

Original article

Interchangeability between first-line generic antiretroviral products prequalified by WHO using adjusted indirect comparisons

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Background: The scaling-up of access to antiretroviral therapy, particularly in low- to middle-income countries, was facilitated by the introduction and widespread use of generic antiretroviral medicines and fixed-dose combinations. Generic medicines are approved by regulatory authorities based on the demonstration of bioequivalence with the innovator or reference product, as well as meeting quality standards. In clinical practice, however, it is not unusual for generics to be interchanged between each other. This study investigated the differences in bioavailability between WHO-prequalified first-line antiretroviral generics by means of adjusted indirect comparisons to ensure interchangeability between these generics.

Methods: Data on 34 products containing emtricitabine, tenofovir disoproxil fumarate, lamivudine and efavirenz in single formulations or fixed-dose combinations were included in the analysis. The 90% CI for the adjusted

indirect comparisons was calculated using the homoscedastic method that uses the conventional *t*-test, and assumes homogeneity of variances between the studies and small sample sizes. The combined standard deviation of both bioequivalence studies was calculated from the variability of each individual study.

Results: The adjusted indirect comparisons between generics showed that the differences, expressed as 90% CIs, are less than 30%. Confidence in the interchangeability of two generic products was reduced if the mean difference between the test and reference in the original studies is more than 10%.

Conclusions: From a bioequivalence perspective, the generic antiretroviral medicines prequalified by WHO are interchangeable with the reference, as well as between each other without safety or efficacy concerns.

Introduction

The HIV epidemic continues to be a major public health threat, especially in sub-Saharan Africa, which accounts for 70% of the 36.9 million people living with HIV globally in 2014 [1]. The goal of antiretroviral therapy (ART) is to ensure sustained and durable viral suppression, reduce morbidity and mortality, and improve the quality of life [2]. According to the

World Health Organization's (WHO) HIV treatment guidelines, the combination of tenofovir disoproxil fumarate, lamivudine or emtricitabine plus efavirenz is the recommended first-line ART for HIV treatment [2]. Globally, ART coverage increased from 2% of people living with HIV in 2000 to 40% in 2014 [3]. Nonetheless, according to the WHO, there are still 22

million people living with HIV globally that lack access to ART [1].

The scaling-up of access to ART, especially in low- to middle-income countries, in the last 15 years was made possible through the introduction and widespread use of generic antiretroviral medicines and fixed-dose combinations (FDCs) [4]. According to the WHO, a generic medicine is a pharmaceutical product that is usually intended to be interchangeable with an innovator product, manufactured without a license from the innovator company, and is marketed after the expiry date of the patent or other exclusivity rights [5]. Use of generic medicines and FDCs transformed treatment for HIV and AIDS by significantly reducing the pill burden, improving adherence and lowering treatment costs [6,7].

One of the priorities of the WHO Prequalification of Medicines Programme is to improve the availability of quality-assured medicines that meet WHO standards for quality, safety and efficacy [8] because ensuring access to quality, safe and efficacious medicines, including generic medicines, is important in public health programmes, particularly in those settings where the regulatory systems are inadequate and the burden of disease is the highest. In addition to meeting the quality requirements, generic medicines are prequalified by WHO after demonstration of bioequivalence to the innovator product or an acceptable reference product [5,9,10]. Two pharmaceutical products containing the same active substance are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (maximum or peak plasma concentration [C_{max}]) and time to reach peak concentrations [t_{max}]) and extent of absorption (area under the plasma concentration versus time plot [AUC]), after administration in the same molar dose under the same conditions, lie within acceptable predefined limits [5,9]. These limits depend on the characteristics of the drug product. Usually the acceptance range is 80–125% (that is, $\pm 20\%$), although for narrow therapeutic index drugs the acceptance range for the 90% CI of AUC and C_{max} is narrowed to 90–111% (that is, $\pm 10\%$) in the European Union for AUC (for example, tacrolimus) and sometimes also C_{max} (for example, cyclosporine) depending on its clinical relevance. On the contrary, in cases where C_{max} is not clinically relevant and highly variable it can be widened proportionally to its intra-subject variability up to 69.84–143.19% (that is, $\pm 30\%$ approximately) when the intra-subject variability is $\geq 50\%$ [5,9]. These studies are usually conducted as single-dose studies in fasted state because these conditions are considered the most sensitive to detect differences in the rate of absorption.

