J Infect Chemother 25 (2019) 687–694

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

A model-based comparative meta-analysis of the efficacy of dolutegravir-based and efavirenz-based regimens in HIV-infected patients☆

Ryosaku Ota [a], Hiromu Ishii [a], Masahiro Tsuda [b], Yuriko Higuchi [a], Fumiyoshi Yamashita [a, b, *]

[a] Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University, 46-29 Yoshidashimoadachi-cho, Sakyo-ku, Kyoto, 606-8501, Japan
[b] Department of Applied Pharmaceutics and Pharmacokinetics, Graduate School of Pharmaceutical Sciences, Kyoto University, 46-29 Yoshidashimoadachi-cho, Sakyo-ku, Kyoto, 606-8501, Japan

ARTICLE INFO

Article history:
Received 8 December 2018
Received in revised form
12 February 2019
Accepted 18 March 2019
Available online 11 April 2019

Keywords:
Combination antiretroviral therapy
Model-based meta-analysis
Dolutegravir
Efavirenz
Nonlinear mixed effect modeling

ABSTRACT

Currently, combinations of typical types of antiretroviral agents have been adopted as chemotherapy for human immunodeficiency virus (HIV) infection, comprising two nucleoside analogue reverse transcriptase inhibitors plus one of a non-nucleoside reverse transcriptase inhibitor, an integrase strand-transfer inhibitor, and a protease inhibitor. Although several meta-analyses have been conducted to determine first-line combination antiretroviral therapy, this has yet to be confirmed due to the technical limitation associated. In the present study, we applied a model-based meta-analysis (MBMA) approach, because it allows integration of information from clinical trials with varying dosing, duration, and sampling time points, resulting in enlargement of available data sources. We performed a bibliographic search to identify clinical trials involving dolutegravir (DTG)-based and efavirenz (EFV)-based regimens in HIV-infected, antiretroviral therapy-naïve adults, and then identified 30 independent trial data. The time course of drug effect was described by a consecutive first-order kinetic model and analyzed using the nonlinear mixed effect modeling approach. The developed model suggests that the DTG-based regimen provides a faster-acting and more sustainable drug effect than the EFV-based regimen. Moreover, the drug effect tends to appear more slowly and decay faster in severe patients having higher viral load or smaller baseline CD4 count.

1. Introduction

Since the first discovery of acquired immunodeficiency syndrome (AIDS) in 1981, the number of human immunodeficiency virus (HIV)-infected patients has been unceasingly increasing, as accounting for approximately 36.9 million people in 2017 [1]. Although no fundamental solutions have been established to date, recent progress in anti-HIV therapy has changed the prognosis of the disease from lethal to chronic illness. Currently, combinations of typical types of antiretroviral agents have been adopted as chemotherapy for HIV infection, which consist of two nucleoside analogue reverse transcriptase inhibitors (NRTI) plus one of a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase strand-transfer inhibitor (INSTI), and a protease inhibitor (PI).

It is known that selection of initial antiretroviral therapy is critical in determining successful long-term virologic suppression [2]. Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, had been used as a key drug of the first-line combination regimen for many years until the advent of integrase strand transfer inhibitors [3]. Particularly, epoch-making change occurred with the approval of dolutegravir (DTG), which overcame the issue of rapid drug resistance development [4,5]. Within two years after the approval in 2013, the Department of Health and Human Services (DHHS) and the European AIDS Clinical Society (EACS) started to recommend DTG-based regimens as the first-line combination

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Graduate School of Pharmaceutical Sciences, Kyoto University, 46-29 Yoshidashimoadachi-cho, Sakyo-ku, Kyoto, 606-8501, Japan.
E-mail address: yama@pharm.kyoto-u.ac.jp (F. Yamashita).

https://doi.org/10.1016/j.jiac.2019.03.015
1341-321X/

antiretroviral therapy [6,7]. Nowadays, EFV is hardly used in developed countries, but a considerable amount of EFV is still being used worldwide [8]. In fact, it was only very recently that the World Health Organization (WHO) gave DTG a higher priority than EFV [9].

Superiority of DTG-based regimens to other key drugs has been demonstrated by systematic reviews and their analyses. Rutherford et al. [10] conducted a meta-analysis to compare efficacy of DTG-based and EFV-based regimens in HIV-infected, combination antiretroviral therapies-naïve adults. They demonstrated that DTG-based regimens appear to be superior to EFV-based regimens in terms of durable viral suppression, absence of resistance, and immunologic recovery. However, the number of trials that allow a direct comparison of efficacy of DTG-based and EFV-based regimens is limited and the meta-analysis of Rutherford et al. [10] covers only two clinical trials. Network meta-analysis, which allows to estimate relative efficacy indirectly from head-to-head study results, has also been adopted to antiretroviral therapies [11,12]. The results have supported superiority of the use of DTG in HIV-1-infected treatment-naive patients. However, these analyses are subject to the limitation of only being applicable to static data at fixed time points (*e.g.*, 48-week or 96-week efficacy).

