

# A NOVEL OF BIOMEDICAL APPROACH FOR HIV PREVENTION: AN INTEGRATED LITERATURE REVIEW

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## ABSTRAK

Secara global, jumlah kasus baru terinfeksi Human Immunodeficiency Virus (HIV) sudah mengalami penurunan yang signifikan. Akan tetapi di beberapa wilayah negara seperti Afrika dan Asia Tenggara, jumlah kasus baru terinfeksi HIV masih mengalami peningkatan. Upaya pencegahan seperti promosi penggunaan kondom, sunat bagi laki-laki, dan skrining HIV sudah diimplementasikan dengan baik. Tetapi, pendekatan tersebut tetap saja tidak menghilangkan seseorang terkena resiko HIV bahkan mungkin untuk pasangan yang hidup dengan penderita HIV malah meningkatkan resiko mereka tertular HIV. Sehingga dibutuhkan suatu pendekatan lain yang efektif dan mampu meminimalkan sekecil-kecilnya resiko seseorang tertular HIV. Tujuan dari review ini adalah untuk mengkaji efektifitas pendekatan baru yang dikenal dengan pendekatan biomedik terhadap penurunan resiko tertular HIV. Melalui pencarian secara komprehensif di beberapa sumber data seperti PubMed, Embase, Cochrane Library, clinicaltrials.gov, htpn.org, and meta-register dilakukan terutama berfokus pada studi yang diterbitkan dalam Bahasa Inggris pada tahun 2005 sampai 2015. Hasil dari pengkajian tersebut menunjukkan bahwa pendekatan biomedik seperti *pre-exposure prophylaxis* (PrEP) dan *post exposure prophylaxis* (PEP) merupakan suatu pendekatan yang terbukti efektif dalam menurunkan penularan HIV terutama pada kelompok-kelompok dengan resiko tinggi seperti homoseksual atau heteroseksual. Sehingga, pemerintah Indonesia mungkin sudah bisa melakukan pengkajian yang dalam dan membuat pedoman tatalaksana pencegahan HIV dengan pendekatan ini.

**Kata Kunci:** HIV, pendekatan biomedik, pencegahan, pengobatan

## ABSTRACT

The number of new cases of Human Immunodeficiency Virus (HIV) infections has decreased significantly worldwide. However, in some regions such as Africa and South East Asian, new HIV infections remain high. Prevention strategies such as promoting condom use, male circumcision, and early HIV detection have been implemented well. However, all those approaches still putting people at high risk of HIV infection. The purpose of this review is to summarize current evidence about biomedical approach as an effective HIV prevention. A comprehensive computerized literature search was conducted using PubMed, Embase, Cochrane Library, clinicaltrials.gov, htpn.org, and meta-register to retrieve relevant literature published from 2005 to 2015 in English to review a current approach for HIV prevention. Biomedical approaches using antiretroviral drugs have shown good efficacy in the prevention of mother-child transmission for post exposure prophylaxis. Recent evidence has also found pre-exposure prophylaxis (PrEP) to be promising in preventing HIV. Both WHO and CDC recommended to integrate PrEP and post exposure prophylaxis for HIV prevention strategies. Health care policy needs to consider the biomedical approach to HIV prevention, especially in Indonesia. Therefore, Indonesia government may start to develop a clinical guideline and deeply assess the possibility to implement this approach in clinical practice.

**Keywords:** biomedical approach, prevention, HIV, treatment

## INTRODUCTION

HIV/AIDS is a new-emerging disease with serious health risks that affected the growth and development of the country. Globally, the estimation of total patients with HIV in 2013 was 35.0 million. There were 2.1 million people newly infected, showing a 33% decline in the number of new infections from 3.4 million in 2001 (UNAIDS, 2013). The mortality in AIDS patients is declining from 2.3 million in 2005 to 1.5 million in 2013 (UNAIDS, 2013). However, HIV/AIDS was the sixth leading cause of death in the world in 2011 (WHO, 2013). The third highest regions of AIDS death in the world was South and South East Asian Regions (SEAR) (WHO, 2013). Then, Indonesia is one country in SEAR and ranked as the fifth-highest HIV/AIDS prevalence rate of 0.7% (UNAIDS, 2013).