Two products that are bioequivalent are considered therapeutically equivalent and can be interchanged,

that is prescribable and switchable, in clinical practice. Furthermore, demonstration of bioequivalence of all the generics with the same reference product is also theoretically assumed as indirect demonstration of switchability between all the generics [11]. Although in clinical settings generic-to-generic switching is widely practiced, the comparison between generics is not a regulatory requirement. Adjusted indirect comparisons have been proposed for those cases where assurance of equivalence between generics is considered essential such as for chronic treatments [12–15].

The objective of this study was to investigate the bioavailability and the interchangeability of the recommended first-line antiretroviral generics prequalified by WHO using adjusted indirect comparisons.

Methods

Identification of products

Products containing emtricitabine, tenofovir disoproxil fumarate, lamivudine and/or efavirenz in single formulations or FDCs as solid oral dosage forms were identified from the list of prequalified products that is available on the WHO Prequalification Team Medicines (WHO PQT-m) website. Data from bioequivalence studies comparing the generic products with corresponding reference products in adult healthy volunteers were obtained from the WHO Public Assessment Reports (WHOPARs) that are available on the WHO prequalification website.

The inclusion criteria for accepting the bioequivalence studies for adjusted indirect comparison were: bioequivalence studies conducted in healthy volunteers and found acceptable as per WHO norms and standards, products currently prequalified (that is, not withdrawn or delisted), and studies conducted with the same reference product. Products for which prequalification was based on *in vitro* comparative dissolution studies such as waivers based on the Biopharmaceutics Classification System (BCS) were excluded from the analysis. FDC products with other active ingredients not under investigation were also excluded from the analysis.

Reference products in the WHO Prequalification Team Medicines

The acceptable reference products for emtricitabine, tenofovir, lamivudine and efavirenz in single formulation or FDCs for demonstrating bioequivalence are as follows: Emtriva® (emtricitabine) 200 mg capsule, Gilead Sciences; Viread® (tenofovir disoproxil fumarate) 300 mg tablet, Gilead Sciences; Epivir® (lamivudine) 150 mg and 300 mg tablet, GlaxoSmithKline; Sustiva® (efavirenz) 100 mg and 200 mg capsule, 600 mg tablet Bristol-Myers Squibb; Truvada® (tenofovir disoproxil fumarate/emtricitabine) 300/200 mg tablet,

Gilead Sciences; and Atripla® (tenofovir disoproxil fumarate/efavirenz/emtricitabine) 300/600/200 mg tablet, Bristol–Myers Squibb and Gilead Sciences.

Statistical method for the adjusted indirect comparison between generic products

The 90% CI for the adjusted indirect comparison of each comparison was calculated as described by Gwaza *et al.* [12]. Briefly, the width of the 90% CI for the adjusted indirect comparisons was calculated using the recommended homoscedastic method [12]. This method uses the conventional *t*-test and assumes homogeneity of variances between the studies and small sample sizes. The combined standard deviation of both bioequivalence studies is calculated from the variability of each individual study.

Although $\pm 20\%$ acceptance range is used for direct comparisons, $\pm 30\%$ acceptance range is proposed for adjusted indirect comparisons [12,14], due to the limited precision of indirect comparisons [16,17].

Results

A total of 34 products met the inclusion criteria and were included in the analysis. Twenty products were dual and triple combinations reflecting the current recommendations and practice of using FDCs to lower treatment costs, pill burden and improve adherence. Figure 1 shows the formulations and frequency in single formulation and FDC included in the analysis. Tenofovir disoproxil fumarate appears as the key drug in the prequalified first-line ART with a total of 26 formulations compared to 14, 12 and 11 for emtricitabine, efavirenz and lamivudine, respectively. Moreover, tenofovir disoproxil fumarate appears in all the FDCs included in the analysis. The combinations also reflect the recommended choice of two nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitor (NNRTI) as part of the first-line treatment for HIV and AIDS [18].