In recent years, increasing attention has been paid to model-based meta-analysis (MBMA) [13,14]. MBMA differs from conventional meta-analysis in terms of dealing with time-series data. By defining a therapeutic response as a function of time, MBMA facilitates the integration of information from clinical trials varying the dosing, duration, and sampling time points [14]. These attractive features prompted us to apply MBMA to compare therapeutic efficacy in HIV-infected patients between DTG-based and EFV-based regimens. In the present study, we refined information of 30 clinical trials through a systematic review and analyzed the compiled data by MBMA. The analysis would quantitatively delineate clinical and programmatic advantages of DTG-based regimens in combination antiretroviral therapies settings.

2. Materials and methods

2.1. Data sources and searches

The present analysis was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [15] and methods described in the Cochrane Handbook [16]. PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov were systematically searched to identify randomized controlled trials (RCTs) that evaluated efficacy of DTG-based and EFV-based regimens in treatment-naive HIV-1 patients. Search terms for DTG were chosen with reference to the report of Rutherford et al. [10], while those for EFV were taken from the report of Kryst et al. [17].

2.2. Inclusion and exclusion criteria

RCTs were retrieved that targeted to either or both of DTG + two NRTIs and EFV + two NRTIs in HIV-infected, combination antiretroviral therapies-naïve adults aged ≥16 years and defined proportion of participants with viral load of <50 copies/mL in plasma as drug effect. Studies were excluded in which; participants were pregnant or tuberculosis co-infected; the number of participants in the arm was lower than 10; and arms were not separated with individual dosage regimens. Concomitant NRTIs were restricted to any two of abacavir (ABC) + lamivudine (3TC), tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC), or TDF + 3TC, which have been widely used as a part of first-line combination antiretroviral therapies.

2.3. Data extraction

We imported search results into a bibliographic citation management software (Refworks 2.0, ProQuest LLC, Ann Arbor, MI) and excluded duplicated references. We initially screened the articles based on their title and abstract, and subsequently reviewed the full-text of each selected paper to extract all the necessary information and to verify if the inclusion criteria were met.

2.4. Model analysis

The time course of drug effect (E) was mathematically described by assuming its onset and decay to obey a consecutive first-order kinetics;

$$E = \widehat{E} + \sqrt{\widehat{E}\left(1-\widehat{E}\right)\Big/N}\cdot\varepsilon$$

$$\widehat{E} = E_{max}\cdot\left(1-e^{-k_o\cdot\left(t-t_{lag}\right)}\right)\times e^{-k_d\cdot\left(t-t_{lag}\right)}$$

$$k_o = \widehat{k}_o\cdot e^{\eta_{ko}}$$

$$k_d = \widehat{k}_d\cdot e^{\eta_{kd}}$$

where E_{max} is the maximum drug effect; k_o is the onset rate constant; k_d is the decay rate constant; t_{lag} is the time lag prior to the onset; N is the number of patients in the study; η_{ko} and η_{kd} are inter-study variabilities, having a normal probability distribution with mean 0 and variance $\omega^2_{k_o}$, $\omega^2_{k_d}$, respectively. ε is a random residual error, having a normal probability distribution with mean 0 and variance σ^2. Considering that E is restricted to the range between 0 and 1, ε was weighted with the standard deviation around fitted values. The model-based analysis was conducted using nonlinear mixed effects modeling with NONMEM software, version 7.3, ICON Development Solutions, Hanover, MD. The models were run with the first-order conditional estimation with interaction (FOCE-I).

Visual predictive checks were performed using 10,000 datasets from original data, and 90% confidence interval (CI) and mean of each regimen were calculated. Bootstrap was performed 1000 times to determine the median and the 95% CI of the parameter estimates.

3. Results

3.1. Data collection

Fig. 1 depicts the PRISMA flow diagram. The literature search in Pubmed, CENTRAL, and clinicaltrials.gov yielded 2622 records. Following duplication removal, abstract screening, and full-text screening, 104 publications remained. The remaining studies contained 30 trials in total, of which 5, 9, 16, and 3 trials dealt with DTG + ABC+3TC, EFV + ABC+3TC, EFV + TDF + FTC, and EFV + TDF+3TC regimens, respectively [18–48].

