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CURRENT OPINION

Lamivudine/Tenofovir Disoproxil Fumarate is an Appropriate PrEP Regimen

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Abstract
Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) co-formulated with emtricitabine (FTC) or lamivudine (3TC) is recommended as an additional prevention option for persons at substantial risk of HIV infection by both the World Health Organization (WHO) and the US President's Emergency Plan for AIDS Relief (PEPFAR). The WHO and PEPFAR consider 3TC clinically interchangeable with FTC for PrEP given comparable pharmacologic equivalence, resistance and toxicity patterns, and indirect clinical trial evidence from TDF-containing studies. Globally, FTC/TDF has been widely used in clinical trials, open-label extension studies and demonstration projects. Thus, most PrEP efficacy and safety data are based on FTC/TDF use in heterosexual women and men, men who have sex with men, and people who inject drugs. However, generic 3TC/TDF is less expensive than FTC/TDF, is already available in supply chains for HIV drugs, and has 60–70% of the global adult market share, making it particularly appealing in settings with limited availability or affordability of FTC/TDF. Compelling indirect evidence suggests that scaling up use of 3TC/TDF is potentially cost saving for HIV programs in settings where restricting drug choice to FTC/TDF would delay PrEP implementation. Guideline committees and public health decision-makers in countries should encourage flexibility in PrEP drug selection, support off-label use of 3TC/TDF, and approve use of generic formulations to decrease the cost of PrEP medications and accelerate PrEP delivery through the public and private sectors.

1 Oral Pre-exposure Prophylaxis (PrEP) is an Effective HIV Prevention Tool

In 2018, an estimated 1.7 million people were newly infected with HIV, a 16% reduction from 2.1 million infections in 2010 [1]. While any decline in new infections is encouraging, the global community will not achieve its 2020 target of fewer than 500,000 new infections [2]. Delivery of proven HIV-prevention tools—including condoms and lubricants, behavioral modification, voluntary male medical circumcision, antiretroviral therapy (ART) to eliminate the infectiousness of people with HIV, harm-reduction services, and pre-exposure prophylaxis (PrEP) for HIV negative persons—in combination and at scale—holds the potential to achieve elimination of HIV [2]. PrEP is the use of antiretroviral (ARV) drugs by HIV-negative persons to prevent the acquisition of HIV [3, 4]. There is high-quality evidence that oral tablets containing tenofovir disoproxil fumarate (TDF) with and without emtricitabine (FTC) are an effective HIV prevention method when used consistently, providing an estimated > 90% protection in adherent individuals [5–9]. Clinical trials of PrEP containing TDF assessed both TDF co-formulated with emtricitabine (FTC/TDF) and TDF alone. A systematic review and meta-analysis of 18 PrEP studies (15 randomized trials and three observational studies) involving 19,491 participants in low-, middle-, and high-income settings concluded that oral TDF-based PrEP protects from HIV infection across HIV risk categories—heterosexual women and men, people who inject drugs (PWID), and men who have sex with men (MSM) [10].

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Key Points

Lamivudine (3TC) and emtricitabine (FTC) are pharmacologically equivalent and clinically interchangeable for HIV prevention and treatment given comparable pharmacologic equivalence, resistance, toxicity patterns, and clinical trial effectiveness.

Normative guideline bodies recommend FTC/TDF or 3TC/TDF for HIV treatment, pre-exposure prophylaxis, and post-exposure prophylaxis, but few countries are using 3TC/TDF as PrEP.

Public health advantages of using 3TC/TDF as PrEP include widespread availability through supply chains for HIV treatment, lower procurement costs than FTC/TDF, and existing registration with drug regulatory bodies.

There were no significant differences in PrEP effectiveness between sexes and regimens. The review also found that PrEP effectiveness was significantly moderated by adherence, as measured by tenofovir diphosphate blood levels in participants from the included studies.

2 Global PrEP Rollout

In January 2011, the USA became the first country to issue recommendations for oral PrEP [3]. In July 2012, the US Food and Drug Administration (FDA) approved use of FTC/TDF to reduce the risk of sexually transmitted HIV in high-risk persons [11], making it the first drug regimen approved to prevent HIV infection. In September 2015, the World Health Organization (WHO) recommended that any person at substantial risk of HIV infection (i.e., populations with ≥ 3% annual HIV incidence) be offered oral PrEP containing TDF as part of combination HIV-prevention approaches [12], based on the meta-analysis by Fonner and colleagues [10]. Following the release of WHO PrEP guidelines, drug regulatory authorities in at least 37 countries have included oral PrEP as FTC/TDF in national guidelines [13]. As of October 2019, generic FTC/TDF was registered in 33 countries and approved as PrEP in India, Lesotho, and Uganda [13]. At least 75 countries worldwide are providing oral PrEP through a variety of delivery models (e.g., fully or partially reimbursed through national programs, and implementation/demonstration projects) [13]. The 2016 United Nations Political Declaration on Ending AIDS aimed to reach 3 million people with PrEP by 2020 [14], but current global coverage is < 20% of this target. In July 2016, the European Medicines Agency (EMA) granted a marketing authorization in the European Union for use of FTC/TDF as PrEP [15]. Oral PrEP taken as TDF monotherapy or in combination with FTC or lamivudine (3TC) was included on the WHO Essential Medicines List in June 2017; an essential medicine addresses priority health needs and is chosen after consideration of efficacy, safety, cost-effectiveness, and public health relevance [16]. As of October 2019, an estimated 380,000–385,000 persons had initiated PrEP globally, of whom 35% were in the USA [13] (Fig. 1).

