

## Pharmacological aspects of prophylaxis pre-exposure (prep) to HIV: a review

Aspectos farmacológicos da profilaxia de pré-exposição (prep) ao HIV: revisão

Aspectos farmacológicos de la profilaxis previa a la exposición (prep) al VIH: una revisión

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### **Edson Bruno Campos Paiva**

ORCID: <https://orcid.org/0000-0002-1074-9790>

Cosmopolitan Faculty, Brazil

E-mail: [bcamposfarma@gmail.com](mailto:bcamposfarma@gmail.com)

### **Caroline Rocha da Silveira**

ORCID: <https://orcid.org/0000-0002-5468-9072>

Cosmopolitan Faculty, Brazil

E-mail: [caroline\\_rocha@live.com](mailto:caroline_rocha@live.com)

### **Isis de Oliveira Kosmisky**

ORCID: <https://orcid.org/0000-0003-4832-0516>

Federal University of Pará, Brazil

E-mail: [isis.kosmisky@gmail.com](mailto:isis.kosmisky@gmail.com)

### **Cleiton da Costa Gomes**

ORCID: <https://orcid.org/0000-0002-2535-7300>

Fibra University Center, Brazil

E-mail: [cleitongomesxp@gmail.com](mailto:cleitongomesxp@gmail.com)

### **Samantha Daniely Gomes Barros**

ORCID: <https://orcid.org/0000-0002-2619-8268>

Higher School of the Amazon, Brazil

E-mail: [samanthaosteus@gmail.com](mailto:samanthaosteus@gmail.com)

### **Roselígia Antônia da Costa Farias**

ORCID: <https://orcid.org/0000-0002-6638-4954>

Higher School of the Amazon, Brazil

E-mail: [ligiafarias6@gmail.com](mailto:ligiafarias6@gmail.com)

### **Zélia de Oliveira Saldanha**

ORCID: <https://orcid.org/0000-0002-3526-5952>

Federal University of Santa Catarina, Brazil

E-mail: [enfzeliasaldanha@yahoo.com](mailto:enfzeliasaldanha@yahoo.com)

### **Antônio Rafael Quadros Gomes**

ORCID: <https://orcid.org/0000-0002-4700-7942>

Cosmopolitan Faculty, Brazil

E-mail: [antonio.quadros@faculdadecosmopolita.edu.br](mailto:antonio.quadros@faculdadecosmopolita.edu.br)

### **Cybelle Silva do Couto Coelho**

ORCID: <https://orcid.org/0000-0002-8579-5249>

Cosmopolitan Faculty, Brazil

E-mail: [cybellecouto@gmail.com](mailto:cybellecouto@gmail.com)

### **Sabrina de Carvalho Cartágenes**

ORCID: <https://orcid.org/0000-0001-6890-0695>

Cosmopolitan Faculty, Brazil

E-mail: [sabrina\\_decarvalho@yahoo.com.br](mailto:sabrina_decarvalho@yahoo.com.br)

### **Abstract**

This article is a narrative review of the literature which aims to describe the main pharmacological aspects of pre-exposure prophylaxis (PrEP) to HIV. The human immunodeficiency virus (HIV) is an infection that has affected people all over the world. However, this number has decreased in recent decades, this is due to the demand for information leading to prevention and adherence to the use of PrEP. PrEP is characterized as a prevention strategy that includes the daily and continuous use of antiretroviral drugs, studies show the effectiveness of the combined use of two daily antiretroviral drugs, tenofovir (TDF) and emtricitabine, commercially known as *truvada*. However, it is extremely important to know and discuss the pharmacological aspects of the drug, and this involves its pharmacokinetics, which in turn includes the mechanisms of absorption, distribution, metabolism and excretion of the drug, as well as other important parameters such as the half-life and elimination time of the drug, and its possible drug interactions, adverse reactions, and its mechanism of action, which is associated with the pharmacodynamic aspects of the drug.