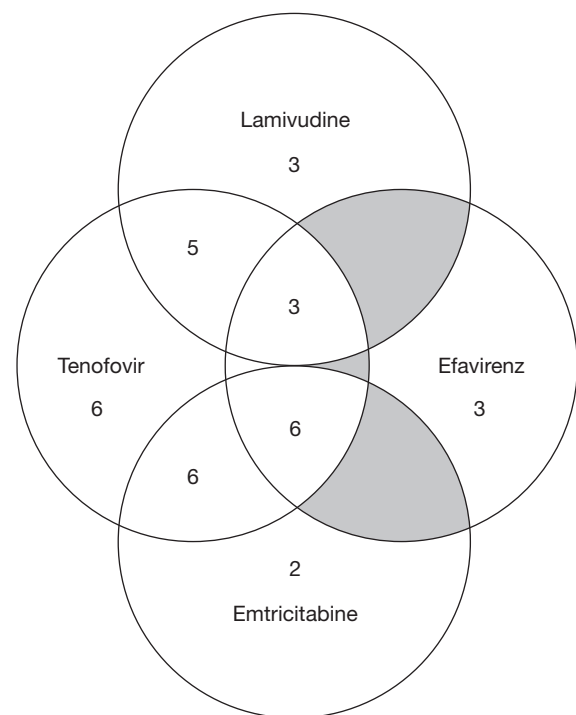
All the studies for the products under consideration were included in the analysis because they were done in healthy volunteers, that is, no study was excluded for being conducted in patients. The products compared directly with the same comparator were grouped together in the indirect comparisons and all products were included since there were at least two generic products for each drug compared with the same comparator product. No product was approved based on BCS-based biowaivers, that is, products had been approved based on an *in vivo* bioequivalence study. Three oral solutions for lamivudine were excluded from the investigation because they are approved without bioequivalence studies based on excipient comparability, since the active substance is already released when administered as a solution.

Figure 2 shows the point estimates and 90% CI for the ratios of C_{\max} and AUC_{0-t} for emtricitabine and efavirenz, while Figure 3 shows the data for lamivudine and efavirenz for the prequalified generic formulations against formulations listed as reference products by WHO [19]. Two mono-component products for emtricitabine are not included in the figures. The 90% CI for these two products were 85.6, 94.8% for C_{\max} , 91.3, 97.5% for AUC_{0-t} (HA418) and 91.3, 108.0% for C_{\max} and 101.0, 107.9% for AUC_{0-t} (HA451). For all the studies, the 90% CI for the ratios of C_{\max} and AUC_{0-t} was within the recommended standard of 80, 125% with the exception of two products that were approved with wider limits for C_{\max} for lamivudine (HA282) and efavirenz (HA306).

Adjusted indirect comparisons between generics

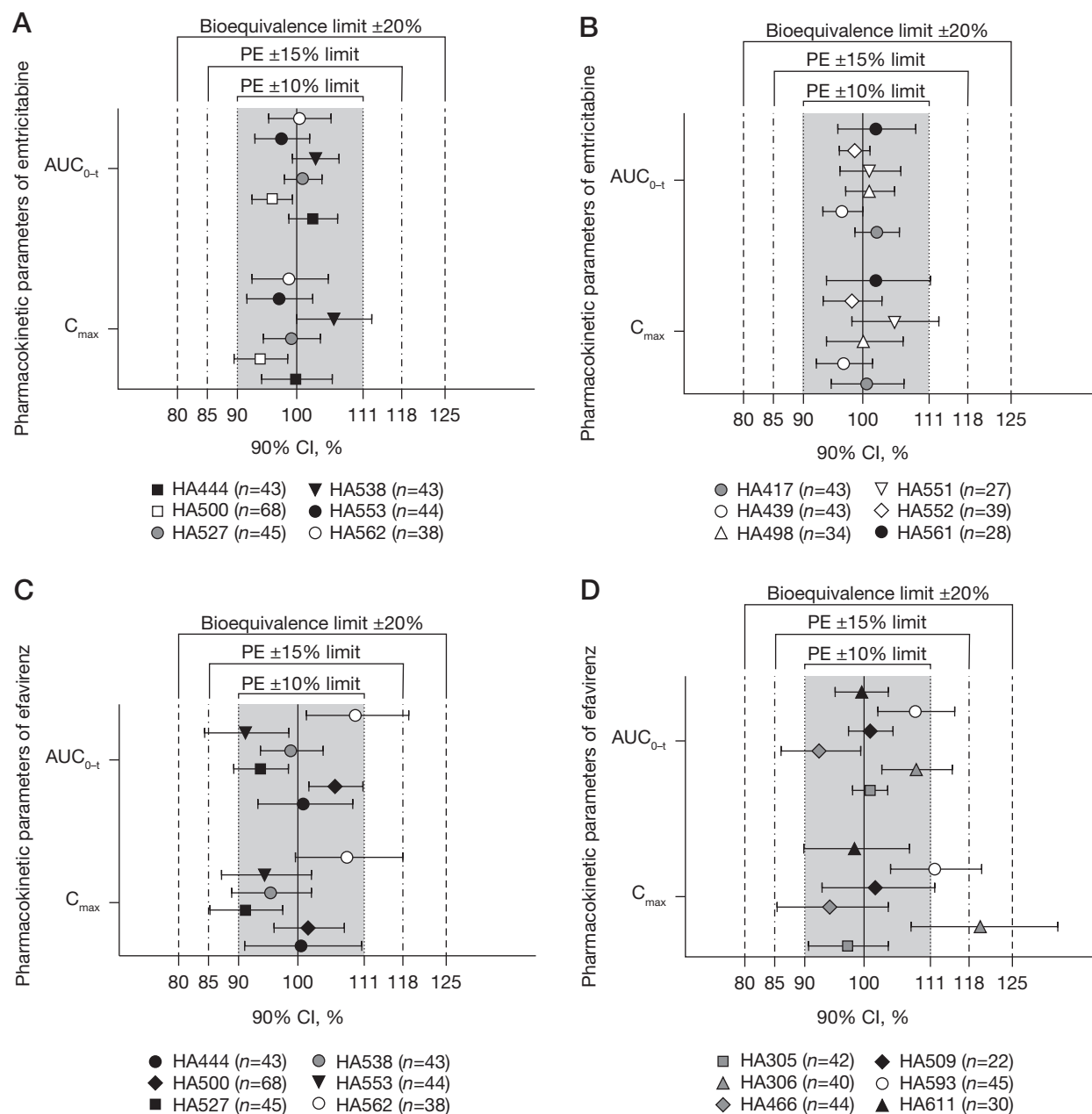
The distribution of the differences in bioavailability (AUC and C_{\max}) between generics calculated by adjusted indirect comparisons is presented in Table 1. The indirectly estimated 90% CI for the comparisons between generics for emtricitabine, tenofovir disoproxil fumarate, lamivudine and efavirenz are presented in Additional files 1, 2, 3 and 4, respectively.