3 Tenofovir Disoproxil Fumarate (TDF) Co-Formulated with Emtricitabine (FTC) or Lamivudine (3TC): Molecular Structure and Pharmacokinetic and Resistance Profiles

The nucleoside reverse transcriptase inhibitors FTC and 3TC are the most widely used antiretroviral medications worldwide [17]. They are structurally similar, anabolized and phosphorylated to their pharmacologically active triphosphates by the same enzymes, and accumulate with daily dosing in peripheral blood mononuclear cells (PBMCs). Few prospective studies have performed head-to-head pharmacokinetic comparisons of 3TC and FTC in plasma, PBMCs, and genital fluids. Available data indicate that 3TC has a shorter plasma half-life (6–8 h) than FTC (8–10 h) (Table 1) [18–20]. FTC-triphosphate (FTC-TP) and 3TC-triphosphate (3TC-TP) have a relatively similar accumulation half-life in PBMCs (27 and 19 h, respectively). Elimination half-life (time taken for a drug concentration in blood to decline by half) is longer for FTC-TP than 3TC-TP (37–45 vs. 16–32 h) [18–27]. The terminal half-lives of 3TC (300 mg) and FTC (200 mg) are 7.9 and 7.4 h, respectively [28]. The FTC half maximal effective concentration (EC_{50}) is lower than 3TC and suggests an 11-fold greater potency for FTC compared with 3TC [29]. Overall, FTC has a longer intracellular half-life than 3TC, but 3TC-TP achieves higher intracellular levels [30]. The intracellular half-life of 3TC is independent of dosing regimen; similar results are obtained with once-daily (300 mg) and twice-daily (150 mg) dosing [20, 31]. Both drugs achieve two- to sixfold higher concentrations in the genital tract relative to blood plasma [32–35], and are similarly distributed in cervicovaginal fluid and semen [32–34, 36, 37]. No data are available on 3TC concentrations in human rectal fluid.

Despite the differences in some pharmacokinetic properties, both drugs have been shown to be effective with daily dosing for treatment and/or prevention [38–40]. A phase 2 dose-escalation randomized trial of FTC and 3TC monotherapy in HIV-positive individuals showed that significantly greater viral load reduction was observed with FTC [41]; however, 3TC- and FTC-containing regimens

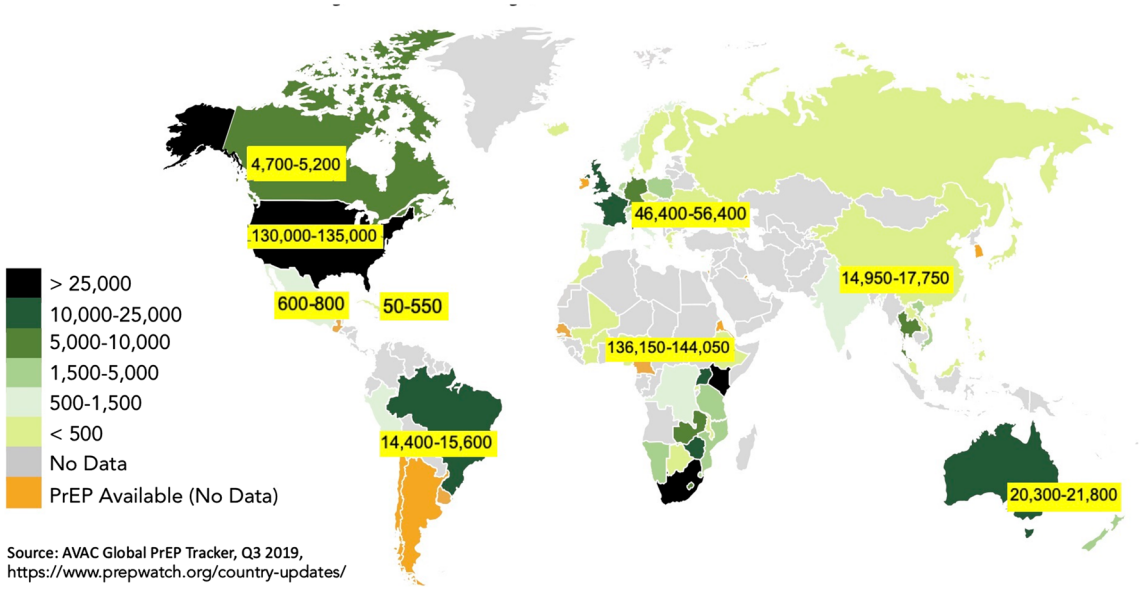


Fig. 1 Global Oral PrEP Initiations (Q3 2019)

