HIV/AIDS Programme

TECHNICAL UPDATE ON TREATMENT OPTIMIZATION

PHARMACOLOGICAL EQUIVALENCE AND CLINICAL INTERCHANGEABILITY OF LAMIVUDINE AND EMTRICITABINE: A REVIEW OF CURRENT LITERATURE

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SUMMARY

Lamivudine (3TC) and emtricitabine (FTC) are antiretroviral drugs included in current World Health Organization (WHO) Model Lists of Essential Medicines[a] (EML) and various international guidelines for the treatment of HIV infection.[b] In these documents, 3TC and FTC are considered clinically equivalent. However, some in vitro studies suggest that there may be pharmacological differences, e.g. FTC may have a longer half-life than 3TC, and these differences could suggest that FTC may have potential advantages compared to 3TC.

To inform this determination about the pharmacological equivalence and clinical interchangeability of 3TC and FTC, a comprehensive review has been undertaken. This review included the 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 fixed-dose combinations.

Although based on few direct comparisons, a recent systematic review indicated that the clinical and virological efficacy and safety of 3TC and FTC are comparable. The systematic review also showed that the development of the M184V/I mutation is associated to a greater extent with the use of a 3TC- rather than a FTC-containing regimen. However, the clinical and public health implications of this difference are not clear, and seem to depend largely on the presence or absence of other concomitant nucleoside analogue mutations.

Despite current data that support the interchangeability of these two antiretrovirals from clinical and programmatic perspectives, the establishment of population-based monitoring of 3TC- and FTC-associated resistance patterns should be considered in order to better inform future decisions on this topic.

This review will inform the revision of WHO HIV treatment guidelines and guidance provided through WHO and UNAIDS Treatment 2.0 initiative. This initiaitive aims to catalyse the next phase of HIV treatment scale up through promoting innovation and efficiency gains, such as the development of more simplified, less toxic and more efficient antiretroviral (ARV) drug regimens.(1) This approach includes establishing optimal dosages of ARVs (including possible dose reductions of existing ARVs), reducing pill burden, using fixed-dose combinations (FDCs), improving paediatric formulations, and expanding access to effective, safer, and affordable first-, second- and third-line drug regimens.

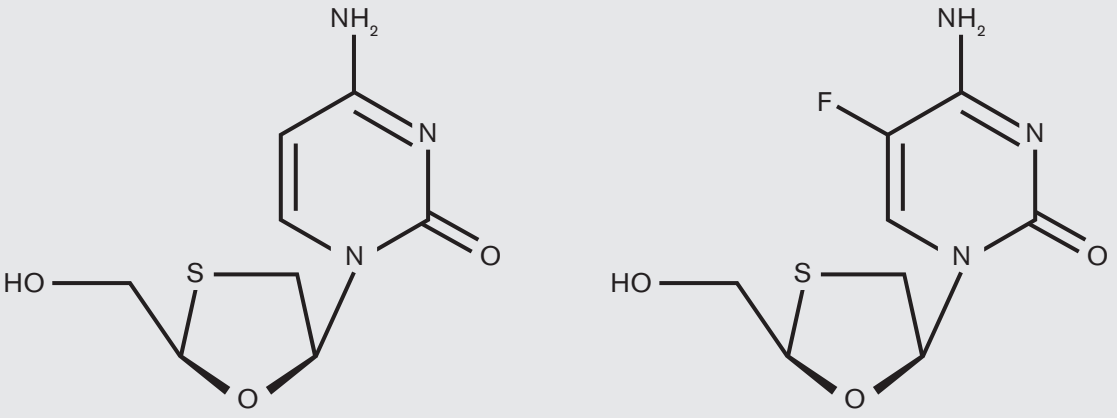
a Available at http://www.who.int/medicines/publications/essentialmedicines/en/

b Available at http://www.who.int/hiv/pub/guidelines/en/

INTRODUCTION

Lamivudine (3TC) has been pivotal to all first-line ARV regimens in industrialized as well as in resource-limited settings since the beginning of triple combination ART. It is a core component of the dual nucleoside reverse transcriptase inhibitor (NRTI) backbone in all currently preferred first-line ARV combinations. It is safe, has an excellent toxicity profile, is non-teratogenic and is effective against hepatitis B virus (HBV).(2, 3) It is widely available in FDCs. However, the lower genetic barrier to resistance of 3TC is a major weakness and specific resistance to 3TC evolves frequently.(4, 5)

Figure 1: Molecular structures of Lamivudine (3TC) and Emtricitabine (FTC).