**Keywords:** Pharmacological aspects; HIV; Pre-exposure prophylaxis; PrEP.

### Resumo

Este artigo é uma revisão narrativa da literatura que visa descrever os principais aspectos farmacológicos da profilaxia pré-exposição (PrEP) ao VIH. O vírus da imunodeficiência humana (VIH) é uma infecção que tem afetado pessoas em todo o mundo. Contudo, este número diminuiu nas últimas décadas, isto deve-se à procura de informação conducente à prevenção e à adesão ao uso da PrEP. PrEP caracteriza-se como uma estratégia de prevenção que inclui o uso diário e contínuo de medicamentos antirretrovirais, estudos mostram a eficácia do uso combinado de dois medicamentos antirretrovirais diários, tenofovir (TDF) e emtricitabina, comercialmente conhecido como truvada. No entanto, é extremamente importante conhecer e discutir os aspectos farmacológicos do fármaco, e isto envolve a sua farmacocinética, que por sua vez inclui os mecanismos de absorção, distribuição, metabolismo e excreção do fármaco, bem como outros parâmetros importantes como o tempo de meia-vida e eliminação do fármaco, e as suas possíveis interações medicamentosas, reações adversas, e o seu mecanismo de ação, que está associado com os aspectos farmacodinâmicos do fármaco.

**Palavras-chave:** Aspectos farmacológicos; HIV; Profilaxia pré-exposição; PrEP.

### Resumen

Este artículo es el resultado de una revisión bibliográfica narrativa que pretende describir los principales aspectos farmacológicos de la profilaxis preexposición (PPrE) al VIH. El virus de la inmunodeficiencia humana (VIH), es una infección que ha afectado a personas de todo el mundo. Sin embargo, este número ha disminuido en las últimas décadas, esto se debe a la demanda de información que lleva a la prevención y a la adherencia al uso de la PrEP. La PrEP se caracteriza por ser una estrategia de prevención que incluye el uso diario y continuo de medicamentos antirretrovirales, los estudios demuestran la eficacia del uso combinado de dos medicamentos antirretrovirales diarios, tenofovir (TDF) y emtricitabina, conocido comercialmente como truvada. Sin embargo, es sumamente importante conocer y discutir los aspectos farmacológicos del fármaco y esto implica su farmacocinética, que a su vez incluye los mecanismos de absorción, distribución, metabolismo y excreción del fármaco, así como otros parámetros importantes como la vida media y el tiempo de eliminación del fármaco, así como sus posibles interacciones farmacológicas, reacciones adversas y su mecanismo de acción, que se asocia con los aspectos farmacodinámicos del fármaco.

**Palabras clave:** Aspectos farmacológicos; VIH; Profilaxis previa a la exposición; PrEP.

## 1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) was discovered in the 80's and became a milestone for humanity, observing the increase in the incidence of women infected by the HIV virus (GIBAS, et. al. 2019). According to Nobre, et al., (2008, p. 12) the human immunodeficiency virus (HIV) "[...] is today the largest and most serious pandemic of this century, according to data from the World Health Organization (WHO) [...]", with large numbers of patients as well as infected individuals in the world, although they are asymptomatic (Nobre, et al., (2008, p. 12))

The human immunodeficiency virus (HIV), is an infection that has affected people around the world. However, that number has been decreasing in recent decades, this occurs due to the search for information that leads to prevention and adherence to treatment with Pre-exposure Prophylaxis - PrEP (Eakle; et al., 2018). However, 1,8 million new infections still occur globally each year and 5 thousand daily 40 thousand in the US (Gibas, et. al. 2019)

In Brazil the rate of infection growth has increased dramatically, according to the (Ministry of Health's, 2017) HIV/AIDS Epidemiological Bulletin, from 2007 to June 2017, 194,217 cases of HIV infection in Brazil were reported in Sinan, 96,439 (49.7%) in the Southeast, 40,275 (20.7%) in the South, 30,297 (15.6%) in the Northeast, 14,275 (7.4%) in the North region and 12,931 (6.7%) in the Midwest region. In 2016, 37,884 cases of HIV infection were reported, of which 3,912 (10.3%) in the North, 7,693 (20.3%) in the Northeast, 15,759 (41.6%) in the Southeast, 7,688 (20.3%) in the South and 2,832 (7.5%) in the Center-West the (Brazil, 2019).

The HIV infection presents a number of events called acute retroviral syndrome (ARS), with findings of fever, cephalgia, asthenia, adenopathy, pharyngitis, sudorese, lymphadenomegaly and digestive symptoms like nausea, vomit, diarrhea and weight reduction (Ministry of Health's, 2017). The diagnostic of HIV infection is performed through detection from HIV viral burden the (Brazil, 2017).

