Review

The evidence for using tenofovir disoproxil fumarate plus lamivudine as a nucleoside analogue backbone for the treatment of HIV

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ARTICLE INFO

Keywords:
Antiretroviral therapy
Tenofovir
Lamivudine
NRTI backbone

ABSTRACT

This article evaluates the evidence supporting use of the tenofovir disoproxil fumarate (TDF) plus lamivudine (3TC) combination as a dual nucleoside backbone within a triple drug antiretroviral regimen. Key trials that assess the relative efficacy, safety and resistance profile of 3TC and emtricitabine (FTC) are discussed. Clinical use of 3TC and FTC with two tenofovir prodrugs – TDF and tenofovir alafenamide (TAF) – is presented. Recommendations from various international guidelines for the construction of triple and emerging dual regimens are summarised. In conclusion, data suggest the therapeutic equivalence of 3TC and FTC, especially when 3TC is combined with TDF.

HIV treatment today

Antiretroviral (ARV) therapy (ART) has transformed the outlook for people living with HIV (PLWH): yielding normal life expectancy and no risk of sexual transmission of HIV. An estimated 23.3 million PLWH were receiving ART globally as of 2018,1 and the successful response to the HIV pandemic has been hailed as a model for public health.2

An understanding of the life cycle of the HIV virus helped identifying the key steps in viral replication and potential therapeutic targets. The critical enzymes for replication are the reverse transcriptase, the protease and the integrase. The first ARV drug class developed targeted the reverse transcriptase enzyme, followed by drugs that targeted the protease and the integrase. A fourth class of drugs target various steps involved in viral attachment and entry into host cells including, most recently licensed, a monoclonal antibody that inhibits CD4 binding.3 Thus, within 25 years of the virus being discovered in 1981, 25 ARV compounds were licensed for clinical use by the United States (US) Food and Drug Administration (FDA).4

The accepted standard of care in HIV treatment involves using a combination of three active drugs from at least two different classes.5 This approach has demonstrated durable viral suppression and consequent immune reconstitution, resulting in a dramatic reduction in morbidity and mortality and near-normal life expectancy. Further, an undetectable viral load prevents HIV sexual transmission, with major implications in terms of public health and individual wellbeing.6

Regimen selection is based on virologic efficacy, potential for adverse effects, pill burden and dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions and cost.6 Given the importance of lifelong treatment adherence to maintain durable virologic suppression, fixed-dose combinations that include two or three drugs are now commonly used.5

Current treatment guidelines recommend first-line regimens comprising of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a third drug from one of three

Drug classes: integrase strand transfer inhibitors (InSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs) (Table 1).7,8 The European AIDS Clinical Society (EACS) guidelines were the first to include a two-drug regimen, dolutegravir (DTG) plus lamivudine (3TC), as a recommended first-line treatment option, though still lists two NRTI combined with an InSTI as preferred.8 The US Department of Health and Human Services (DHHS) followed, including DTG plus 3TC as one of the recommended initial regimens for most people.7 Thus, NRTIs form the backbone of, the still largely preferred, triple ART, and first-line dual ART approaches to treatment.

Nucleoside reverse transcriptase class evolution

The first ARV drug for clinical use was the NRTI zidovudine (ZDV)
This review article and its effects. TDF has now become one of the most frequently prescribed drugs of nucleotide reverse transcriptase inhibitor (NtRTI), i.e. TDF was introduced and boosted; DRV/r: darunavir and ritonavir; DTG: dolutegravir.

Current recommendations for fixed-dose combinations (FDC) available today.