The HIV prevalence in Indonesia was increased significantly unlike many other countries in SEAR, from 5,846 people in 2004 to 118,792 people in 2013 (Indonesia Ministry of Health, 2013). Simultaneously, the number of patients with AIDS also increased from 4,973 in 2004 to 45,650 in 2013 (Indonesia Ministry of Health, 2013). In contrast with the total number and the mortality rate, the number of new HIV infections decreased from 7,004 in 2011 to 5,666 in 2012, it is one of the Indonesian government achievements in preventing HIV transmission (The HIV prevalence in Indonesia was increased significantly unlike many other countries in SEAR, from 5,846 people in 2004 to 118,792 people in 2013 (Indonesia Ministry of Health, 2013). Simultaneously, the number of patients with AIDS also increased from 4,973 in 2004 to 45,650 in 2013 (Indonesia Ministry of Health, 2013). In contrast with the total number and the mortality rate, the number of new HIV infections decreased from 7,004 in 2011 to 5,666 in 2012, it is one of the Indonesian government achievements in preventing HIV transmission (Indonesia Ministry of Health, 2013).

In Indonesia, in 2000, HIV/AIDS was the third leading cause of death after stroke and cardiovascular diseases due to access to get antiretroviral therapy were limited at that time (Health, 2013). The Indonesian government issued a policy to provide antiretroviral (ARVs) freely for patients with HIV/AIDS since 2004. Nowadays, the mortality rate caused by HIV/AIDS dramatically decline from 18.16% in 2000 to 3.12% in 2012 (Health, 2013). It showed that antiretroviral therapy has been successful in reducing the mortality rate caused by AIDS (Chu & Selwyn, 2011). However, in 2012, HIV/AIDS is still the sixth leading cause of death after cardiovascular disease, cancer, diabetes mellitus and COPD in Indonesia (Health, 2013).

Until now, the available treatment for HIV is antiretroviral therapy (ART) (WHO, 2014). In 1996, ART firstly widely adopted in the US and Europe with profound impact on HIV-related morbidity and mortality (Easterbrook, 2001). Hence In 2002, WHO has published the first guidelines for the use of ART for adult HIV (+). The global scale-up of ART over the past decade was lead to the increasing number of people living with HIV because more people were receiving antiretroviral therapy for life-saving (UNAIDS, 2013). It is one of the great achievement of the public health responses to HIV. Approximately, at the end of 2012, an estimated 9.7 million people in low- and middle-income countries were receiving ART. This represents 65% of the global target of 15 million on ART by 2015 set by the UN General Assembly in 2011, and an increase of 1.6 million from the end of 2011 (UNAIDS 2013).

In Indonesia, before the ART was introduced, HIV/AIDS became the third leading cause of death after cardiovascular diseases and diabetes mellitus due to the limitation of antiretroviral therapy at that time. The Indonesian government was launched ART for AIDS patients as part of public health service scaled up in 2005, initially with support from Global Fund. Data from Indonesian

Ministry of Health indicated that by the end of that first year, 2.381 patients were receiving ART. Then in 2013, 33.114 people were receiving ART regularly from 378 health care services (Indonesian Ministry of Health, 2013).

Prevention strategies such as promoting condom use, male circumcision, and early HIV detection have been implemented. However, all those strategies still have risk of people to get HIV infection still (Padia, 2008; Okwunda, 2012). Therefore, effective HIV prevention is imperative and needed. One of the popular HIV prevention nowadays is using the HIV treatment as prevention. Previous evidence has demonstrated that ART can prevent mother-child transmission (Cohen, 2011) and also used as a post-exposure intervention (WHO, 2013). A current study suggested that utilization of ART on the prevention and treatment can reduce half of developing new HIV infection, from 3 million to 1.3 million by 2025 (Schwartlander, 2011). Thus, The President's Emergency Plan for AIDS Relief (PERFAR) and the World Health Organization (WHO) recommend to integrate HIV treatment as prevention especially for high risk groups (WHO, 2014; PERFAR, 2014). Therefore, the purpose of this review is to summarize the evidence of the effectiveness of treatment as prevention in reducing the new HIV cases.