Figure 1. Number of formulations included in the analysis



Number of formulations of efavirenz, emtricitabine, lamivudine and tenofovir included in the analysis. The shaded area indicates absence of prequalified products or products meeting the inclusion criteria.

Figure 2. 90% CI of the original bioequivalence studies



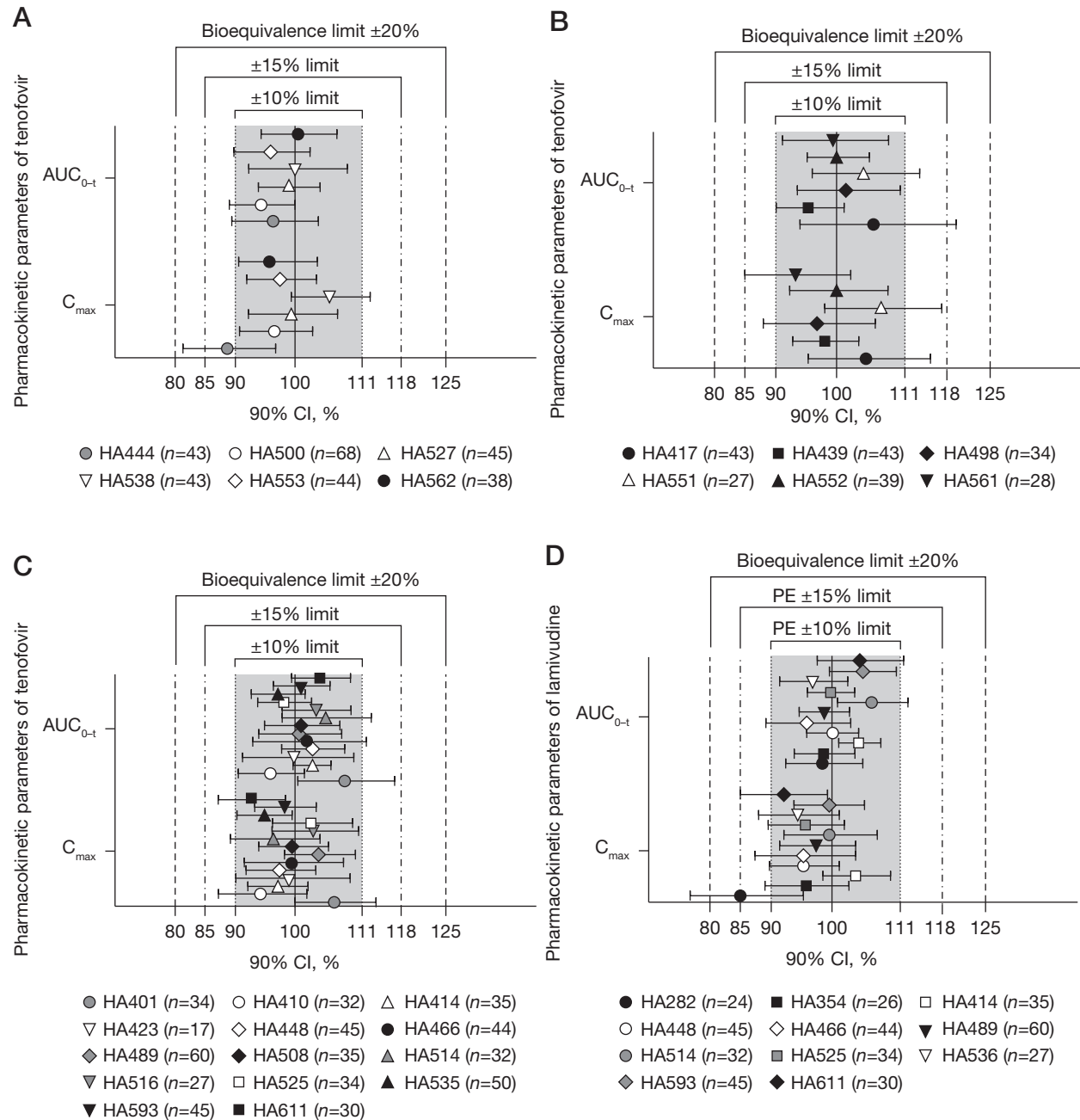
Geometric mean ratios of generic versus WHO approved reference with corresponding 90% CIs of the pharmacokinetic parameters (maximum or peak plasma concentration [C_{max}], area under the curve of the plasma concentration versus time from time 0 to the last measurable concentration [AUC_{0-t}]) in the original bioequivalence studies for emtricitabine and efavirenz; reference product for emtricitabine is (A) Atripla®, Gilead Sciences and (B) Truvada®, Gilead Sciences; reference product for efavirenz is (C) Atripla®, Gilead Sciences and (D) Sustiva®, Bristol-Myers Squibb. Data points are the point estimates (PE) of the pharmacokinetic parameters, with 90% CI. The shaded region indicates the $\pm 10\%$ limit. The light dotted lines at 85% and 118% indicate $\pm 15\%$ limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. In the legend, n denotes the sample size in the bioequivalence study.