Table 1 Human pharmacokinetic properties of emtricitabine (FTC) and lamivudine (3TC)

Pharmacokinetic parameter	*N* or median (IQR)			
	FTC	FTC-TP	3TC	3TC-TP
Mean steady-state plasma half-life ($t_{1/2}$, h)	11 [34]	39 [19]	5.71 [18]	
		19 [34]	8.65 [20]	
Mean intracellular half-life ($t_{1/2}$, h)	8–10 [19]	33 [22]	6.1–7.9 [14]	21 [25]
				22 [27]
Median intracellular half-life ($t_{1/2}$, h)				16.1 [24]
				32 [23]
PBMC accumulation half-life (h)		19 [36]		27 [21]
PBMC elimination half-life (h)		37–45 [26]		16–32 [18]
Cervicovaginal fluid [32]				
$AUC_{0\text{-}24\,h}$* (μg·h/mL)		30.8 (25.6, 52.6)		26.3 (1.12, 49.0)
C_T+ (ng/mL)		596 (537, 644)		1731 (1,083, 3,265)
Genital tract: blood plasma AUC ratio (%)	75 (37, 645)		395 (187, 671)	
Semen $AUC_{0\text{-}12\,h}$* (h·ng/mL; h·fmol/10^6 cells) [33]			31,084 (28,071, 44,184)	82,068 (64,342, 139,404)
Semen plasma/blood plasma ratio [33, 35]	2.91 (0.84–10.08)		6.67 (4.10–9.14)	1.0 (0.62–1.30)

N number, *PBMC* peripheral blood mononuclear cell

*Area under the curve (AUC) values represent 12- or 24-h intervals

+Genital tract concentrations at end of dosing interval

have comparable virologic efficacy [42]. Since the advent of combination ART, 3TC has been a core component of backbone and alternative regimens for first-line and second-line ART for adults, adolescents, and children [43, 44]. Like FTC, 3TC is safe, with an excellent toxicity profile and non-teratogenic, is effective against hepatitis B virus (HBV), and is widely available in fixed-dose combinations in resource-limited settings [14, 45]. Both 3TC and FTC have a low genetic barrier to resistance and resistance quickly occurs in vitro [46] and in vivo [47, 48]; specifically, mutations of codon 184 arise when isoleucine (M184I) or valine (M184V) are substituted for wild-type methionine [46]. The M184V mutation affects the catalytic function of reverse transcriptase resulting in reduced viral replication capacity

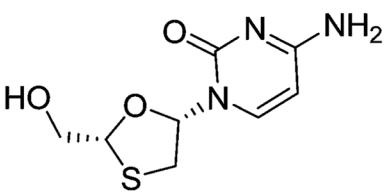
and low viral fitness [49], but also induces re-sensitization to tenofovir [50] and zidovudine [51]. There are significantly lower levels of tenofovir resistance in viruses carrying thymidine analogue mutations (TAMs) with M184V than with M184M [50]. The synergistic activity of 3TC or FTC and TDF results in sustained antiviral activity and supports the continued use of 3TC in combination with TDF or zidovudine (AZT) even when the M184V mutation is present (e.g., in second-line ART) [44, 52]. Therefore, 3TC is considered an acceptable alternative to FTC [42], and the WHO and US Department of Health and Human Services consider 3TC clinically interchangeable with FTC for HIV treatment and prevention given comparable pharmacologic equivalence, resistance and toxicity patterns, and clinical trial effectiveness (Fig. 2) [14, 40]. Importantly, 3TC is also less expensive than FTC [53]. Overall, available evidence from pre-clinical, in vitro, and clinical studies suggests comparative pharmacologic and virological efficacy and clinical equivalence, and supports the interchangeability of 3TC and FTC despite limited data from direct comparisons.

4 Pharmacokinetics of 3TC in Macaques

The mucosal pharmacokinetic (PK) profile in rhesus macaques suggests potential pharmacological equivalence between 3TC and FTC for oral PrEP. A single-dose pharmacokinetic study in rhesus macaques found that 3TC achieves high concentrations in rectal and vaginal fluids [54]. Twelve macaques were provided with a single oral dose of 10, 20, or 30 mg/kg of 3TC (four animals per dose) by gavage under anesthesia based on body weight. Blood and vaginal and rectal secretions were collected at baseline and at 2 h, 6 h, 24 h, and 48 h; vaginal and rectal biopsies were collected at 6 and 24 h. Validated liquid chromatography-tandem mass spectrometry methods were used to measure 3TC and 3TC-triphosphate (3TC-TP; the active intracellular moiety) concentrations; 3TC-TP was also quantified in vaginal biopsies. The 30 mg/kg dose achieved a plasma drug exposure (median $AUC_{0-24\,h}$ 16.8 (13.4–28.7) µg·h/mL and median C_{max} 3.0 (1.8–5.8) µg/mL, respectively) comparable to an oral 3TC dose of 300 mg in humans (median $AUC_{0-24\,h}$ 16.7 ± 4.1 µg·h/mL and median C_{max} 3.5 ± 0.9 µg/mL, respectively) [28]. Peak 3TC-TP concentrations in PBMCs in macaques were also comparable to humans [1.8 (95% confidence interval (CI) 1.4–1.9) pmols/10^6 cells vs. 1.8 (95% CI 0.5–1.9) pmols/10^6 cells, respectively] [21]. Importantly, 24-h 3TC-TP concentrations in macaque vaginal biopsies were similar to FTC: 135 (9–208) versus 151 (145–179) fmol/mg of tissue, respectively. These PK data provide indirect evidence supporting the use of 3TC/TDF as PrEP.