Emtricitabine (FTC) is a NRTI structurally related to 3TC (Figure 1) and shares the same efficacy against HBV, has the same toxicity and resistance profiles, and also is available in FDCs.[c] Both drugs were included in the WHO Model Lists of Essential Medicines (EML) and WHO ART guidelines, and were considered clinically equivalent. However, laboratory studies suggest that FTC may have a longer half-life than 3TC, which could be a potential advantage.(6) Moreover, there is in vitro evidence suggesting that FTC favourably interacts with tenofovir (TDF), which further extends its half-life.(7)

While both 3TC and FTC are associated with the emergence of the M184V resistance mutation, which is the most common NRTI mutation, the clinical consequences of this mutation are not obvious. Wainberg has summarised the effects in terms of increased reverse transcriptase fidelity (reducing the chances of further spontaneous mutagenicity) and lowered viral fitness.(8) Although, in vitro, M184V/I mutations cause high-level resistance to 3TC and FTC, and low-level resistance to didanosine (ddI) and abacavir (ABC), the mutation increases susceptibility to zidovudine (AZT), stavudine (d4T), and TDF.(9) These considerations informed the decisions to retain 3TC in second-line regimens in the 2006 and 2010 revisions of WHO ART guidelines.[d]

c A fixed-dose triple combination of FTC, TDF and EFV was approved by the U.S. Food and Drug Administration (FDA) on July 12, 2006 under the brand name Atripla. Prescribing information, September 2011 available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021937s023lbl.pdf

d Available at http://www.who.int/hiv/pub/guidelines/en/

However, pharmacological data are limited, particularly in adolescents, children and infants, and usually come from individuals in industrialized countries. Different genetic backgrounds, differing epidemiologies, and the balance between desired and undesired effects may not be comparable with populations in resource-limited settings.

Furthermore, the impact of some adverse drug reactions can have important programmatic implications, such as the selection of preferred ARVs for first-line regimens, and need to be better evaluated. A review of the current recommendations on the use of ART regimens in the management of HIV infection is planned for the development of the 2013 WHO ART guidelines.[e]

In making a determination about the pharmacological equivalence and clinical interchangeability of 3TC and FTC, the following issues were considered in this technical update:

- Evidence from preclinical and in vitro studies;
- Clinical efficacy and safety data from randomised controlled trials;
- The development of resistance;
- The relative availability of preferred FDCs for use in resource-limited settings, including the existence of patent or other barriers.

PRECLINICAL AND IN VITRO DATA

Based on several in vitro studies that evaluated the potential impact of the structural differences between 3TC and FTC, Gilead Sciences[f] claims in vitro superiority of FTC.

- Longer intracellular half-life compared to 3TC — 39 hours vs. 15–22 hours (10,11-13)
- Greater potency against HIV-1 compared to 3TC — average of 11-fold by EC50 (14) approximately 3-fold by dual infection/competition assay (15)
- Superior inhibition of viral replication when combined with TDF compared to 3TC+TDF ($P<0.0005$)(16)
- Greater synergy with TDF compared to 3TC (7)
- Higher binding affinity for reverse transcriptase and lower affinity for mitochondrial DNA polymerase compared to 3TC (17)

However, data supplied by ViiV Healthcare[g] has questioned the potency difference, pointing out that "antiviral effects in vitro are not reliable predictors of in vivo clinical activity".(18)

CLINICAL DATA: EFFICACY AND SAFETY

Comparisons in clinical trials of 3TC and FTC have been conducted with differing companion nucleosides, which introduces imprecision to the comparison; it is the FDCs that are compared rather than 3TC and FTC.

