# Tenofovir disoproxil fumarate

Essential medicine status

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.2. Antiretrovirals > 6.4.2.1. Antiretrovirals > Nucleoside/Nucleotide reverse transcriptase inhibitors

ATC codes: J05AF07

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| **Indication** | Contact with or exposure to human immunodeficiency virus ICD11 code: QC90.6 |
| **INN** | Tenofovir |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | Oral > Solid: 300 mg tablet (equivalent to 245 mg tenofovir disoproxil) |
| **EML status history** | First added in 2017 (TRS 1006) |
| **Sex** | All |
| **Age** | Adolescents and adults |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Tenofovir disoproxil fumarate |
| **DrugBank** | Tenofovir disoproxil fumarate (Tenofovir disoproxil) |

## Expert Committee recommendation

The Expert Committee recommended the additional indication for single-agent tenofovir disoproxil fumarate (TDF) and the fixed-dose combinations of emtricitabine + TDF (and lamivudine + TDF as an alternative, where FTC is not available) on the EML for use as preexposure prophylaxis (PrEP) of HIV infection. The Committee noted evidence of reduced risk of HIV infection associated with TDF-containing PrEP in study populations demonstrating high adherence to therapy, and the recent inclusion of oral PrEP containing TDF in WHO guidelines for patients at substantial risk of HIV infection.

## Background

TDF and FTC + TDF are currently included on the EML for the treatment and prevention of HIV infection. Prevention is specified as post-exposure prophylaxis and prevention of mother-to-child transmission. The current listing for FTC + TDF notes that FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, resistance patterns and clinical trials of antiretrovirals. This should be interpreted to mean that 3TC + TDF is included on the EML (by proxy).

## Public health relevance

Globally, the estimated annual number of new HIV infections among adults has remained reasonably static since 2010, at an estimated 1.9 million infections. No decrease or small declines (<5%) have been achieved in most world regions, while a 57% increase in new HIV infections was reported in eastern Europe and central Asia between 2010 and 2015. This represents a challenge for achievement of the milestone agreed by the United Nations General Assembly in 2016 – that is, to reduce new HIV infections to fewer than 500 000 globally by 2020 (1, 2). In 2015, WHO recommended use of daily oral PrEP containing TDF (i.e. not limited to only FTC + TDF) for individuals at substantial risk of HIV infection as part of combination prevention approaches, based on clinical trial evidence supporting efficacy of TDF for PrEP across a variety of settings and populations. This

recommendation was made available on an early-release basis, in advance of the 2016 revision of Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3). The rationale for the early release was to help countries anticipate the implications of the recommendation and allow them to initiate necessary steps to ensure that national standards for HIV prevention and treatment would keep pace with scientific developments (4).

## Benefits

The application from the WHO Department of HIV/AIDS presented the findings of a systematic review and meta-analysis of 17 studies (14 randomized controlled trials (RCTs) and three observational, open-label extension cohort studies; more than 15 000 participants), investigating the effectiveness of PrEP using TDF either alone or in combination with FTC in people at substantial risk of HIV infection (5). Study populations included serodiscordant couples, people who inject drugs, men who have sex with men, female sex workers, transgender women, and heterosexual men and women. The quality of evidence for efficacy outcomes was rated as high following the GRADE approach. Ten RCTs in the meta-analysis compared PrEP with placebo. A 51% reduction in risk of HIV infection was associated with PrEP (TDF +/– FTC) across populations (risk ratio (RR) 0.49; 95% confidence interval (CI) 0.33–0.73; P = 0.001). In studies that measured adherence, PrEP was found to be most efficacious in reducing risk of HIV infection in the subgroup with high (≥70% drug detection) adherence (RR 0.30; 95% CI 0.21–0.45; P < 0.0001). Among studies with low adherence, PrEP was not associated with a reduced risk of infection (RR 0.95; 95% CI 0.74–1.23; P = 0.7). There was no significant difference in risk reduction between PrEP regimens: TDF alone (RR 0.49; 95% CI 0.28–0.86; P = 0.001) and FTC+TDC (RR 0.51; 95% CI 0.31–0.83; P = 0.007). Two RCTs compared PrEP with no PrEP and contributed HIV-infection data to the metaanalysis. PrEP was associated with an 85% reduction in the risk of HIV infection compared with delayed PrEP (RR 0.15; 95% CI:0.05–0.46; P = 0.001). No studies involving 3TC + TDF were included in the systematic review. The application states that there have been two clinical studies of this combination for prevention of mother-to-child transmission of HIV, which provide indirect evidence and serve as “proof of principle” for use of this combination for PrEP. The application from Gilead Sciences Inc. described efficacy results of the iPrEx (6) and the Partners PrEP (7) studies, both of which were included in the WHO-commissioned systematic review (described above). The iPrEx study compared PrEP using FTC + TDV with placebo in HIV-negative men or transgender women who have sex with men. FTC + TDF was associated with a 44% reduction in the incidence of HIV compared with placebo (hazard ratio (HR) 0.56; 95% CI 0.37–0.85; P = 0.005). Efficacy was related to adherence, with patients with detectable study-drug levels having a relative risk reduction of 92% (95% CI 40–99%; P < 0.001) (6). The Partners PrEP study compared PrEP using TDF alone, FTC + TDF and placebo in 4747 HIV-serodiscordant heterosexual couples in Kenya and Uganda. Compared with placebo, relative reductions in the incidence of HIV infection of 67% and 75%, respectively, were observed for TDF alone (HR 0.33; 95% CI 0.19–0.56; P < 0.001) and FTC + TDF (HR 0.25; 95% CI 0.13–0.45; P < 0.001). The difference between TDF and FTC + TDF with regard to HIV-protective effects was not significant (7).