All the 31 generic adjusted indirect comparisons for emtricitabine satisfy the conventional bioequivalence criterion of 80, 125% for C_{max} and AUC_{0-t} , which corresponds to $\pm 20\%$.

The 91 adjusted indirect comparisons between tenofovir generics with Viread® as reference in the original

studies satisfy the conventional 80, 125% acceptance range for all the pharmacokinetic parameters, except for one borderline case for C_{max} (105.28, 125.35%). Similarly, 15 adjusted indirect comparisons between tenofovir generics with Truvada® as reference in the original studies satisfy the conventional 80, 125% acceptance

Figure 3. 90% CI of the original bioequivalence studies



Geometric mean ratios of generic versus WHO approved reference with corresponding 90% CIs of the pharmacokinetic parameters (maximum or peak plasma concentration [C_{max}], area under the curve of the plasma concentration versus time from time 0 to the last measurable concentration [AUC_{0-t}]) in the original bioequivalence studies for tenofovir disoproxil fumarate and lamivudine; reference product for tenofovir is (A) Atripla®, Gilead Sciences, (B) Truvada®, Gilead Sciences, and (C) Viread®, Gilead Sciences; reference product for lamivudine is (D) Epivir® GlaxoSmithKline. Data points are the point estimates (PE) of the pharmacokinetic parameters, with 90% CI. The shaded region indicates the $\pm 10\%$ limit. The light dotted lines at 85% and 118% indicate $\pm 15\%$ limit. The heavy dotted lines at 80 and 125% indicate the standard 90% CI limit for bioequivalence. In the legend, n denotes the sample size in the bioequivalence study.

range for most comparisons except two borderline cases for AUC_{0-t} (97.29, 126.65% and 90.58, 125.47%) and three cases for C_{max} (97.94, 129.08%, 79.20, 102.79% and 101.34, 130.44%). The same trend was observed with Atripla® as a reference since the adjusted indirect

comparisons for AUC_{0-t} and C_{max} were within the acceptance range of 80, 125% in all the 15 comparisons, except 2 cases for C_{max} (79.77, 99.93% and 75.54, 93.27%).