In 2012 the use of PrEP was approved in the United States. And recently, the Centers for Disease Control (CDC), an agency of the U.S. Department of Health and Human Services, recommended the use of this medication to prevent HIV infection for people at higher risk of acquiring this virus (Hendrix, 2018)

In the year 2015, specifically in September, the WHO recommended all countries to start using Prep as an additional form of prevention for people at substantial risk of HIV infection as part of combination prevention (World Health Organization, 2017).

In 2016, the United Nations Assembly concluded that by 2030 there is a need to eradicate AIDS cases and decrease the number of new cases of HIV infection worldwide (Hiilis et al, 2020). For this reduction in cases to be possible, there is a need to use the five pillars of prevention against HIV, among them the use of Prep (Hiilis et al, 2020).

Pre-exposure prophylaxis to HIV (PrEP) is characterized as a prevention strategy that includes the use of antiretroviral drugs for daily and continuous. From 2010 results of several studies show the effectiveness of the combined use of two daily antiretrovirals, tenofovir (TDF) and emtricitabine, commercially known as truvadase (Brazil, 2020).

PrEP has been shown to be effective in the acquisition of HIV through sex, among men who have sex with other men, transvestites, and women sex workers, showing an effectiveness of 99% in the individual who uses it on a regular basis (Brazil, 2020).

According to Hills (2020), The use of the Prep should be associated with other extremely important precautions, such as sex education, health education, human rights programs for special groups, condom use programs, and voluntary male circumcision, thus forming the five pillars of prevention.

The World Health Organization (WHO) has recognized PrEP as a drug with strong potential that is essential to confront the HIV/AIDS pandemic, recommending the development of new studies to evaluate how this prevention strategy can be used in the whole world, since each country has a different health system from the others (World Health Organization, 2010).

The objective this article is to describe and discuss the pharmacological aspects of HIV pre-exposure prophylaxis (PreP), in terms of pharmacokinetics, pharmacodynamics, as well as possible adverse effects and potential drug interactions.

## **2. Methodology**

This is a review study of narrative literature of qualitative nature, for this research was conducted a bibliographic survey in databases such as: Scielo (Scientific Electronic Library Online); MEDLINE (National Library of Medicine); LILACS (Latin American and Caribbean Literature), BVS (Virtual Health Library), as well as books and periodicals, specialized journals, dissertations, and theses (Gonçalves, 2019).

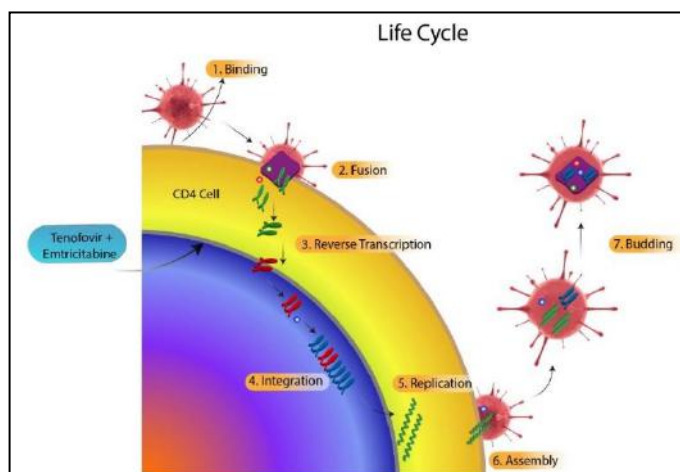
As for the inclusion criteria: articles were selected in full which addressed the subject and these published in the year 2011 to 2022, in the aforementioned databases, and the following descriptors were used: pharmacology and prep, pharmacokinetics and pharmacodynamics, prep and drug interactions, prep and adverse effects. Exclusion criteria: articles that did not fit the above criteria were not selected for the study.

## **3. Results and Discussion**

### **3.1 General Feature, Pharmacological Agents and Description**

The Prep has emerged as a new weapon of combination prevention for people who are not living with HIV, according to Anderson et al (2011), the Prep is a combination of antiretroviral drugs (tenofovir and emtricitabine), both are nucleotide and reverse transcriptase inhibitor analogues (NRTIs) [Anderson et al, 2011; NIH, 2021).

