usage of condoms in MSM that participated in receptive anal sex was made [13].

2.7. Mother-to-child transmission (MTCT)

MTCT may happen in pregnancy, labor, or through breastfeeding. 1.7 million of the total patients are children (0-14 years). Most are acquired through vertical transmission. Without interventions, the rate of MTCT of HIV-1 may range from 30-45% [14].

During pregnancy, there are multiple modes in which the child can come to contact with maternal viruses, through the amniotic fluid, placenta, and or direct contact of blood through the placenta 10-12 weeks into gestation. Other research examined when and how HIV may be transmitted from mother to child in the uterus, but the results were inconclusive [15, 16].

The most common mode of MTCT of HIV, in women that do not take ARV drugs, is during labor, the major reason for this cause is the high viral load in the mother's body and the infant's mucous coming into contact with the mother's blood or secretion. The reduced placental barrier when time is near delivery may cause the infant to come into direct contact with the contaminated blood of the mother. After birth, an infant may still be vulnerable to receiving HIV from the mother, through breastfeeding and other feeding methods. A lactating mother that is not involved in ART program may have detectible viral loads of HIV in the breast milk. Though breast milk has a substantially lower viral load than blood, unhealthy breastfeeding habits may lead to inflammation and cause increasing viral loads in the milk [15, 16].

A study conducted between 2011 to 2014 investigated the maternal antiretroviral therapy (mART) and infant nevirapine prophylaxis (iNVP). The study was carried out and followed up on 2430 mother-infant pairs (the mother having CD4+ cells concentration of ≥350cells/mm3) randomly assigned to one of two groups: mART (n=1219) or INVP (n=1211). The results revealed that 7 infants were infected in both the mART (0.57%) and iNVP (0.58%) groups. After 24 months 97.1% of infants in the mART group were HIV-free, and in the iNVP group, the rate of HIV-free infants was 97.7% [17].

It is clear that TDF/FTC has very few side effects and is certainly effective at preventing HIV-1 infections. The comparison of Apretude injected PrEP and Truvada indicates no inferior effectiveness of Apretude in preventing HIV-1, and since Apretude is an injection enrolled every 2 months, it is able to provide a stronger adherence in comparison to taking pills daily with Truvada. ART is a rather developed form of medication; very few cases of infection are observed in serodifferent couples with one partner enrolled in ART and a suppressed concentration of virus. The prevalence of ARV for HIV prevention is not discussed in the review but suppressed viral load from participating in ART highly reduces transmission. Male condoms are a very cost-effective method of preventing HIV

transmission, as it is unethical to conduct an RCT on condom use, considering the no condom use control group, there are only cohort studies to be analyzed on. The results indicate a significant impact of condom use on HIV transmission. The government might want to look at the benefits that come along with the bimonthly injections and emphasize the promotion of Aperture. Given the effectiveness of condoms, ARV, and PrEP, the use of these prevention methods should be accentuated among the population. PEP's effect is profound for preventing the virus but only if it is consumed as early as possible. It is critical to identify those with HIV and those who had sexual intercourse with (or were assaulted by) a potentially HIV-positive individual self-identify. Mother-to-child transmission is another concern, although the exact path of transmission might be under investigation. Reducing viral concentration in the mother is an effective and crucial method to scale down the MTCT rate.

3. Conclusions

This review provides an overview of the available prevention methods, together with an overview of a common form of prevention. For MSM and heterosexual serodifferent couples, the use of condoms and PrEP can significantly lower the chance of HIV transmission. If the HIV-positive partner participates in ART and viral load is inhibited, the transmission approximately equal to zero. To reduce vertical transmission, drug use is very important. After all, the use of different prevention methods stated in the review does not have to be used exclusively. Multiple preventions can be used at the same time. The review is therefore restricted to the analysis of single prevention's effectiveness in reducing HIV transmission. Future studies may explore further the effectiveness of multiple prevention methods combined, and more precise comparisons and data analyses could then be made.

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