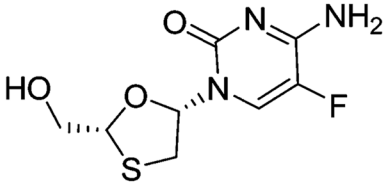
5 3TC/TDF is an Appropriate PrEP Regimen

Clinical studies of 3TC/TDF for prevention of mother-to-child HIV transmission (PMTCT) provide indirect evidence and serve as proof-of-principle for the use of 3TC/TDF as HIV prophylaxis [55–58]. In the Kesho Bora study ($n = 805$), infants of mothers randomly assigned to the zidovudine/lamivudine/lopinavir-ritonavir group had a 43% lower cumulative rate of HIV acquisition (5.4 vs. 9.5%; $p = 0.029$) and a 36% lower cumulative rate of HIV transmission or death (10.2 vs. 16.0%; $p = 0.017$) at 12 months compared with the AZT and single-dose nevirapine group [57]. The ANRS 12174 randomized trial ($n = 1273$ infants) found that



1 (3TC)

Lamivudine



2 (FTC)

Emtricitabine

Fig. 2 Lamivudine (3TC) and emtricitabine (FTC) are clinically interchangable

WHO document	WHO position
WHO Technical Update 3TC FTC, 2012	Clinical and virological efficacy and safety of 3TC and FTC are comparable. Development of the M184V/I mutation is associated to a greater extent with 3TC.
WHO ART Guidelines, 2013	3TC and FTC are pharmacologically comparable.
WHO PEP Guidelines, 2014	TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for adults and adolescents.
WHO ART Guidelines, 2015	TDF + 3TC (or FTC) is recommended.

cumulative HIV infection rates did not differ between the lopinavir-ritonavir and lamivudine groups (HR 0.90; 95% CI 0.35–2.34; $p=0.83$) [58]. In the Mitra Study ($n=398$ infants), vertical transmission of HIV was 62% lower in breastfed infants who received 3TC prophylaxis for 6 months than in those who stopped receiving 3TC after 7 days of age (adjusted relative hazard 2.61; 95% CI 1.44–4.73; $p=0.001$) [56]. In the SIMBA study ($n=397$ infants), postpartum HIV transmission was observed in 1.1% of infants receiving 3TC prophylaxis compared with 10% of infants on nevirapine [55]. These data suggest that infant HIV prophylaxis with 3TC containing regimens is effective for HIV prevention. In the first study of 3TC/TDF as PrEP (a phase I trial), 40 MSM in Brazil were followed for 4 months and 33 completed study follow up [59]. There were no breakthrough infections reported by the completion of the study. A phase II trial is ongoing [60]. To date, no clinical trial data are available on the use of 3TC/TDF for prevention of HIV acquisition through heterosexual contact or PWID. However, indirect evidence from the Partners PrEP Study, which found no significant differences in the protective effects of FTC/TDF and TDF (hazard ratio 0·67, 95% CI 0·39–1·17; $p=0·16$) [61], supports the use of TDF alone as PrEP. An ongoing stepped-wedge cluster randomized trial ($n=1440$ couples) is evaluating the effectiveness of delivering an integrated PrEP and ART intervention at public health clinics in Uganda on: (a) 3TC/TDF PrEP initiation, (b) 3TC/TDF PrEP adherence, (c) ART initiation, and (d) ART adherence among HIV serodiscordant couples in Uganda (www.ClinicalTrials.gov NCT03586128).

6 Global Recommendations for 3TC/TDF

The existing recommendation of WHO for oral PrEP specifies the use of medicines "containing TDF", i.e., FTC/TDF or 3TC/TDF. Oral PrEP is contraindicated for persons with an estimated creatinine clearance < 60 mL/min [44]. For the most part, PrEP implementation has used FTC/TDF as the PrEP agent, and regulatory approvals have resulted in the extension of a PrEP indication to FTC/TDF products, both originator and generic. However, TDF is also commonly co-formulated with lamivudine (3TC/TDF) [14], and 3TC is generally considered equivalent to FTC in its mechanism of action and clinical effect when used as ART for HIV treatment as noted above [17]. Yet, no completed clinical trials have evaluated the efficacy or effectiveness of 3TC/TDF as PrEP. The WHO recommends XTC/TDF (i.e., FTC or 3TC) for HIV treatment and for post-exposure prophylaxis (PEP) [44]. This recommendation was based on a systematic review of 12 clinical trials that evaluated the pharmacological equivalence and clinical interchangeability of FTC and 3TC [42]. In studies of HIV treatment, virologic suppression was not significantly different among any of the 12 trials evaluated; the pooled RR for viral suppression comparing three-drug regimens containing 3TC or FTC was not significantly different (relative risk [RR] 1.00; 95% CI 0.97–1.02). Three trials that directly compared 3TC and TDF did not find a significant difference in viral suppression (RR 1.03; 95% CI 0.96–1.10). These compelling data informed the WHO decision in the absence of a head-to-head comparison.