## METHOD

Initial keywords utilized the MeSH terms. Keyword combination utilizes boolean operator with used "AND" and "OR". The search terms were "pre-exposure prophylaxis", "post-exposure prophylaxis", "anti-retroviral chemoprophylaxis", "PrEP", "PEP", "HIV", "prevention". A comprehensive computerized literature search was conducted in PubMed, Embase, Cochrane Library, clinicaltrials.gov, htpn.org, and meta-register to retrieved relevant literature published from 2005 to 2015 in the English language.

The inclusion criteria for studies to be reviewed were Subject were high risk groups included MSM and transgender, heterosexual

man and women, serodiscordant couple. The intervention was pre-exposure prophylaxis and/or post-exposure prophylaxis. Type of study including a systematic review and randomized control trial. Unpublished English paper and observational study were excluded from the review. A total of 765 articles were searched through all data base. Of them, 36 articles were deeply reviewed and critical appraisal all of these articles has been applied.

## RESULTS

### Pre exposure Prophylaxis (PrEP)

PrEP is a new approach prescribes antiretroviral drugs to an HIV-uninfected individual prior to HIV exposure to reduce the likelihood of being infected (Okwunda, 2012; Spinner, 2015; Underhill, 2010). Studies conducted in a variety of high risk groups such, including Men who have Sex with Men (MSM) and transgender, serodiscordant couple, heterosexual, & Injection Drug Use (IUD) have been reported the effectiveness of PrEP to prevent HIV acquisition (Grant, 2010; Beaten, 2012; Anderson, 2012; Thigpen, 2012; Choopaya, 2013). Meta analyses have also highlighted the efficacy of PrEP in HIV prevention with lower adverse events (Okwunda, 2012; Jiang, 2013).

PrEP have shown good efficacy in preventing HIV transmission. A randomized control trial, double blinded was conducted to 2499 HIV-sero negative MSM and transgender women in South America, Africa, and Southeast Asia, to test the effectiveness of tenofovir and emtricitabine. The result of this study showed 44% preventive efficacy of tenofovir and emtricitabine (Grant, 2010). Another study conducted in the HIV serodiscordant couples in Africa to 4758 heterosexual, which the HIV infected partners were not taking antiretroviral therapy and had CD4+ cell counts greater than 495/ $\mu$ L, 52 HIV infections occurred among 1584 couples in the placebo group, 17 HIV infections among 1584 couples in which the HIV uninfected partner

received tenofovir and 13 HIV infections among 1579 couples in which the HIV-uninfected partner received tenofovir and emtricitabine. The result of this study showed that tenofovir had 67% efficacy, and the combination of tenofovir and emtricitabine had 75% efficacy of prevention (Baeten, 2012).

Potential inadvertent consequences with PrEP use, including medication toxicities, drug resistance, and risk compensation has been identified as a challenge in promoting PrEP. Several studies have been reported the use of tenofovir and emtricitabine has associated with a non-progressive decrease in renal function, gastrointestinal symptoms, anorexia, or malaise (Krakower, 2015). Issues of adherence are more prominent in serodiscordant couples. According to a study conducted by Lehman (2015) during the period immediately after PrEP was withdrawn, 121 of 122 serodiscordant were tested for resistance at the visit serodiscordant. The study showed that one or more PrEP-associated resistance mutations were detectable in 23 of 121 serodiscordant (19%).