e Available at http://www.who.int/kms/guidelines_review_committee/en/index.html

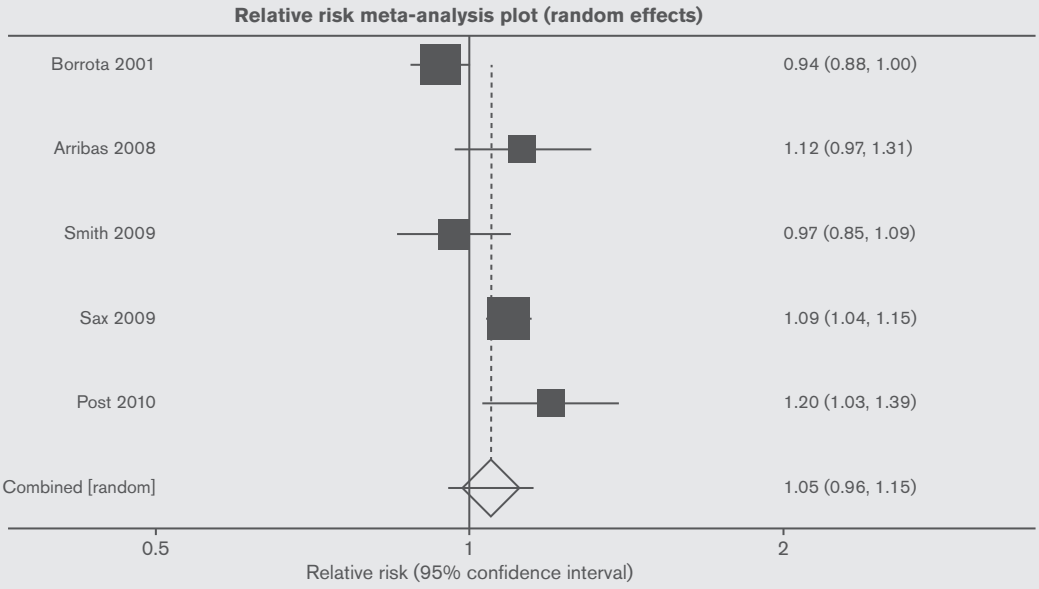
f Gilead Sciences is a research-based biopharmaceutical company. Two of its products are emtricitabine (FTC) and tenofovir (TDF).

g ViiV Healthcare is a global specialist HIV company established by GlaxoSmithKline and Pfizer

A systematic review has been conducted comparing the efficacy and safety, and the pharmacological equivalence of 3TC and FTC.(19) The review concluded that the efficacy and safety of FTC and 3TC are comparable. Where pooled estimates were possible, no significant difference in the relative risk of attaining a target viral load could be shown between those trial participants treated with a FTC-containing regimen and those treated with a 3TC-containing regimen (Figure 2).

An open-label, 10-day monotherapy study in 81 patients demonstrated a greater mean reduction in viral load with FTC than with 3TC (-1.7 log compared to -1.5 log respectively; P <0.05), and that more patients on FTC achieved HIV-1 RNA <400 copies/mL or >2 log decrease from baseline during the study than patients on 3TC (53% vs. 29% respectively).(19) However, these data from this open-label, non-randomized trial do not add significantly to the available data from randomized, controlled trials (RCTs) in treatment-naive patients, or from switch studies, using single agents or FDCs.(20-25)

Figure 2: Relative risk of reaching VL target (50 or 400 copies/mL) when treated with FTC rather than 3TC.



Source: Gray, 2012 (19)

This review noted that there were few available direct comparisons of 3TC to FTC. As stated above, assessing differences in the safety of these two drugs is complicated by the presence of other ARVs, and studies generally have concentrated on the effects associated with other medicines (such as the renal effects associated with TDF). For instance, in describing the differences in efficacy seen in comparisons of FTC+TDF with 3TC+AZT and with 3TC+ABC, one possible explanation is that 3TC+ABC is less potent than FTC+TDF. Another possible explanation may be differences in the pharmacokinetics of the individual drugs(26), or a true difference in potency as TDF and FTC have longer half-lives than ABC and 3TC.(27) A review of the four WHO-recommended first-line ARV regimens (TDF + [either FTC or 3TC] + [either EFV or NVP])[h] found that TDF+3TC+NVP was virologically inferior to the other regimens in two of three studies. Possible explanations for these

h EFV = efavirenz, NVP = nevirapine

findings include the greater antiviral activity of EFV versus NVP and longer intracellular half-life of FTC-triphosphate versus 3TC-triphosphate.(28) However, there were no indications of differences in the safety profiles of 3TC and FTC.

EVIDENCE CONCERNING THE DEVELOPMENT OF RESISTANCE

There are several studies that infer a lower rate of resistance mutations (M184V) with FTC-containing regimens when compared to 3TC-containing regimens.(29-32) The reasons cited were the greater potency or longer half-life of FTC compared to 3TC or potential pharmacokinetic differences, but no definite conclusions were reached.

Similar differences in the rates of developing mutations were seen in data from a retrospective cohort(33) and from routine population data.(34) The systematic review concluded that there were consistent data to support the view that the development of M184V/I mutations is associated to a greater extent with the use of a 3TC- rather than a FTC-containing regimen (Figure 3), but that the clinical implications of this difference are difficult to predict.(19) It has been suggested that the phenotypic and clinical significance of the M184V mutation is influenced by the presence or absence of other NRTI resistance mutations.

Figure 3: Relative risk of developing M184V/I mutation in those with virological failure, when treated with FTC rather than 3TC.