WHO also recommends interchangeability of 3TC/TDF and FTC/TDF as PrEP [44]. Similarly, to enable flexibility in PrEP drug selection, the US President's Emergency Plan for AIDS Relief (PEPFAR) Scientific Advisory Board recommended 3TC/TDF as an acceptable alternative to FTC/TDF for PrEP in December 2015. This recommendation was based on the limited availability of TDF alone or co-formulated FTC/TDF; the widespread availability of 3TC/TDF for PMTCT, treatment, and PEP in several PEPFAR countries; and the similar pharmacoavailability of 3TC and FTC in heterosexual populations [62]. The WHO estimates that 3TC/TFC represents 60–70% of global adult market share [14]. This widespread availability also provides the rationale for a public health advantage—inclusion of 3TC/TDF as PrEP in national guidelines.

7 Inclusion of 3TC/TDF as PrEP in National Programs

The WHO's prequalification program has "approved" over ten FTC/TDF and 3TC/TDF products by generic manufacturers [14]. Flexibility in drug selection (i.e., choice of 3TC/TDF, FTC/TDF, or TDF alone) is intended to support PrEP implementation in varied settings; generic formulations of 3TC/TDF and FTC/TDF are already in supply chains. European AIDS Society Guidelines suggest use of generic formulations to increase the cost-effectiveness of PrEP [63]. Globally, an estimated 15 million packs (monthly supplies) of FTC/TDF and 3TC/TDF were procured in 2016 and 2017 [53]. At least 21 countries in Africa, Asia and North, Central and South America now recommend use of 3TC/TDF as PrEP in addition to FTC/TDF in accordance with WHO recommendations; Lesotho recommends exclusive use of 3TC/TDF [64]. Six of the 21 countries that recommend use of 3TC/TDF are in sub-Saharan Africa, where 3TC/TDF is already procured through supply chains for HIV treatment. In this setting, use of 3TC/TDF saves money and does not require registration, which would delay implementation. According to the WHO Global Price Reporting Mechanism, the median cost of 3TC/TDF and FTC/TDF in 2017 was US$36.76 and US$48.83 per person per year, respectively [53]. As of May 2019, use of 3TC/TDF by the estimated 113,750 PrEP initiates in sub-Saharan Africa would result in an estimated annual saving of US$1,145,463.

8 Conclusion

Rapid scale-up of oral PrEP as part of combination HIV prevention approaches is critical if global targets for HIV elimination are to be met. The nucleoside reverse transcriptase inhibitors FTC and 3TC in combination with TDF are clinically interchangeable when used for PrEP, PEP, and HIV treatment. Ministries of Health should adopt WHO and PEPFAR recommendations for use of 3TC/TDF as an acceptable alternative to FTC/TDF PrEP, as it confers public health advantages. From a supply chain standpoint, 3TF/FTC is already being procured by HIV programs across Asia, Latin America, and sub-Saharan Africa. 3TC/TDF is an acceptable PrEP regimen according to normative international guidelines and may be particularly appealing in settings with limited availability or affordability of FTC/TDF. Most countries recommending the use of 3TC/TDF as PrEP are in sub-Saharan Africa, where use of this regimen saves US$10.07 per person per year. The recent decision by India to recommend 3TC/TDF for PrEP, given its population size, will likely influence other countries in moving towards policy adoption of 3TC/TDF. Furthermore, regulatory authorities should facilitate registration of 3TC/TDF for a PrEP indication. In closing, national-level guideline committees should encourage flexibility in PrEP drug selection by recommending 3TC/TDF, and, where relevant, support off-label use of 3TC/TDF and conduct routine pharmacovigilance monitoring. Public health decision-makers in countries should advocate for the use of generic formulations to decrease the cost of PrEP programs, and thereby accelerate PrEP delivery through the public and private sector.

Declarations

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Conflict of Interest JMB served as an advisor for Gilead Sciences, Janssen, and Merck. JEH is a consultant for Merck. AM received donated FTC/TDF from Gilead Sciences for an investigator-sponsored study.

Ethics Approval Not applicable.

Consent for Publication Not applicable.

Availability of Data and Materials Not applicable.

Code Availability Not applicable.

Author Contributions AM, JMB, and JEH conceptualized the paper. AM wrote the first draft along with JEH. IHM, JMB, JEH, and AM reviewed drafts and provided substantial edits. All authors read and approved the final manuscript.