Similarly, the adjusted indirect comparisons between lamivudine generics satisfy the conventional

Table 1. Distribution of the differences in bioavailability (AUC and C_{max}) between generics calculated by adjusted indirect comparisons

Drug	Reference	Number of products	Number of indirect comparisons	Difference between generics based on 90% CIs calculated by adjusted indirect comparisons ^a							
				≤20% C_{max}	≤20% AUC	>20–25% C_{max}	>20–25% AUC	>25–30% C_{max}	>25–30% AUC	>30% C_{max}	>30% AUC
Emtricitabine	Emtriva®	2	1	1	1	–	–	–	–	–	–
	Truvada®	6	15	15	15	–	–	–	–	–	–
	Atripla®	6	15	15	15	–	–	–	–	–	–
Tenofovir	Viread®	14	91	90	91	1	–	–	–	–	–
disoproxil fumarate	Truvada®	6	15	12	13	3	2	–	–	–	–
	Atripla®	6	15	15	13	–	2	–	–	–	–
Lamivudine	Epivir®	11	55	46	55	8 ^b	–	1 ^b	–	–	–
Efavirenz	Sustiva®	6	15	7	13	3	2	4 ^c	–	1 ^c	–
	Atripla®	6	15	12	12	3	2	–	1	–	–
Total			237	213	228	18	8	5	1	1	0

^aA difference of 20% corresponds to an acceptance range of 80–125% if expressed as ratio since the inverse of 0.8 is 1.25, similarly a difference of 25% corresponds to 75–133.33% and a difference of 30% corresponds to 70–142.86%. ^bThese indirect comparisons are comparisons with HA282, prequalified with wider maximum or peak plasma concentration (C_{max}) limits for lamivudine. ^cThese indirect comparisons are comparisons with HA306, prequalified with wider C_{max} limits for efavirenz. AUC, area under the curve of the plasma concentration versus time from time 0 to the last measurable concentration.

bioequivalence criterion of 80, 125% for AUC_{0-t} for all the 55 comparisons. Further, 46 comparisons satisfy the conventional limits for C_{max} , while 8 comparisons satisfy the wider acceptance limits of 75, 133% and one was outside this $\pm 25\%$ range, but inside the $\pm 30\%$ range.

For efavirenz, in the generics that were compared with Atripla®, the 90% CI for C_{max} and AUC_{0-t} falls within 80, 125% acceptance limits for the 15 comparisons except in 3 cases for C_{max} and AUC_{0-t} , but results were within $\pm 30\%$ range. For the generics compared with Sustiva®, 8 comparisons were outside 80, 125% for C_{max} but within $\pm 30\%$ except 1. Two comparisons were outside the conventional 80, 125% for AUC_{0-t} , but within $\pm 30\%$ range.

Discussion

This work describing the adjusted indirect comparisons for first-line HIV medicines is an extension of previous work on use of adjusted indirect comparisons to investigate the bioequivalence between WHO prequalified generics for artemether/lumefantrine [12], and first-line anti-tuberculosis medicines [14]. This assessment demonstrates that first-line antiretroviral generics prequalified by WHO can be interchanged without any safety and efficacy concerns in clinical settings. Notwithstanding that some comparisons were outside the conventional acceptance limits of $\pm 20\%$ for direct comparisons, in part, due to the reduced precision of the adjusted indirect comparisons, there were no generic–generic comparisons outside a wider limit of $\pm 30\%$ for the highly soluble drugs emtricitabine, tenofovir disoproxil fumarate and lamivudine.

For efavirenz, a poorly soluble drug, however, only one out of 30 generic–generic comparisons for C_{max} was outside $\pm 30\%$.

Failure to show equivalence within a $\pm 30\%$ acceptance range in 1 out of 30 adjusted indirect comparisons should be interpreted as insignificant number since it is in less than 5% of the comparisons (3.33%). Furthermore, in clinical practice the difference in C_{max} at steady state between test and reference product is known to be much lower than the difference observed in the single dose bioequivalence study [20]. In fact, bioequivalence studies are conducted as single dose studies because a single dose study is the worst-case scenario where the difference in C_{max} is detected with higher sensitivity [5,9,10].

Generic prescribing and substitution policies are widely adopted in many countries. In these situations, the physician can prescribe using international non-proprietary (generic) names and the dispenser has discretion to dispense any available product containing the same drug, strength and dosage form. Demonstration of bioequivalence between the generic and the innovator ensures prescribability of the generic in place of the innovator for new patients. This applies for all generic products either for acute or chronic treatments. Furthermore, for chronic conditions such as HIV and AIDS, the dispenser may substitute the previously administered product with the available product (generic substitution or switching) based on availability, price, patients' preference or restrictions by third party insurers. In these cases, generics need not only to be prescribable, but also switchable between themselves.

