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.

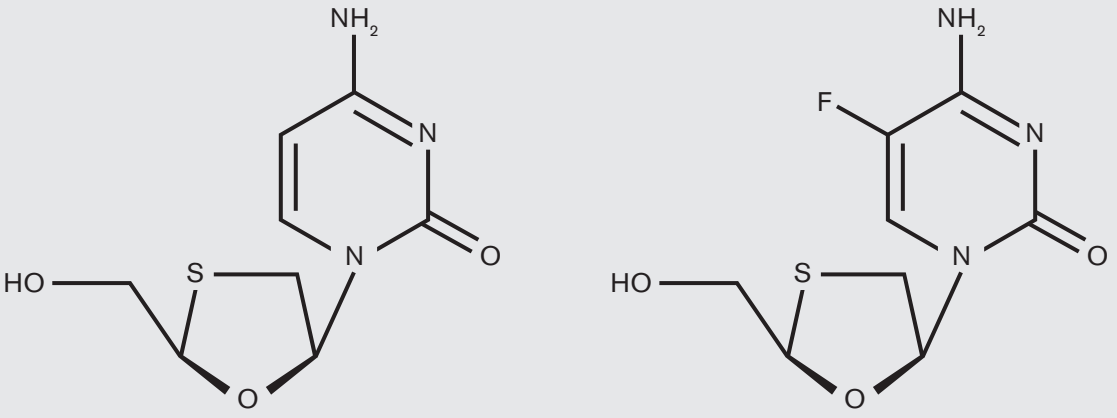
a Available at http://www.who.int/medicines/publications/essentialmedicines/en/

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

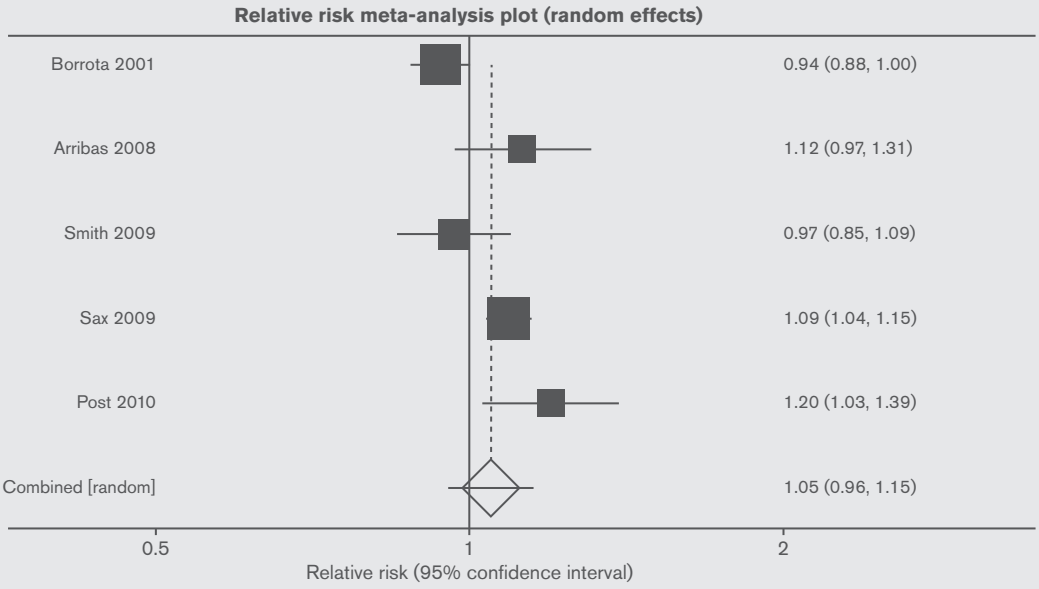
f Gilead Sciences is a research-based biopharmaceutical company. Two of its products are emtricitabine (FTC) and tenofovir (TDF).