1. TDF + FTC + efavirenz (branded)
2. TDF + 3 TC + efavirenz (generic)
3. TAF + FTC + bictegravir (branded)
4. TAF + FTC + dolutegravir + bictegravir (branded)
5. TDF + FTC + elvitegravir + bictegravir (branded)
6. TAF + FTC + dolutegravir + bictegravir (branded)
7. TDF + FTC + ritonavir (branded)
8. TAF + FTC + rilpivirine (branded)
9. TDF + 3 TC + dolutegravir (generic)
10. TDF + 3 TC + doravirine (combination of brand new compound and generic backbone)

TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; 3 TC = lamivudine.

licensed by the US FDA in 1987. The timeline for the US FDA approval of the NRTI class of drugs is depicted in Table 2. In 2001, the first nucleotide reverse transcriptase inhibitor (NtRTI), i.e. TDF was introduced. TDF has now become one of the most frequently prescribed drugs for HIV treatment. In 2009, it was estimated that if ART had saved three million lives, tenofovir alone may be responsible for two-thirds of the three million years of life saved. TDF description is beyond the scope of this review article and its efficacy and safety profiles are extensively described in the literature.

Both NRTIs and NtRTIs interact with the catalytic site of the HIV reverse transcriptase enzyme. Before these drugs can interact with the substrate-binding site, they need to be phosphorylated intracellularly to the triphosphate and diphosphate forms, respectively. The phosphorylated forms then act as a competitive inhibitor/alternate substrate causing chain termination.

As new drug classes became available, the combination of two NRTI plus an agent from a different class was proven to be the optimal ‘recipe’ for sustained viral suppression and the two NRTI backbone established itself as the cornerstone of regimens recommended by consensus guidelines globally. Further, extensive use of potent triple regimens resulted in increased life expectancy, and the realisation that regimens needed to be friendlier – in terms of tolerability, pill burden, frequency of dosing and that co-formulations improve patient adherence.

The first two NRTI fixed-dose combination (FDC) of ZDV + 3 TC was licensed by the US FDA in 1997. This was followed by abacavir (ABC) + 3 TC and TDF + FTC, both in 2004. Importantly, TDF + 3 TC was also approved for use by the US FDA under the President’s Emergency Programme for AIDS Relief (PEPFAR) programme in 2011, and tenofovir alafenamide (TAF) + FTC in 2016.

Are lamivudine and emtricitabine interchangeable?

Today, 3 TC or FTC are an almost universal component of all first-line regimens used globally and listed as a “preferred” option by all HIV treatment guidelines. In the published literature, the abbreviation “XTC” is often used to denote either 3 TC or FTC.

Efficacy

A systematic review and meta-analysis of randomised trials were performed to assess the comparative efficacy of 3 TC and FTC within a triple ART combination in treatment-naïve or experienced patients. Twelve trials published between 2002 and 2013 provided data on 2251 and 2662 individuals who received 3 TC or FTC, respectively. Treatment success did not differ significantly in any of the 12 trials.

The difference in relative risk for achieving treatment success was non-significant in three trials that compared 3 TC and FTC directly (p = 0.3), nor was the difference in pooled relative risk for treatment success (RR 1.00, 95% CI 0.97–1.02), with no observed heterogeneity. For treatment failure, all but one study found no difference in risk with no statistically significant difference in the pooled relative risk for treatment failure (RR 1.08, 95% CI 0.94–1.22) with no subgroup differences (p > 0.1), and low heterogeneity (I² = 3.4%).

This analysis was robust since only randomised trials with comparable background regimens were included, with outcomes from more than 4500 randomisations. Further, the search strategy allowed for both published and unpublished trials. The authors opine that the overall findings provide supportive evidence for the recommendations of current international guidelines to treat 3 TC and FTC as interchangeable.