The WHO and the USA Central Disease Prevention was recommended PrEP for HIV Prevention. PrEP should be offered to individuals at high risk for HIV infection based on background incidence (>2%) or recent diagnosis of sexually transmitted infection (especially syphilis, gonorrhea, or chlamydia), individuals who have taken PEP more than twice in the past year. PrEP should be part of an integrated risk-reduction strategy and may become unnecessary with behavioral changes. Patient at risk should be regularly assessed and PrEP discontinuation considered if behavioral modifications (ie, reduction in high-risk sexual or injection drug use practices) have been made. PrEP considerations for HIV-serodiscordant couples should include whether the HIV-infected partner is taking antiretroviral therapy, the HIV-uninfected partner's access to care, and associated costs (Marazola, 2014; Del Rio, 2015). CDC guidance on PrEP recommends

prescribing a once-daily tablet of tenofovir and emtricitabine after a negative HIV antibody test result is obtained. A 90-day supply of tenofovir and emtricitabine should be given and a follow-up HIV test and assessment of adherence performed before refill. Monitoring for sexually transmitted infections (STIs) should be performed every 6 months and blood urea nitrogen and serum creatinine levels should be assessed every 12 months (CDC, 2012).

### **Post exposure prophylaxis (PEP)**

Previously, guidelines for PEP separated risks that occurred in the context of occupational for health care workers who have been exposed to HIV-infected material via needle sticks or cuts (Kuhar, 2013). The WHO was recommended applying the same principles for sexual or other exposures is administered to those who have had mucosal contact with an HIV-infected individual's blood or genital secretions (Del Rio, 2015). The CDC also recommends non-occupational PEP (NPEP) for HIV uninfected patients after having possible exposures to HIV infected blood, genital secretions, and rectal secretions. Such exposures in adults typically occur in the setting of condom less sex, protected sex with condom failure (CDC, 2012).

PEP is most effective when started as soon as possible after high-risk exposures, ideally within 72 hours but ideally as soon as possible after the exposure (CDC, 2012). Since PEP is more likely to be effective when given sooner rather than later, PEP should be initiated while awaiting test results. Exposures from HIV-infected source patients with undetectable HIV RNA on antiretroviral therapy may be deemed lower risk based on the results of studies with HIV serodiscordant couples, but this assessment should be based on having access to the source's recent laboratory results, as opposed to relying on source self-report (Kuhar, 2013). PEP is warranted if the adherence patterns of an HIV-infected source are unknown. If the HIV status unknown source of the exposure that warranted PEP subsequently tests negative for HIV, PEP can be discontinued. Follow-up HIV testing for the exposed person should occur at

4–6 weeks, 3 months, and 6 months after the exposure, if HIV rapid tests or other third generation antibody tests are used (Kuhar, 2013).

On December 1, 2014, the World Health Organization released its revised PEP guidelines. They recommended using a three-drug low pill burden regimen, favoring tenofovir-emtricitabine plus raltegravir or ritonavir-boosted darunavir, or where these newer agents may not be available, ritonavir-boosted lopinavir or atazanavir. The guidelines also recommended that patients should receive the full 28-day regimen at the initial visit in order to optimize regimen completion (WHO, 2014). Despite the efficacy of PrEP as

prevention other issues such have been raised such as drug resistance and adherence. Adherence to PrEP medications also plays important role in supporting the successful efficacy of PrEP in a prevention program. It was emphasized that non-adherence was associated with both lifetime and recent high-risk sexual behavior (Krakower, 2015). So providing enhanced counseling may be beneficial if resources are available to support this practice.

According to the United States CDC guideline in 2014 and 2016, they provided recommendation guideline for PrEP and PEP as described in Table 1.