3.2. Model construction and validation

Assuming that the onset and decay of drug effect obeys sequential first-order kinetics with inter-study variability, nonlinear mixed effect modeling was performed. Table 1 summarizes parameter estimates for the base model. The model equations fitted reasonably to observed data (Fig. 2), where drug effect increased in a time-dependent manner before it gradually decayed.

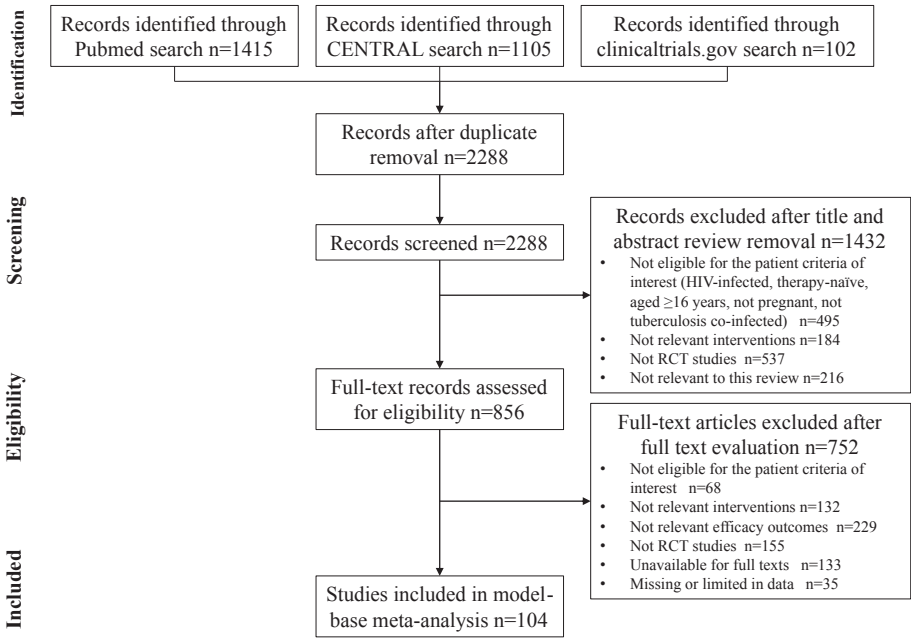

Fig. 1. PRISMA statement 2009 flow diagram. The diagram depicts the selection process of studies undertaken in the present meta-analysis. Reasons for exclusion are provided along with their relevant counts.

Table 1
Parameter estimates for each regimen based on the base population model.

Parameters	Parameter estimates			
	DTG + ABC+3TC	EFV + ABC+3TC	EFV + TDF + FTC	EFV + TDF+3TC
E_{max}	0.833 ± 0.014	0.905 ± 0.052	0.963 ± 0.015	0.910 ± 0.076
k_o	0.474 ± 0.052	0.0779 ± 0.0087	0.0862 ± 0.0076	0.118 ± 0.021
η_{ko}[a]	0.0720 ± 0.0274			
$k_d(\times 10^{-3})$	0.864 ± 0.356	3.83 ± 1.41	2.81 ± 0.47	1.72 ± 0.26
η_{kd}[a]	0.149 ± 0.018			
t_{lag}[a]	1.55 ± 0.07			
ϵ[a]	1.95 ± 0.36			

[a] t_{lag}, inter-individual variation of k_o and k_d (η_{ko} and η_{kd}), and intra-individual variation (ε) were assumed to be constant irrespective to any of regimens, in order to inflation of number of parameters to be estimated by curve-fit.

Using computer-calculated standard errors of the parameter estimates, we computed the 90% confidence intervals for the drug effect-time profiles (represented with red-colored dotted lines in Fig. 2). Almost all observed data points fell within the 90% confidence intervals and evenly distributed within the range. Thus, the visual predictive check proved good accordance between observed and predicted values.

Table 1 also allows the parameter estimates to be compared among four regimens. The E_{max} value was comparable between regimens. However, the k_o value largely differed; i.e., DTG + ABC+3TC was approximately five times higher than the EFV-based regimens. This reflects that the DTG-based regimen reaches a maximum effect much faster. Additionally, the DTG-based regimen appears to be superior in terms of sustainability. The decay of effect (k_d) for DTG + ABC+3TC was approximately three times slower than that for EFV-based regimens.

Fig. 3 shows the goodness-of-fit plot and conditional weighted residual errors (CWRES) against time plot of base model. The goodness-of-fit plot provided an adjusted coefficient of determination of 0.89, indicating a reasonable accuracy of curve fitting. The CWRES versus time plot assures that the errors symmetrically distribute centering on zero, and ranged between as small as ±3.