An analysis from the Dutch ATHENA cohort compared the treatment responses to 3 TC versus FTC, in combination with TDF and a boosted PI. One-thousand and eighty-two ART-naïve PLWH were followed up for 48 weeks in this observational study, and virologic failure rates were comparable – 8.9% with 3 TC and 5.6% with FTC (p = 0.208). Over five years of follow-up, 3 TC was not significantly associated with decreased virological responses in comparison with FTC (adjusted hazard ratio for treatment failure was 1.15). Additional support for the interchangeability of 3 TC and FTC comes from the observations that the time to two consecutive HIV RNA measurements < 400 copies/mL and the time to treatment failure after suppression < 400 copies/mL were not significantly influenced by the use of 3 TC versus FTC in TDF/boosted PI-containing regimens. The authors concluded that generic 3 TC can be used instead of FTC in PI-based regimens without increased risk for...
virological failure and, furthermore, the use of generics would have benefits in cost containment strategies globally.

However, when combined with the first generation NNRTI efavirenz (EFV) or nevirapine (NVP), FTC seemed to be associated with better virological responses compared to 3 TC in the ATHENA cohort. Nevertheless, this finding was never demonstrated by an appropriately powered randomised trial or by the registration studies showing non-inferiority of TDF/3TC/doravirine (DOR) versus FTC containing ART, supporting similar efficacy of 3 TC and FTC with a later generation NNRTI.2,7,15

Safety

Pollock et al.18 assessed the incidence of FTC-associated adverse events by switching 158 patients on a stable 3 TC-containing regimen to FTC, without altering any other drugs in the triple regimen. Switches were made between May 2004 and July 2005 based on patient and/or physician preferences. Overall, switch to FTC was well tolerated with no Grade 3 or 4 toxicities reported.

However, within a month of switch to FTC, 13 patients had re-initiated 3 TC. In 11 patients, this was triggered by patient-reported adverse effects, and resolution of clinical symptoms was reported by all 11 cases within 72 h of re-initiating 3 TC. This translates into a 7% incidence of intolerance to FTC in this cohort (11 out of 158). Six of the 11 cases reported Grade II central nervous system (CNS) toxicity – feeling strange or unwell. This has not been assessed in the randomised trials that predated this cohort.

Hyperpigmentation has been reported with FTC, with an overall incidence of 3.4%, usually affecting the palms of the hands or the soles of the feet.19 Similarly, an incidence of 3.9% has been reported by a study in 155 Japanese patients.20

In pooled data from adults, aspartate transaminase (AST) increase, alanine transaminase (ALT) increase, and pneumonia have been reported as the most serious adverse effects with FTC.21 The majority of these were felt to be unrelated to FTC. Adverse events most frequently leading to study discontinuation were AST increase (2 versus 2.3% control), ALT increase (2% versus 2.3% control), hyperamylasaemia (0.6% versus 1.2% control) and rash (0.7% versus 0.8% control).

Finally, Venhoff et al.22 investigated the mitochondrial toxicity of various NRTI backbones. TDF plus 3 TC was the only combination with no additive or synergistic toxic effects, while a dose-dependent reduction of a mutation, and the rate of an event (according to whether the regimen contained 3 TC or FTC) was calculated by dividing number of number of events by patient-time. Person-time was calculated from the start date of the regimen to detection of the mutation(s) being analysed. An event was defined as detection of a mutation, and the rate of an event (according to whether the regimen contained 3 TC or FTC) was calculated by dividing number of number of events by person-time. FTC- based regimens (n = 5190) were used more commonly than 3 TC-based regimens (n = 1228).

The overall event rate for detection of M65R was 0.38/100 PYFU. Although patients on 3 TC were more likely to develop resistance, this was not statistically significant in univariable (OR 1.85, \( p = 0.09 \)) or multivariable analyses (OR 1.89, \( p = 0.1 \)). The study concluded that there was no evidence of an increased risk of development of M184V and K65R at failure of 3 TC-based, as compared to FTC-based, ART. Other studies, have shown statistically significant differences between FTC and 3 TC but these were small and retrospective.24

Pharmacokinetics

3 TC and FTC share an intracellular mode of action against HIV reverse transcriptase and are pharmacokinetically very similar. They are both cytosine analogues which are phosphorylated intracellularly to interfere with HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.