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

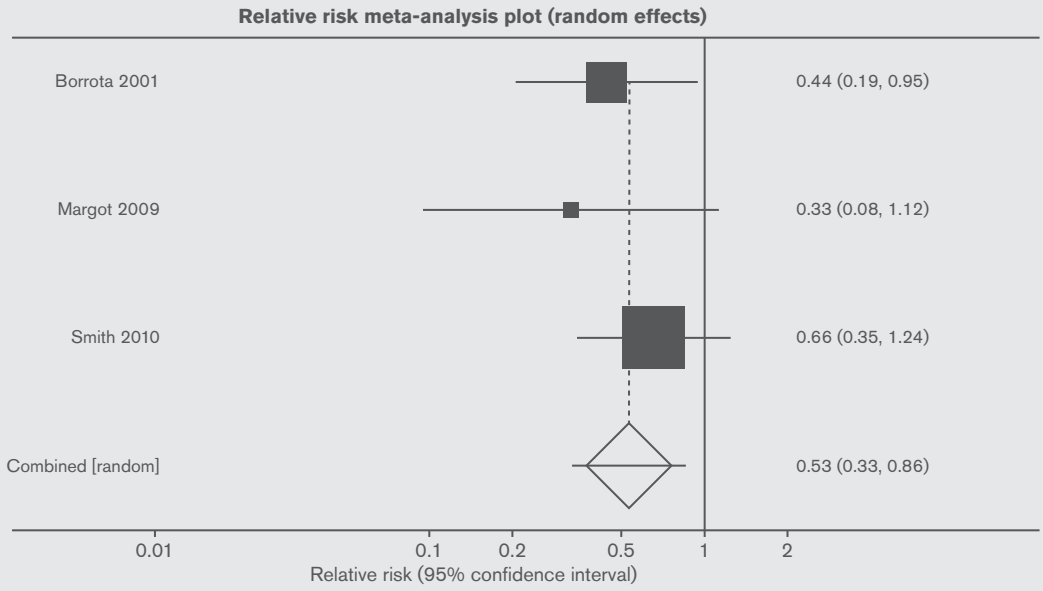
findings include the greater antiviral activity of EFV versus NVP and longer intracellular half-life of FTC-triphosphate versus 3TC-triphosphate.(28) However, there were no indications of differences in the safety profiles of 3TC and FTC.

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.



Source: Gray, 2012 (19)

AVAILABILITY

A biowaiver[i] monograph for 3TC was published in 2011.(36) Literature relevant to the decision to allow a waiver of in vivo bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing 3TC as the only active pharmaceutical ingredient were reviewed. The solubility and permeability data of 3TC as well as its therapeutic index, its pharmacokinetic properties, data indicating excipient interactions, and reported BE/bioavailability (BA) studies were taken into consideration. A biowaiver was recommended for new 3TC multisource IR products and major post-approval changes of marketed drug products.

This process is included in the WHO Prequalification of Medicines Programme (PQP), and is detailed in the report of the WHO expert committee on specifications for pharmaceutical preparations[j]. This mechanism allows for the simplified approval of generic 3TC, thereby possibly making 3TC more readily available.

As of November 2011, FTC was identified by WHO PQP to be eligible for Biopharmaceutics Classification System (BCS)-based biowaiver applications.[k]

The current WHO PQP[l] contains a large number of approved 3TC formulations (with AZT, ABC, TDF, with AZT+ABC, AZT+EFV, d4T+EFV, and with d4T+NVP[m]), but a far more restricted list of FTC formulations (with TDF and with TDF+EFV)[n].