If bioequivalence is demonstrated with the innovator or acceptable reference using the current regulatory

limits of 80, 125% for the 90% CIs of the ratio test/reference for AUC and C_{\max} , should clinicians and patients be concerned with generic–generic switching for antiretroviral medicines? If the same dose is administered without any dose titration, as it is with the products under investigation, it should not matter if one generic or another one is administered. These investigated products are prescribable and switchable with the reference as bioequivalence was demonstrated with the reference within the conventional acceptance limits. However, regulatory authorities and clinicians have to be careful in some cases when it comes to substitution of the generics between themselves. While this is not critical for most drugs including the antiretrovirals investigated in this study, a point estimate constraint may be relevant for drugs with a narrow therapeutic index or for patients close to the border of its therapeutic window. In fact, narrow therapeutic drugs are usually assessed with a narrowed acceptance range (for example, 90, 111%) [5,9,10].

With regard to the drugs under investigation we must take into account that the prevalence of central nervous system (CNS) adverse events for efavirenz increases with plasma concentrations above 4 µg/ml [21–24]. This is higher in specific populations, such as the African population, with higher prevalence of CYP2B6 single nucleotide polymorphisms that result in reduced clearance. Therefore, these patients are likely to have higher plasma concentrations on the border of the therapeutic window with the standard dose of 600 mg once per day. Some authors [25,26] have argued for therapeutic drug monitoring for efavirenz or dose adjustments based on genotyping to reduce the incidence of CNS adverse events. Thus, failure to show equivalence in indirect comparisons within wider limits of $\pm 30\%$ may be of concern for efavirenz for which changes in C_{\max} may result in increased incidence of adverse events when patients are switched between generics. Moreover, this confirms our previous recommendation that regulatory authorities may consider point estimate constraint of $\pm 10\%$ [14,27], particularly when generic substitution is recommended by national governments.

The drugs under investigation, emtricitabine, lamivudine and tenofovir disoproxil fumarate, are highly soluble drugs according to the BCS [28–30] without known bioavailability problems. If formulated correctly to show similar *in vitro* dissolution profiles to those of the reference product and without critical excipients that may affect bioavailability, generics of these products are likely to have very similar point estimates of the ratio test/reference of AUC and C_{\max} in the bioequivalence studies. For emtricitabine, the point estimates were within $\pm 5\%$ of the unity value (100%) in the direct comparisons in most studies and never in

excess of 10%. In addition, it has a low intra-subject variability in pharmacokinetics thus, the width of the CIs are narrow in the direct comparisons. All the products considered for emtricitabine, except two, were formulated as FDCs. If the original studies are over-powered (that is, $>90\%$) for emtricitabine because the sample size has been calculated to compensate for the more variable active pharmaceutical ingredients tenofovir and efavirenz co-formulated with emtricitabine, the reduced precision associated with indirect comparisons becomes inconsequential [27]. Therefore, indirect comparisons for emtricitabine were able to meet the acceptance criterion of 80, 125% for C_{\max} and AUC_{0-t} in all comparisons.

Tenofovir disoproxil fumarate is a BCS class III drug (highly soluble and poorly permeable) [28,30] without bioavailability problems, thus the indirect comparisons were able to meet the acceptance criterion of 80, 125% in all 121 comparisons for AUC_{0-t} , except two borderline cases. Two of the three cases that were outside the 80, 125% for C_{\max} were due to one product (HA444) for which the point estimate difference in direct comparisons was greater than 10%. Similar to tenofovir disoproxil fumarate, lamivudine is a BCS class III [28], though lamivudine C_{\max} is problematic, its indirect comparisons were able to meet the acceptance criterion of 80, 125% for AUC_{0-t} and C_{\max} in all the comparisons, except comparisons with one product (HA282) for C_{\max} . HA282 was prequalified with wider limits of 75, 133% for C_{\max} and the point estimate difference in the direct comparison was greater than 10%. Consequently, all the comparisons for C_{\max} with this product satisfied this wider limit of 75, 133%, except one indirect comparison. These wider limits were accepted because at that time the WHO [31] and the European Union [32] guidelines allowed the widening of the acceptance range of C_{\max} if it was considered clinically irrelevant for the drug under investigation and it met the Health Canada requirement of point estimate within the 80, 125% limits for C_{\max} [33].