The main difference between the two drugs is their intracellular half-life, which is approximately 38 h for FTC triphosphate,23 compared with approximately 16 h for 3 TC triphosphate.20

However, both drugs can be administered once daily and when co-administered with TDF are able to provide sufficient symmetry to the ARV combination, especially with third agents characterised by similarly prolonged plasma half-lives.

Finally, because renal excretion of unchanged drug is the principal route of FTC and 3 TC elimination, the potential for these drugs to cause metabolic drug interactions is low and to date, no specific drug interactions have been reported in the literature.

**FTC and 3 TC in combination with TAF versus TDF**

One limitation is the inability to use 3 TC in combination with TAF, since all TAF products for HIV are co-formulated with FTC. Although the International Antiviral Society-USA (IAS-USA) guidelines express a preference for TAF over FTC, DHHS7 and EACS guidelines do not. Although TDF is associated with changes in renal and bone biomarkers, differences in clinical end-points seem to be largely limited to when TDF is combined with a boosted 3rd agent.20,21 In addition, TAF is associated with a less favourable lipid profile than TDF and, although lipid difference in trials were small, they may be more pronounced and of clinical consequence in real-life populations.

**Recommendations from international guidelines**

In 2012, the World Health Organisation (WHO) published a Technical Update on the pharmacological equivalence and clinical interchangeability of 3 TC and FTC. This was based on a comprehensive review that examined preclinical studies, efficacy and safety data from clinical trials, comparative data concerning the development of resistance, considerations of patent barriers, comparative cost analysis and the availability of FDCs, and concluded that the available data support the clinical and programmatic interchangeability of 3 TC and FTC.29

Furthermore, the 2019 DHHS (December 2019) and EACS antiretroviral guidelines recommend that 3 TC and emtricitabine may be considered interchangeable.7

**NRTI backbones in current use**

International guidelines7–9 recommend the NRTI backbones illustrated in Table 1, in combination with a third agent, for initiation of ART.

Today, tenofovir-based two-NRTI backbones are the cornerstone in the treatment of HIV. Several tenofovir-based regimens are available as fixed dose combinations (FDC), of which some are branded and some generic formulations and some are composed by the mixture of the two (Table 3).

A drawback to branded FDC is that they traditionally come at an increased cost. However, as more components of first-line regimens become generic, clinicians and third-party payers will need to define the true cost-benefit associated with using some generics, and the clinical relevance of taking a single pill compared to multiple pills once daily.5

The availability of generic formulations has facilitated the “unbundling” of prescriptions, i.e. using individual generic formulations of the
Table 3
Timelines of US FDA approvals for the N(R)RTI class of antiretrovirals 10.

| Year | NRTI/NRRTI |
|------|------------|
| 1987 | Zidovudine |
| 1991 | Didanosine |
| 1992 | Zalcitabine |
| 1994 | stavudine |
| 1995 | Lamivudine |
| 1997 | ‘Combivir’ (FDC of zidovudine 300 mg + lamivudine 300 mg) |
| 1998 | Abacavir |
| 2000 | Didanosine EC |
| 2001 | Tenofovir DF |
| 2003 | Emtricitabine |
| 2004 | “Epizicom” (FDC of abacavir 300 mg + lamivudine 300 mg) |
| 2004 | “Truvada” (FDC of tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg) |
| 2011 | Tenofovir 300 + Lamivudine 300 mg tablets (FDC) |
| 2016 | “Descovy” (FDC of tenofovir alafenamide 25 mg + emtricitabine 200 mg) |

* Cipla formulation tentatively approved as an NDA (number 200623) on March 5, 2011.

FDC to cut costs. Published evidence from the National Health Service (NHS) cohort in the UK indicates a favourable experience when the FDC of TDF/FTC/efavirenz was replaced with one pill of TDF/FTC plus one pill of EFV. Of 230 patients who were switched away from the single-tablet regimen between December 2016 and October 2017, 177 (77%) patients remained on TDF/FTC + EFV at December 2018. Although the increased pill burden was a significant concern for prescribers, this was not reflected in the attitude of patients. The authors concluded that pill burden is not a major consideration for switching stable patients.