References

1. Joint United Nations Programme on HIV/AIDS (2019). UNAIDS Data 2019. Available from: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf. Accessed 20 Feb 2020.
2. Joint United Nations Programme on HIV/AIDS (2018). Miles to go—closing gaps, breaking barriers, righting injustices. Available from: http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf. Accessed 20 Feb 2020
3. MMWR Morbidity and mortality weekly report. Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. 2011;60(3):65–8.
4. MMWR Morbidity and mortality weekly report. Centers for Disease Control and Prevention (CDC). Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. 2012;61(31):586–9.
5. 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. https://doi.org/10.1056/NEJMoa1011205.
6. Baeten JMDD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410. https://doi.org/10.1056/NEJMoa1108524.
7. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34. https://doi.org/10.1056/NEJMoa1110711.
8. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015;373(23):2237–46. https://doi.org/10.1056/NEJMoa1506273.
9. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387(10013):53–60. https://doi.org/10.1016/s0140-6736(15)00056-2.
10. 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. https://doi.org/10.1097/qad.0000000000001145.
11. US Food and Drug Administration (2014). Truvada for PrEP fact sheet: Ensuring safe and proper use. Available from: https://www.fda.gov/media/83586/download. Accessed 20 Feb 2020.
12. World Health Organization (2015). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Available from: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed 9 Nov 2019.
13. AVAC (2018). PrEPWatch. Country Updates. Available from: https://www.prepwatch.org/in-practice/country-updates/. Accessed 9 Nov 2019.
14. World Health Organization (2017). Technical Update on Appropriate Medicines Options for Pre-Exposure Prophylaxis. Available from: https://apps.who.int/iris/bitstream/handle/10665/273934/WHO-CDS-HIV-18.22-eng.pdf?ua=1. Accessed 9 Nov 2019.
15. European Medicines Agency (2016). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP). Available from: https://www.ema.europa.eu/news/first-medicine-hiv-pre-exposure-prophylaxis-recommended-approval-eu. Accessed 20 Feb 2020.
16. World Health Organization (2018). WHO essential medicines and health products: annual report 2017: towards access 2030 (No.