**Figure 1:** PrEP's Mechanism of action.



Source: Prepared by the authors according to the article retrieval process in the databases.

### 3.2 Pharmacokinetic And Pharmacodynamic Aspects of Tenofovir (TFV).

Tenofovir disoproxil fumarate (TDF) is already used by people living with HIV, but this drug is also used in the composition of PrEP and presents a water-soluble characteristic, showing low absorption by the oral route, thus, it is presented as a prodrug in order to improve its performance in the systemic circulation (Yager & Anderson 2020; Kearney et, al 2004).

TDF presents in its pharmacokinetic characteristic an average oral bioavailability of 25%, while its plasma half-life and elimination time is around 14-17 hours, as for binding to plasma proteins, TDF shows significantly low binding, which is around <8%. (Chapman & cols, 2003; Goodman & Gilman, 2014. (p. 1837)).

It is worth noting that this drug goes through the process of metabolism after its distribution in the bloodstream, because TDF is a prodrug that becomes active in the first-pass effect, making the molecule already active and water soluble, thus being more likely to be excreted. (goodman). Its excretion process occurs by glomerular filtration and active tubular secretion, which causes the drug to be excreted from the body in about 70-80% (Goodman & Gilman, 2014. (p. 1837); Yager & Anderson 2020)

TDF is shown to be well tolerated at usual doses, with few adverse effects of significance observed, with the exception of flatulence which is very present. Clinical studies applied to renal tubular cells in vitro, have shown that the drug does not present toxicity levels, however episodes of acute renal failure and Fanconi syndrome have been observed, this means that this drug should be used with caution in patients who have pre-existing renal disease (Gallant & Moore, 2009; Goodman & Gilman, 2014. (p. 1837)).

Regarding possible drug interactions, TDF has a low metabolism by CYP type enzymes, this means that the drug neither inhibits nor induces the enzymes. But the few pharmacokinetic interactions that this drug has shown cannot be underestimated, as they are potentially important (Gallant & Moore, 2009; Goodman & Gilman, 2014. (p. 1837))

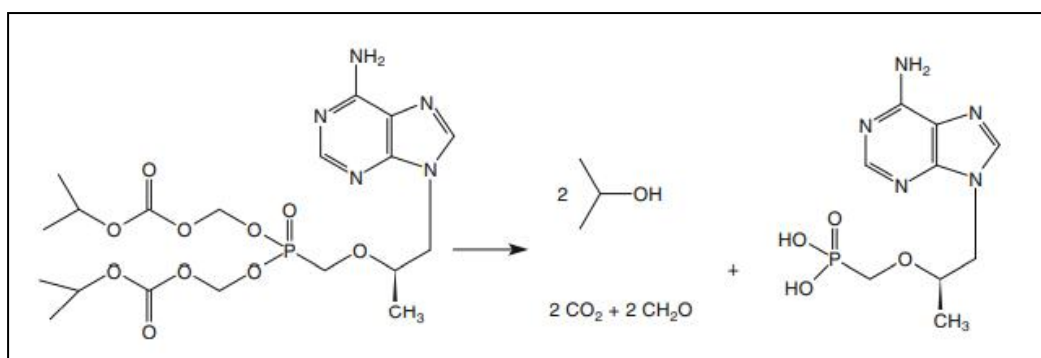
Although TDF does not show strong induction of CYP, studies also show a reduction in the ASC of atazanavir by 26%; moreover, the use of ritonavir even in low doses such as 100mg 2 times/day increases the ASC of tenofovir by 34% (Robbis & cols, 2003, Chapman & Cols, 2003, Goodman & Gilman, 2014. (p. 1837)).

Studies have shown that the use of TDF in doses of 300mg ended up increasing the area over the curve (ASC) of didanosine by an average of 44-60%, this may be due to possible inhibition of purine nucleoside phosphorylase by tenofovir and tenofovir monophosphate (referencia). Thus, despite the low scientific evidence of drug interactions, it is possible to observe that TDF can act by modulating the action of other drugs (Foster & cols, 2009, Goodman & Gilman, 2014, (p. 1638))

About pharmacodynamic aspects, the TDF is a prodrug derived from adenosine nucleotide 5'-monophosphate, composed of an incomplete ribose ring (Ganesh, 2019). It is a competitive inhibitor of reverse transcriptase, which competes with deoxyadenine 5'-triphosphate the TDF molecule, after losing two ester molecules through hydrolysis, is transformed into Tenofovir (TFV), acting intracellularly (Jayachandran, 2020).