TDF/3 TC as a viable option

Several studies have demonstrated the interchangeability of FTC with 3 TC, as aforementioned, this has also been recommended by the DHHS, WHO, and EACS guidelines. Of all the ARVs approved by the US FDA more than 20 years ago, only 3 TC continues to be recommended in the most recent guidelines globally. This is supported by extensive clinical experience garnered over 25 years, which has characterised efficacy and safety across patient populations.

Data from clinical studies support the efficacy and safety of the combination of TDF + 3 TC. Further, this combination has been used extensively as per WHO guidelines in various combination formulations with EFV and DTG. Recently, the TDF/3TC/DoR fixed-dose combination has received EMA and US FDA approval. Within Europe, the TDF/3 TC fixed-dose combination has received marketing authorisation in different European countries. The inclusion of 3 TC rather than FTC may offer some economic benefits, as well as assurance of an alternative supply for the NRTI backbone. Availability of this quality assured generic FDC offers an opportunity for reduced healthcare costs, as well as the construction of a triple drug regimen as per patient need.

Conclusion

The majority of evidence to date, ranging from pharmacological data to observational studies to direct and indirect comparisons in randomised trials, suggests that 3 TC and FTC are therapeutically interchangeable; differences, if any, are likely to be very small and not of clinical significance, especially when 3 TC is combined with TDF. This is today important as new drug formulations and generic combinations are becoming available globally which can benefit patients, institutions and healthcare programmes, and help bridging the global ART coverage gap when cost effective.

Declaration of competing interest

The authors declare no conflict of interest.

References

1. Global HIV and AIDS statistics – 2019 fact sheet. Available at: https://www.unaids.org/en/resources/fact-sheet Last; 2020. Accessed February 19.
2. Piot P, Quinn TC. Response to the AIDS pandemic – a global health model. NEJM. 2013;368:2210–2218.
3. Troganove SPC. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch;process; 2020. Last accessed February 19.
4. Clercq ED. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. Int J Antimicrob Agents. 2009;33:307–320.
5. Kaplan MR, Duan ES, Corado KC. Next generation fixed dose combination pharmacotherapies for treating HIV. Expert Opin Pharmacother. 2018;19(6):589–596.
6. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. Current Opinion in Virology. 2016;18:50–56.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV, Department of Health and Human Services. Available at: https://files.aidsinfo.nih.gov/contentfile/iv/guidelines/AdultandAdolescentGL.pdf; 2020. Last accessed February 19.
8. European AIDS Clinical Society (EACS). Guidelines version 10.1 October 2020. Available at: eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html; 2020. Last accessed December 17.
9. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. 2018 recommendations of the international antiretroviral society-US panel. J Am Med Assoc. 2018;320(4):379–396.
10. FDA approved drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm; 2020. Last accessed February 19.
11. Hill A, Hughes SL, Goham D, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? Journal of Virus Eradication. 2018;4:72–79.
12. ART Cohort Collaborations. Lancet. 2008;372:292–299.
13. Ford N, Vitoria M, Doherty M, et al. Candidates for inclusion in a universal antiretroviral regimen: are lamivudine and emtricitabine interchangeable? Curr Opin HIV AIDS. 2017;12(4):334–338.
14. Roko C, Gras L, van de Vijver D, et al. Virological responses to lamivudine or emtricitabine when combined with tenofovir and a protease inhibitor in treatment-naive HIV-1-infected patients in the Dutch AIDS Therapy Evaluation in The Netherlands (ATHENA) cohort. HIV Med. 2016;17(8):571–580.
15. Molina JM, Squires K, Saéz EE, et al. Doravirine versus rilpivirine-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, doubleblind, phase 3, non-inferiority trial. Lancet HIV. 2018:e211–e220.
16. Orrin C, Squires K, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emintricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. Clin Infect Dis. 2019;68(4):535–544.
17. Roko C, Fibriani A, van de Vijver D, et al. More virological failure with lamivudine than emtricitabine in efavirenz and nevirapine regimens in the Dutch Nationwide HIV Cohort. J Int AIDS Soc. 2014;17(4 Suppl 3):19491. Nov 2 eCollection.
18. Pollock K, Stebbing J, Bower M, et al. Emtricitabine intolerance in treatment-experienced patients switched from lamivudine: a method of assessing toxicity. J Antimicrob Chemother. 2006;58(1):227–228.
19. Borra’s-Blasco J, Navarro-Ruiz A, Borra’s C, et al. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemother. 2016;71(8):2047–2056.
20. Shisakala T, Talukder T, Yamamoto Y, et al. Investigation of emtricitabine-associated skin pigmentation and safety in HIV-1-infected Japanese patients. J Infect Chemother. 2017;23:602–608.
21. Nelson M, Schiaveone M. Emtricitabine (FTC) for the treatment of HIV infection. J Clin Pract. 2004;58:504, 10.
22. Venhoff N, Sterer B, Melkaoui K, et al. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional nucleoside reverse transcriptase inhibitors. Antivir Ther. 2007;12(7):1075–1085.
23. Bulteel N, Bansi-Matharu L, Churchill D, et al. The emergence of drug resistant HIV variants at virological failure of HAART combinations containing efavirenz, tenofovir and lamivudine or emtricitabine within the UK Collaborative HIV Cohort. J Infect. 2011;63(4):277–84.
24. Marcelin AG, Charpentier C, Wirden M, et al. Resistance profile of emtricitabine and lamivudine in tenofovir-containing regimens. J Antimicrob Chemother. 2012;67:1475–1478.
25. Moore KH, Barrett JE, Shaw S, et al. The pharmacokinetics of lamivudine phosphorylation in peripheral blood mononuclear cells from patients infected with HIV-1. AIDS. 1999;13(16):2239–2250.