**Table 1. The US CDC guideline recommendation for PrEP (2014) and PEP (2016)**

| <b>PrEP</b>  | <b>PEP</b>   |
|--|--|
| Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults  | All persons offered nPEP should be prescribed a 28-day course of a 3-drug antiretroviral regimen. [VII-B1] [VII-C]The preferred regimen for otherwise healthy adults and adolescents<br>1) tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily plus<br>2) mg) once daily plus<br>3) raltegravir (RAL) 400 mg twice daily or dolutegravir (DTG) 50 mg daily. [VI-A2ci]<br>4) [VII-C]<br>5) Alternative regimen for otherwise healthy adults and adolescents is<br>6) Tenofovir DF (300 mg) with emtricitabine (FTC) (200 mg) once daily plus<br>7) darunavir (DRV) (800 mg) and ritonavira (RTV) (100 mg) once daily. [VII-C] |
| PrEP is given for:<br>A. PrEP is recommended as one prevention option for sexually-active adult MSM (men who have sex with men) at substantial risk of HIV acquisition<br>1. PrEP is recommended as one prevention option for adult heterosexually active men and women who are at substantial risk of HIV acquisition.<br>a. PrEP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk of HIV acquisition.<br>b. PrEP should be discussed with heterosexually-active women and men whose partners are known to have HIV infection (i.e., HIV-discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus | Health care providers should evaluate persons rapidly for nPEP when care is sought $\leq 72$ hours after a potential non-occupational exposure that presents a substantial risk for HIV acquisition.<br><br>C. All persons considered for nPEP should have determination of their HIV infection status by HIV testing, preferably by using rapid combined Ag/Ab, or antibody blood tests.<br>• If rapid HIV blood test results are unavailable, and nPEP is otherwise indicated, it should be initiated without delay and can be discontinued if the patient is later determined to have HIV infection already or the source is determined not to have HIV infection.        |

## DISCUSSION

Several evidence supported that treatment as prevention is a promising approach for HIV prevention. According to the CDC guidance on PrEP recommends to prescribe a single-daily table of tenofovir and emtricitabine after the results of HIV test is negative. However, there are some of concern have to consider; pregnant women should be rule out from women, patients should be screened for co-infection, patients should receive a counseling regarding safe sexual practices. Moreover, within a 90-day, patients should be follow up and asses for their adherence. Monitoring for sexual transmitted for every six month and the kidney function also important. Beside that there is also some important consideration regarding the use of PrEP. Whether PrEP can reduce the sexual risk behavior or increase unsafe sexual practice. Those important question is not well-understood yet. Due to people feel safe using the PrEP they might tend to have uncontrolled or less awareness for unsafe sexual practices. Therefore combination of bio behavior and biomedical approach to prevent HIV may be better solution.

In Indonesia, until now, there is only guideline for treatment for HIV and post-exposure prophylaxis which might be not update it yes. No the guideline published for PrEP implementation. Developing guideline for PrEP is important to provide clear direction how to implement PrEP in Indonesia. Although the medication might be not influence recourse ability and capacity may influence the guideline. Therefore, future study on developing guideline specific for HIV population in Indonesia is important. Moreover, the development guideline also need to consider the Indonesia specific culture that especially for screening or to make the guideline received by all Indonesia people. Beside that the most important issues also need to be consider before implementation of PrEP is increasing linkage to HIV care. Because according to data from Indonesia AIDS

commission, the utilization of health care services for HIV is still low. It might due to stigma that prevent people from seeking the health and do not want their HIV status being known by other people.

For almost 30 years, many efforts have been dedicated to reducing HIV transmission. Nowadays, it still seems possible to achieve the goal of an AIDS-free generation. PrEP and PEP can be effective away to prevent HIV transmission, especially among serodiscordant couples. However, linkage to HIV care should be emphasized and supported. Finally, to achieve the AIDS-free generation, we still have to work hard in promoting prevention as paramount part. Despite promoting treatment as prevention to reduce the risk of infection, a behavioral approach for prevention also needs to integrate into prevention strategies. HIV testing as early detection for HIV also should be regularly assessed. Further studies have indicated a role for antiretroviral as pre exposure prophylaxis for HIV-negative individuals and longer follow up of PrEP and PEP in medication toxicity such as renal insufficiency and bone demineralization.

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