WHO/EMP/2018.01). Available from: https://apps.who.int/iris/handle/10665/272972. Accessed 20 Feb 2020.
17. Ford N, Vitoria M, Doherty M, Gray A. Candidates for inclusion in a universal antiretroviral regimen: are lamivudine and emtricitabine interchangeable? Curr Opin HIV AIDS. 2017;12(4):334–8. https://doi.org/10.1097/coh.0000000000000377.
18. Else LJ, Jackson A, Puls R, Hill A, Fahey P, Lin E, et al. Pharmacokinetics of lamivudine and lamivudine-triphosphate after administration of 300 milligrams and 150 milligrams once daily to healthy volunteers: results of the ENCORE 2 study. Antimicrob Agents Chemother. 2012;56(3):1427–33. https://doi.org/10.1128/aac.05599-11.
19. Wang LH, Begley J, St Claire RL, 3rd, Harris J, Wakeford C, Rousseau FS. Pharmacokinetic and pharmacodynamic characteristics of emtricitabine support its once daily dosing for the treatment of HIV infection. AIDS Res Human Retrovir. 2004;20(11):1173–82. https://doi.org/10.1089/aid.2004.20.1173.
20. Yuen GJ, Lou Y, Bumgarner NF, Bishop JP, Smith GA, Otto VR, et al. Equivalent steady-state pharmacokinetics of lamivudine in plasma and lamivudine triphosphate within cells following administration of lamivudine at 300 milligrams once daily and 150 milligrams twice daily. Antimicrob Agents Chemother. 2004;48(1):176–82. https://doi.org/10.1128/aac.48.1.176-182.2004.
21. Rower JE, Meditz A, Gardner EM, Lichtenstein K, Predhomme J, Bushman LR, et al. Effect of HIV-1 infection and sex on the cellular pharmacology of the antiretroviral drugs zidovudine and lamivudine. Antimicrob Agents Chemother. 2012;56(6):3011–9. https://doi.org/10.1128/aac.06337-11.
22. Seifert SM, Glidden DV, Meditz AL, Castillo-Mancilla JR, Gardner EM, Predhomme JA, et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. Clin Infect Dis. 2015;60(5):804–10. https://doi.org/10.1093/cid/ciu916.
23. Rodriguez JF, Rodriguez JL, Santana J, García H, Rosario O. Simultaneous quantitation of intracellular zidovudine and lamivudine triphosphates in human immunodeficiency virus-infected individuals. Antimicrob Agents Chemother. 2000;44(11):3097–100. https://doi.org/10.1128/aac.44.11.3097-3100.2000.
24. Moore KH, Barrett JE, Shaw S, Pakes GE, Churchus R, Kapoor A, et al. The pharmacokinetics of lamivudine phosphorylation in peripheral blood mononuclear cells from patients infected with HIV-1. Aids. 1999;13(16):2239–50. https://doi.org/10.1097/00002030-199911120-00006.
25. Bazzoli C, Bénech H, Rey E, Retout S, Salmon D, Duval X, et al. Joint population pharmacokinetic analysis of zidovudine, lamivudine, and their active intracellular metabolites in HIV patients. Antimicrob Agents Chemother. 2011;55(7):3423–31. https://doi.org/10.1128/aac.01487-10.
26. Dickinson L, Yapa HM, Jackson A, Moyle G, Else L, Amara A, et al. Plasma tenofovir, emtricitabine, and rilpivirine and intracellular tenofovir diphosphate and emtricitabine triphosphate pharmacokinetics following drug intake cessation. Antimicrob Agents Chemother. 2015;59(10):6080–6. https://doi.org/10.1128/aac.01441-15.
27. Anderson PL, Kakuda TN, Kawle S, Fletcher CV. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals. Aids. 2003;17(15):2159–68. https://doi.org/10.1097/00002030-200310170-00003.
28. Bruno R, Regazzi MB, Ciappina V, Villani P, Sacchi P, Montagna M, et al. Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily administration in patients with HIV. Clin Pharmacokinet. 2001;40(9):695–700.
29. Schinazi RF. Assessment of the relative potency of emtricitabine and lamivudine. J Acquir Immune Defic Syndr. 2003;34(2):243–5 **(author reply 5–6)**.
30. Bushman LR, Kiser JJ, Rower JE, Klein B, Zheng JH, Ray ML, et al. Determination of nucleoside analog mono-, di-, and tri-phosphates in cellular matrix by solid phase extraction and ultra-sensitive LC-MS/MS detection. J Pharm Biomed Anal. 2011;56(2):390–401. https://doi.org/10.1016/j.jpba.2011.05.039.
31. Maserati R. Differentiating emtricitabine (FTC) from lamivudine (3TC): what a "fine-tuning" of antiretroviral therapy might entail. Available from: http://win.mnlpublimed.com/public/HA10-A04.pdf. Accessed 11 Sept 2020.
32. Dumond JB, Yeh RF, Patterson KB, Corbett AH, Jung BH, Rezk NL, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre- and post-exposure prophylaxis. Aids. 2007;21(14):1899–907. https://doi.org/10.1097/QAD.0b013e328270385a.
33. Dumond JB, Reddy YS, Troiani L, Rodriguez JF, Bridges AS, Fiscus SA, et al. Differential extracellular and intracellular concentrations of zidovudine and lamivudine in semen and plasma of HIV-1-infected men. J Acquir Immune Defic Syndr. 2008;48(2):156–62. https://doi.org/10.1097/QAI.0b013e31816de21e.
34. Hendrix CW, Andrade A, Bumpus NN, Kashuba AD, Marzinke MA, Moore A, et al. Dose frequency ranging pharmacokinetic study of tenofovir-emtricitabine after directly observed dosing in healthy volunteers to establish adherence benchmarks (HPTN 066). AIDS Res Hum Retroviruses. 2016;32(1):32–433. https://doi.org/10.1089/aid.2015.0182.
35. Valade E, Tréluyer JM, Illamola SM, Bouazza N, Foissac F, De Sousa MM, et al. Emtricitabine seminal plasma and blood plasma population pharmacokinetics in HIV-infected men in the EVARIST ANRS-EP 49 study. Antimicrob Agents Chemother. 2015;59(11):6800–6. https://doi.org/10.1128/aac.01517-15.
36. Seifert SM, Chen X, Meditz AL, Castillo-Mancilla JR, Gardner EM, Predhomme JA, et al. Intracellular tenofovir and emtricitabine anabolites in genital, rectal, and blood compartments from first dose to steady state. AIDS Res Hum Retrovir. 2016;32(10–11):981–91. https://doi.org/10.1089/aid.2016.0008.
37. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011;3(112):112re4. https://doi.org/10.1126/scitranslmed.3003174.
38. Zemlicka J. Enantioselectivity of the antiviral effects of nucleoside analogues. Pharmacol Ther. 2000;85(3):251–66.
39. Liou JY, Dutschman GE, Lam W, Jiang Z, Cheng YC. Characterization of human UMP/CMP kinase and its phosphorylation of D- and L-form deoxycytidine analogue monophosphates. Cancer Res. 2002;62(6):1624–31.
40. World Health Organization (2012). Technical update on treatment optimization: pharmacological equivalence and clinical interchangeability oflamivudine and emtricitabine: a review of current literature. Available from: https://apps.who.int/iris/handle/10665/70936. Accessed 20 Feb 2020.
41. Rousseau FS, Wakeford C, Mommeja-Marin H, Sanne I, Moxham C, Harris J, et al. Prospective randomized trial of emtricitabine versus lamivudine short-term monotherapy in human immunodeficiency virus-infected patients. J Infect Dis. 2003;188(11):1652–8. https://doi.org/10.1086/379667.
42. Ford N, Shubber Z, Hill A, Vitoria M, Doherty M, Mills EJ, et al. Comparative efficacy of Lamivudine and emtricitabine: a systematic review and meta-analysis of randomized trials. PLoS ONE. 2013;8(11):e79981. https://doi.org/10.1371/journal.pone.0079981.