## Harms

The WHO-commissioned systematic review concluded that TDC-containing PrEP presented few significant safety risks and no evidence of behavioural risk compensation (5). Among 10 RCTs comparing PrEP with placebo, there was no difference in the rates of any adverse event (RR 1.01; 95% CI 0.99–1.03, P = 0.27). Similarly, there was no difference in rates of any grade 3 or 4 adverse events between PrEP and placebo groups (RR 1.02; 95% CI 0.92–1.13; P = 0.76). No increases in sexual risk behaviour, pregnancy-related adverse events or hormonal contraception effectiveness were associated with PrEP. Participants randomized to PrEP had a higher risk of developing TDF- or FTC-resistance compared with placebo among those infected with HIV at the start of therapy (RR 3.34; 95% CI 1.11–10.06; P = 0.03). There was a greater risk of developing FTC-resistance than TDF-resistance. The risk of drug resistance in the PrEP setting must be considered in the context of the prevention of HIV infection and the reduction in lifelong antiretroviral therapy (ART). The risk of drug resistance due to ART is likely to be greater than the risk of drug resistance due to PrEP (8). The application from Gilead Sciences Inc. described the known adverse effects of FTC + TDF on renal and bone health, and the events that occurred with greater frequency in patients given FTC + TDF treated in the RCTs and open-label extension trials (nausea, headache, weight loss). The application noted the findings in a meta-analysis by Fonner et al., which are the published results of the WHO-commissioned review described above (9).

## Additional evidence

N/A

## Cost / cost effectiveness

The HIV incidence threshold for cost-saving implementation of PrEP will vary with the relative costs of PrEP versus HIV treatment and the expected effectiveness of PrEP. A systematic review of cost–effectiveness studies of PrEP concluded that providing PrEP to populations at the highest risk of HIV exposure was the more cost-effective strategy (10). The Gilead application stated that the wholesale acquisition cost of FTC + TDF in USA is US$ 1466 for 30 days' supply (30 tablets). It stated that developing countries classified as low or lower-middle-income by the World Bank, and countries with unmet HIV/AIDS disease burden, are designated as "access countries", which are charged only for production and related costs. The application also stated that the price for a 30-day supply of FTC + TDF to access countries is US$ 20 (approximately US$ 240 per year). The WHO Global Price Reporting Mechanism reports that the median treatment cost per year in 2016 for FTC + TDF is US$ 55.10. Refer to TRS 1007 for further information regarding the Expert Committee's consideration of cost/cost-effectiveness.

## WHO guidelines

WHO's 2016 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (3) recommend that oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence). "Substantial risk" is currently defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP. Risk thresholds for offering PrEP are likely to vary on the basis of local considerations such as epidemiological factors, available resources, cost, feasibility and demand.

## Availability

There are several manufacturers of TDF-containing products for PrEP, many with WHO prequalification status. There is some question regarding the ready availability of single-agent TDF products for treatment and prevention programmes, with low demand due to the availability of preferred fixed-dose combination formulations containing TDF. To date, only FTC + TDF has approval from stringent regulatory authorities for use as PrEP.

## Other considerations

N/A


1. Prevention Gap Report 2016. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2016 (http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf, accessed 20 February 2017).
2. Global AIDS Update 2016. Geneva: Joint United Nations Programme on HIV/AIDS; 2016 (http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf, accessed 20 February 2017).
3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 20 February 2017).
4. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1, accessed 20 February 2017).
5. Fonner V, Grant G, Baggaley R. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, and sexual and reproductive health outcomes. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/189977/1/WHO_HIV_2015.36_eng.pdf?ua=1, accessed 20 February 2017).
6. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.
7. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
8. van de Vijver DA, Nichols BE, Abbas UL, Boucher CA, Cambiano V, Eaton JW et al. Preexposure prophylaxis will have a limited impact on HIV-1 drug resistance in sub-Saharan Africa: a comparison of mathematical models. AIDS. 2013;27(18):2943–51.
9. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS. 2016;30(12):1973–83.
10. Gomez GB, Borquez A, Case KK, Wheelock A, Vassall A, Hankins C. The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies. PLoS Med. 2013;10(3):e1001401.