A monophosphate intermediate (TFVmp) is generated as result of phosphorylation of the TFV molecule, which is mediated by adenosine monophosphate kinase (AMP), thus converting the molecule into its biophosphated form (TFVdp) by nucleoside diphosphate kinase (NDP), which enables its integration into the nascent viral DNA chain and disruption of replication due to the absence of the 3'hydroxyl grouping in its ribose ring. (Jayachandran, 2020).

**Figure 2.** Conversion of tenofovir disoproxil fumarate to tenofovir.

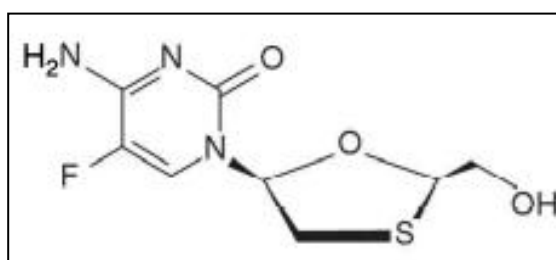


Source: Prepared by the authors according to the article retrieval process in the databases

### 3.3 Pharmacokinetic And Pharmacodynamic Aspects of Emtricitabine

Emtricitabine is a cytidine analog that is chemically similar to lamivudine, meaning that both have similar modulating properties at their receptors, this similarity is due to the two chiral centers which are produced in the pure enantiomer form (2R,5S-5-fluoro-1-[2-(hydroxymethyl)-1,3oxhiatiolan-5-yl] cytosine (Saag, 2006; Bernardo 2020)

**Figure 3:** Chemical structure of emtricitabine.



Source: Prepared by the authors according to the article retrieval process in the databases.

Emtricitabine presents in its pharmacokinetic characteristic an oral bioavailability of 93%, this means that the drug is well absorbed, it is important to emphasize that in the presence of food emtricitabine will present alteration in the C<sub>max</sub> (which occurs within 1.5h after oral administration), however this will not affect the ASC, this means, that the drug can be administered at any time of the day (Wang, 2004; Goodman & Gilman 2014, p.1638))

Emtricitabine has a very long intracellular half-life, approximately 39h, which justifies the once-daily dosage, the drug also has a long-lasting elimination half-life of around 8-10h (Muller & Kalhil; Bernardo 2020)

According to Bang and Scott (2003), the elimination half-life of the drug averages 8-10h in people living with HIV, however there are no reports on the exact elimination time in patients not living with HIV, what can be observed is that after multiple doses of emtricitabine at a concentration of 200mg/day its half-life is close to 39h

Regarding its metabolism, studies show that emtricitabine is not metabolized by cytochrome P450 enzymes, this justifies its low drug interaction with drugs metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C9 and CYP2C19, CYP2D6 CYP3A4 (Gilead Sciences, 2004; Kiang, 2016)

The drug is recovered after its oral administration, approximately 86% of its metabolites in urine and 13% in feces and its elimination in its unchanged form occurs by glomerular-type filtration, since the clearance of emtricitabine is higher than creatinine (Bang; Scott 2003; Goodman & Gilman 2014, (p.1638))

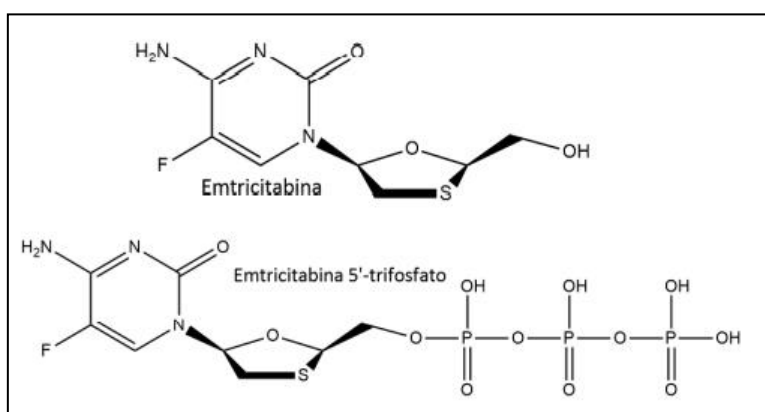
According to Saag (2006) and Goodman and Gilman (2014, p.1638), emtricitabine is the antiretroviral drug with the lowest level of toxicity compared to other drugs, which justifies its similarity to lamivudine, meaning that the drug has no significant toxic effect on mitochondrial DNA in vitro (Bernardo, 2020)