43. World Health Organization (2002). Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach: executivesummary. Available from: https://apps.who.int/iris/bitstream/handle/10665/42514/9241545674.pdf. Accessed 20 Feb 2020.
44. World Health Organization (2016). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Available from: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf. Accessed 20 Feb 2020.
45. Derdelinckx I, Wainberg MA, Lange JM, Hill A, Halima Y, Boucher CA. Criteria for drugs used in pre-exposure prophylaxis trials against HIV infection. PLoS Med. 2006;3(11):e454.
46. Boucher CA, Cammack N, Schipper P, Schuurman R, Rouse P, Wainberg MA, et al. High-level resistance to (−) enantiomeric 2'-deoxy-3'-thiacytidine in vitro is due to one amino acid substitution in the catalytic site of human immunodeficiency virus type 1 reverse transcriptase. Antimicrob Agents Chemother. 1993;37(10):2231–4.
47. Diallo K, Gotte M, Wainberg MA. Molecular impact of the M184V mutation in human immunodeficiency virus type 1 reverse transcriptase. Antimicrob Agents Chemother. 2003;47(11):3377–83.
48. Turner D, Brenner B, Wainberg MA. Multiple effects of the M184V resistance mutation in the reverse transcriptase of human immunodeficiency virus type 1. Clin Diagn Lab Immunol. 2003;10(6):979–81.
49. Quercia R, Perno CF, Koteff J, Moore K, McCoig C, St Clair M, et al. Twenty-five years of lamivudine: current and future use for the treatment of HIV-1 infection. J Acquir Immune Defic Syndr. 2018;78(2):125–35. https://doi.org/10.1097/qai.0000000000001660.
50. Wolf K, Walter H, Beerenwinkel N, Keulen W, Kaiser R, Hoffmann D, et al. Tenofovir resistance and resensitization. Antimicrob Agents Chemother. 2003;47(11):3478–84.
51. Larder BA, Kemp SD, Harrigan PR. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. Science. 1995;269(5224):696–9.
52. Pillay D, Albert J, Bertagnolio S, Boucher C, Brun-Vezinet F, Clotet B, et al. Implications of HIV drug resistance on first- and second-line therapies in resource-limited settings: report from a workshop organized by the Collaborative HIV and Anti-HIV Drug Resistance Network. Antiviral Therapy. 2013;18(6):831–6. https://doi.org/10.3851/imp2650.
53. World Health Organization (2017). Global Price Reporting Mechanism for HIV, tuberculosis and malaria. Available from: http://www.who.int/hiv/amds/gprm/en/. Accessed 20 Feb 2020.
54. Massud I, Sykes C, Cong ME, Ellis S, Kelly K, Heneine W et al. Pharmacokinetic profile of lamivudine (3TC) in macaques and relative drug exposure in rectal and vaginal tissues. abstracts of the HIV research for prevention meeting, HIVR4P, 17–20 October, 2016, Chicago, USA. AIDS Res Human Retrovir. 2016;32(S1):1–409. https://doi.org/10.1089/aid.2016.5000.abstracts.
55. Vyankandondera J, Luchters S, Hassink E, Pakker N, Mmiro F, Okong P et al., editors. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA-study). In: 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris; 2003.
56. Kilewo C, Karlsson K, Massawe A, Lyamuya E, Swai A, Mhalu F, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. J Acquir Immune Defic Syndr. 2008;48(3):315–23. https://doi.org/10.1097/QAI.0b013e31816e395c.
57. de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171–80. https://doi.org/10.1016/s1473-3099(10)70288-7.
58. Nagot N, Kankasa C, Tumwine JK, Meda N, Hofmeyr GJ, Vallo R, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. Lancet. 2016;387(10018):566–73. https://doi.org/10.1016/s0140-6736(15)00984-8.
59. Mancuzo AV, Carvalho LV, Carvalho GC et al. Evaluation of the acceptability, feasibility, safety and adherence to pre-exposure prophylaxis (PrEP) forHIV prevention in men who have sex with men (MSM): Phase 1 study (submitted abstract) [cited inhttps://apps.who.int/iris/bitstream/handle/10665/273934/WHO-CDS-HIV-18.22-eng.pdf?ua=1].
60. Hodges-Mameletzis I. TDF/3TC for PrEP: the rationale and the evidence. Geneva: World Health Organization; 2019.
61. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infect Dis. 2014;14(11):1055–64. https://doi.org/10.1016/s1473-3099(14)70937-5.
62. PEPFAR. Recommendations on the Use of PrEP for All Populations. PEPFAR Scientific Advisory Board (SAB). 2015.
63. European AIDS Clinical Society Guidelines (Version 9.0, October 2017). Available from: https://www.eacsociety.org/files/guidelines_9.0-english.pdf. Accessed 20 Feb 2020.
64. Hodges-Mameletzis I, Dalal S, Msimanga-Radebe B, Rodolph M, Baggaley R. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. Sexual health. 2018;15(6):489–500. https://doi.org/10.1071/sh18125.