ACCESS

The patent status of 3TC and FTC may be relevant to access. Access to patent information in relation to medical products has a major, and growing, importance for public health. Many stakeholders need to know about the patent status of specific products in specific markets in order to determine their freedom to operate in research and development, in manufacture, to design access strategies, to assess which products can be produced and marketed without infringing patents, and to determine with whom and the extent to which licenses have to be negotiated.[o] Assessing the patent status of medical products is not always easy. The Medicines Patent Pool Patent Status Database for Selected HIV Medicines[p] provides information on the patent status of selected antiretrovirals in a large number of low- and middle-income countries. It enables users to search by country and region, and by medicine, to obtain information on the key patents relating to each medicine.

i A biowaiver is a document or process which demonstrates the bioequivalence by in vitro instead of more expensive and time-consuming in vivo PK studies for the simplified approval for immediate release generic solid oral products, allowing companies to forego clinical bioequivalence studies, provided that their drug product meets the specification detailed in the guidance. http://apps.who.int/prequal/

j http://www.who.int/medicines/services/expertcommittees/pharmprep/en/index.html

k http://apps.who.int/prequal/info_applicants/BE/BW_general_2011November.pdf

l http://apps.who.int/prequal/default.htm

m The use of d4T is no longer a recommended first-line option. However, many patients are well controlled on d4T combinations and do not have an option to switch. Therefore, the use of d4T will continue for some time.

n The FDA in August 2011 approved FTC+TDF+rilprivarine (Complera).

o Access to medicines, patent information and freedom to operate. WHO. Geneva, February 18, 2011. Available at: http://www.wto.org/english/news_e/news11_e/trip_21jan11_bkgd_paper_e.pdf

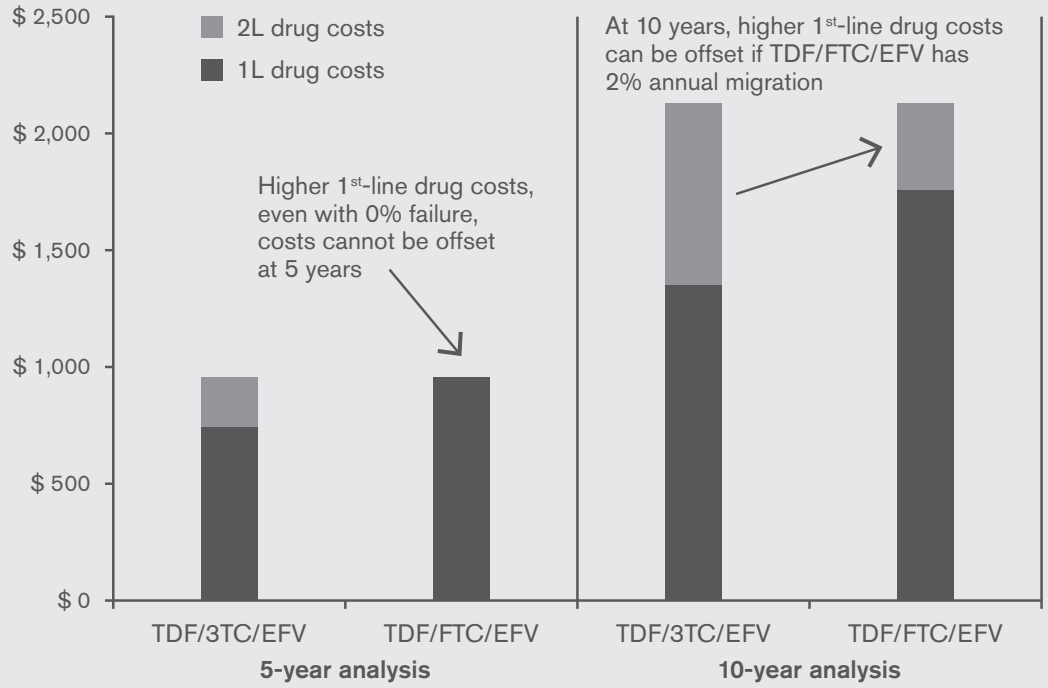
p http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs

The original US patent on 3TC (EP0382526) expired in February 2010. A UK patent on the crystal form (WO9111186) expires in June 2012. However, patents on new formulations (US 1997 60/042,353 and GB 1997 9706295.4) expire only in 2018. The equivalent patent on FTC, held by Emory University (WO9111186), expired in January 2011. Patents subsequently granted in other jurisdictions may still be in effect. While the new formulation patent for 3TC has been lodged in India, no barriers exist to active pharmaceutical ingredient production or formulation in that country at this time.