However, a prolonged exposure to the drug is associated with the process of hyperpigmentation of the skin, especially in areas exposed to sunlight, another report that has also been made is in relation to the occurrence of elevated markers of liver transaminases, hepatitis and pancreatitis, since this prolonged exposure is also associated with the use of other antiretroviral drugs (Saag 2006; Goodman & Gilman 2014, p.1638)

About its pharmacodynamic aspects, it is through passive diffusion that FTC penetrates into cells and is phosphorylated by the enzyme Deoxycytidine kinase, then taking on the form of FTC-monophosphate (FTCmp). (Muller & Khalili 2021; Goodman & Gilman 2014)

The second phosphorylation is mediated by cytidine monophosphate kinase (CMP), transforming FTC-mp into FTC-diphosphate (FTC-dp). Finally, the FTCdp undergoes a last phosphorylation through the action of nucleoside diphosphate kinase (NDP), assuming the active form FTC-triphosphate (FTCtp) capable of binding to the nascent portion of the viral DNA chain, ending the TR (Muller & Khalili 2021; Goodman & Gilman 2014)

**Figure 4:** Chemical structure of emtricitabine and its active metabolite.



Source: Prepared by the authors according to the article retrieval process in the databases.

### 3.4 PrEP Adverse Reactions

The most common side effects seen are principally gastrointestinal tract origin and more prevalent at the start of use, but subside within amonth of useas PrEP, and include headache, abdominal pain, nausea, vomiting or diarrhoea. Moreover,

other adverse events are observed, such as, dizziness, headache, fatigue, weight loss, shortness of breath, cough, anxiety, fever or joint and muscle pain (Tetteh et al., 2017).

It is important to emphasize that prolonged use offers risk factors such as include age, duration of treatment, especially with TDF. In addition, antiretroviral prophylaxis can result in elevated baseline creatinine and transaminases. These enzymes are related to kidney and liver damage markers, so high levels of these markers indicate damage to these organs (Thigpen et al., 2014; Mugwanya et al., 2016).

Furthermore, there are reports of potentially serious side effects in the daily use of PrEP or TDF, including liver, kidney, pancreatic problems, hypophosphatemia, proteinemia or glucosuria, in addition to reducing bone mineral density, which increases the likelihood of osteoporosis (Berg et al., 2010; Baeten et al., 2012). Other studies also point to increased levels of lactic acid in the blood, in some people taking tenofovir and emtricitabine (Berg et al., 2010; Baeten et al., 2012; Choopanya et al., 2013).

According to Medland et al. (2017), TDF is associated with nephrotoxicity in HIV-infected patients, with an incidence of 1.09/1000 person-years, where this nephrotoxicity tends to develop later in the course of therapy (ie, approximately  $55 \pm 28$  months after initiation of therapy [range, 12-98]) [Medland et al., 2017]. Another relevant finding concerns kidney damage, which is usually due to interference in DNA synthesis and mitochondria, generating metabolic disturbances and loss of cell function, especially in use over time. These observed changes may be associated with the development of Fanconi syndrome or type IV renal tubular acidosis (Riddell et al., 2018)

#### 4. Final Considerations

Decreasing HIV transmission is a major public health challenge. HIV transmission rates increase worldwide, especially during the COVID-19 pandemic period (WHO, 2021). But frequent use of PrEP can prevent the emergence of additional new cases of HIV infection. Given this scenario, in 2012 the safety and efficacy of TDF/emtricitabine for PrEP, as a possibility to slow down viral transmission. The healthcare team has invested in health education for promiscuous patients about the risks and benefits of PrEP, physicians emphasizing that, when taken consistently, TDF/emtricitabine is effective in preventing HIV infection (Mayer et al., 2016). However, TDF/emtricitabine does not protect against other STIs; therefore, the continuing importance of condom use.

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