26. Stevens RC, Blum MR, Rousseau FS, et al. Intracellular pharmacology of emtricitabine and tenofovir. Clin Infect Dis. 2004;39(6):877–878.

27. Pepperrell T, Hughes S, Gotham D, et al. Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate - Is There a True Difference in Safety? 17th European AIDS Conference Nov 6-9; 2019. Basel, Switzerland; P13/3.

28. Milinkovic A, Berger F, Arenas-Pinto A, et al. Reversible effect on lipids by switching from tenofovir disoproxil fumarate to tenofovir alafenamide and back. AIDS. 2019;33(15):2387–2391.

29. Technical Update on Treatment Optimisation: Pharmacological Equivalence and Clinical Interchangeability of Lamivudine and Emtricitabine: A Review of Current Literature. WHO June; 2012.

30. Buckberry K, Kegg S. Audit - what happened to patients after Atripla was unbundled?. In: 25th Annual Conference of British HIV Association (BHIVA) April 2-5. Poster abstracts P5; 2019.

31. Quercia R, Perno CF, Koteff J, 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(5):125–135.

32. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available on who.int/hiv/pub/arv/arv-2016/en/ June 2018. Last accessed September 30th, 2019.

33. Delstrigo EMA approval dated September 29th, 2018 (EMA/CHMP/619909/2018, MSD). Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positiveopinion-delstrigo_en.pdf Last; 2020. accessed February 19.

34. Delstrigo US FDA approval august 30th, 2018 (NDA 210807Orig1s000, MSD). Available at: https://www.mrknewsroom.com/news-release/prescription-medicine-news/mercks-pifeltrodoravirine-and-delstrigo-doravirinelamivudin; 2020. Last accessed February 19.

35. Mhra, BfArM, Anm (RO), AEMPS. Data on File, Cipla Ltd.