Data on global access and pricing can be found in the reports of the Médecins Sans Frontières (MSF) Untangling the Web of Antiretroviral Price Reductions[q]. Best prices for 3TC 300 mg remain lower than for FTC 200 mg. An oral liquid formulation of 3TC is available, but no similar formulation of FTC has been prequalified[r]. Combinations with 3TC are still less expensive than those containing FTC.

The issue of price has been considered in a modelling exercise recently conducted by the Clinton Health Access Initiative (CHAI).[s] Based on the assumption of a more favourable durability profile of TDF/FTC/EFV compared with TDF/3TC/EFV and the existing cost differentials, the CHAI team concluded that in the short- to medium-term, it is unlikely that the efficacy differential of TDF/FTC/EFV can offset its higher cost. For long-term forecasting at 10 years, cost parity is achieved only if TDF/FTC/EFV migration rates to second-line regimens are half that of TDF/3TC/EFV (Figure 4)[t].

Figure 4. Five- and 10-year cost analysis of TDF/3TC/EFV vs. TDF/FTC/EFV assuming 4% migration rate for TDF/3TC/EFV and CHAI price forecasts.



Source: CHAI, 2012[xviii]

q Accessible at http://utw.msfaccess.org

r MSF has summarised the data for TDF/FTC (http://utw.msfaccess.org/drugs/tdf-ftc), TDF/FTC/EFV (http://utw.msfaccess.org/drugs/tdf-ftc-efv), TDF/3TC (http://utw.msfaccess.org/drugs/tdf-3tc), TDF/3TC/NVP (http://utw.msfaccess.org/drugs/tenofovir-disoproxil-fumaratelamivudinenevirapine) and TDF/3TC/EFV (http://utw.msfaccess.org/drugs/tdf-3tc-efv).

s Personal communication

t This analysis assumed a 4% failure rate of TDF/3TC/EFV and CHAI price forecasts and AZT/3TC/ATV/r is used for second-line in both the TDF/3TC/EFV and TDF/FTC/EFV arms.

However, another simulated cost effectiveness model using 3TC and FTC regimens showed that, when substituting 3TC for FTC in regimens containing TDF and NVP, FTC could promote savings as its higher efficacy may decrease the potential need for more expensive second-line regimens. (37) According to this model, the TDF/FTC/NVP regimen would be more cost-efficient as a first-line ART in resource-limited settings if its efficacy was >2% compared to the TDF/3TC/NVP regimen. However, because a very large sample size is required to detect a 2% difference, an RCT is not likely to be funded to verify this model.

CONCLUSIONS

Despite limited direct comparisons, the available data support the clinical and programmatic interchangeability of 3TC and FTC.

The current edition of the WHO Model List of Essential Medicines (March 2011)[u] states that FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. This echoes the guidance provided by current WHO and United States Department of Health and Human Services guidelines[v,w] that state that 3TC may substitute for FTC or vice versa.

Clinically, there is little direct evidence comparing 3TC with FTC as most studies have been conducted with differing companion nucleosides introducing imprecision to the analysis. However, a systematic review concluded that the clinical efficacy and safety of FTC and 3TC are comparable. Also, it is evident that the development of M184V mutations is associated more with the use of a 3TC- rather than a FTC-containing regimen, but the clinical implications of this difference are not clear.

However, despite some recent reductions, prices remain higher for FTC, and FDCs containing 3TC are less expensive and more available than those containing FTC in low- and middle-income countries. Modelling projections using current prices showed that development of virological failure over time and the need for more expensive second-line regimens are strongly influenced by the other drug components of the regimen, and any significant difference on efficacy can only be verified by controlled trials.

u http://www.who.int/medicines/publications/essentialmedicines/en/index.html

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

w http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

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