Efavirenz is a lipophilic drug with low solubility in water and buffers across the physiological pH range of 1.2 to 6.8. It is classified as either a BCS class II drug [34,35] or as a BCS class II/IV drug [36]. Thus, efavirenz oral absorption is limited by both dissolution rate and solubility. In addition, variation in excipients or in the manufacturing process was reported to impact the rate and extent of efavirenz oral absorption and *in vitro* dissolution profiles are not able to predict *in vivo* bioequivalence [37]. Thus, marked point estimate differences are more likely to occur for efavirenz compared with the other drugs under investigation. This will impact on the outcome of the indirect comparisons. Two products, HA593 and HA306, with point estimate difference greater than 10% and 14%, respectively, for efavirenz

C_{\max} in the original studies, accounted for 7 of the 8 indirect comparisons outside the 80, 125% limit. HA306 was able to show bioequivalence with the reference in the original study, despite such large point estimate difference, because efavirenz has low intra-subject variability and the studies are usually overpowered. The results for HA306 are consistent with computations that have shown that adjusted indirect comparisons are unlikely to meet the 80, 125% criterion even for overpowered studies when point estimate difference is greater than 14% [27].

The major limitation associated with adjusted indirect comparison is the reduced precision which makes them less effective as compared with direct comparisons [16,17]. Therefore, on one hand, if bioequivalence between generics is shown with conventional limits of 80, 125% in indirect comparisons, which was the case for more than 90% of the comparisons, we can consider the generics not only to be bioequivalent but also quite similar. On the other hand, the cases (10% for C_{\max} and 4% for AUC) that failed to show equivalence within the 80, 125% acceptance limits in indirect comparisons, do not indicate that the generics differ by more than 20% as the null hypothesis is never demonstrated, but that the data are inconclusive.

Although these results are based on data submitted at the time of prequalification, the results can be extrapolated to future batches because the generics are subjected to the same quality standards and specifications as the innovator products, and there are requirements on post-approval changes to ensure that future batches perform to the same standard as the batch used in the bioequivalence studies (biobatch) throughout the product's life cycle. In some instances, a new bioequivalence study is required to support such post-approval changes. A limitation of this study is that it only considers the studies submitted at the time of prequalification based on the available data in the WHOPARs and may not reflect results of new bioequivalence studies submitted to support such post approval changes. Further, this study relates to products prequalified by WHO and caution should be applied when extrapolating results to products approved by national authorities applying different bioequivalence acceptance principles. Nevertheless, the results obtained in this study are consistent with the outcomes reported elsewhere using data from other regulatory authorities [13,38,39].

In conclusion, this study provides confidence that prequalified generic antiretroviral medicines may be switched between them without any concerns for safety and efficacy if bioequivalence was demonstrated with the same reference product. In addition, most of the studied cases met the proposed limit of $\pm 30\%$ range for adjusted indirect comparisons due to the limited precision of indirect comparisons. Thus, interchangeability in practice should not be of concern in these cases except for poorly

soluble drugs, with a narrow therapeutic index or for patients close to the border of the therapeutic window, because generics containing poorly soluble drugs are more likely to exhibit a larger deviation relative to the reference (for example, 10, 15%), causing larger differences in bioavailability between generics, in contrast to generics containing highly soluble drugs, where differences are expected to be negligible. Lastly, these results confirm our previous findings that approval of products with no constraint on the point estimate or mean difference between the test and the reference may result in failure to demonstrate equivalence in indirect comparisons as shown by the cases for lamivudine and efavirenz.

Acknowledgements

This manuscript represents the personal opinion of the authors and does not necessarily represent the views or policy of their corresponding Regulatory Agencies or the World Health Organization.

A version of this manuscript was published in a PhD thesis for LG conducted at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands.

Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: 90% confidence interval for C_{\max} and AUC_{0-t} of emtricitabine obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing emtricitabine in single or fixed dose combination with other antiretroviral medicines can be found at https://www.intmedpress.com/uploads/documents/3830_Gwaza_Addfile1.pdf

Additional file 2: 90% confidence interval for C_{\max} and AUC_{0-t} of tenofovir obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing tenofovir in single or fixed dose combination with other antiretroviral medicines can be found at https://www.intmedpress.com/uploads/documents/3830_Gwaza_Addfile2.pdf

Additional file 3: 90% confidence interval for C_{\max} and AUC_{0-t} of lamivudine obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing lamivudine in single and fixed dose combination with other antiretroviral medicines https://www.intmedpress.com/uploads/documents/3830_Gwaza_Addfile3.pdf

Additional file 4: 90% confidence interval for C_{\max} and AUC_{0-t} of efavirenz obtained by adjusted indirect comparisons of bioequivalence studies of generic products containing efavirenz in single or fixed dose combination with other antiretroviral medicines https://www.intmedpress.com/uploads/documents/3830_Gwaza_Addfile4.pdf

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Accepted 14 September 2016; published online 20 September 2016