3.3. Covariate analysis

Supplementary Fig. S1 shows mutual correlation of viral load (*BSL*), baseline CD4 count (*CD4*), $\log_{10} k_o$ and $\log_{10} k_d$ in a scatter plot matrix format. $\log_{10} k_o$ showed weakly positive and negative correlations with *BSL* and *CD4*, respectively. On the other hand, $\log_{10} k_d$ showed weakly positive and negative correlations with *BSL* and *CD4*. These suggest that the drug effect tends to appear more slowly and decay faster in more severe patients. To eliminate an effect of regimen on the relationships, regimen-stratified regression analysis was conducted (Fig. 4 and Table 2). Stratification with regimens clearly indicated strong correlations between the kinetic parameters and the patient's severity indicators.

On the basis of these findings, a nonlinear mixed effect model analysis was performed by introducing *BSL* or *CD4* to the kinetic parameters as covariates:

$$k_{o,i} = \theta_1 \times \theta_2^{COV_i - COV_{med}}$$

where $k_{o,i}$ is the covariate-adjusted mean rate constant for study arm i, θ_1 and θ_2 are parameters to be estimated, COV_i is a covariate value of study arm i, and COV_{med} is the median of the covariate. COV_i was set to COV_{med} unless specified in the literature.

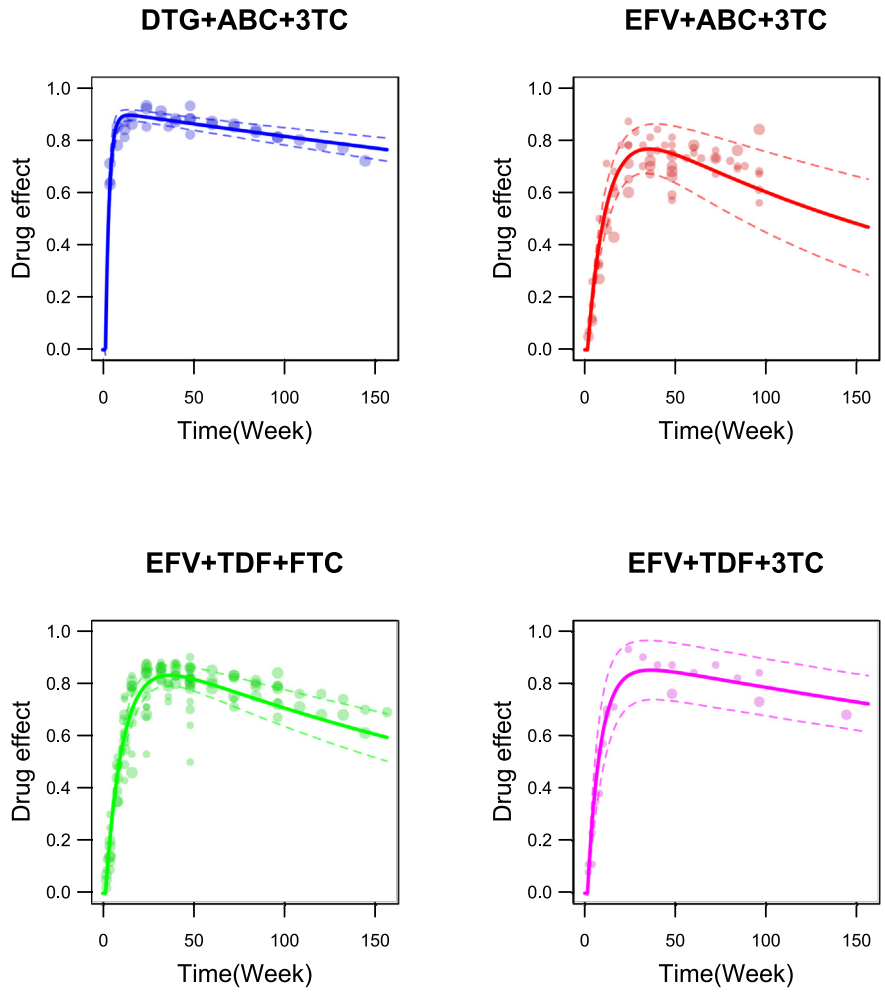

Fig. 2. Time courses of observed and simulated drug effect for each regimen. The drug effect was defined as proportion of participants with viral load of <50 copies/mL in plasma. Symbols represent observed data, of which the size is proportional to the number of patients in the studies. Each solid line represents the median, and the corresponding dashed lines represent the 5th and 95th percentiles estimated by exploiting 1000 times Monte Carlo simulations. Parameters used for the simulation are summarized in Table 1.

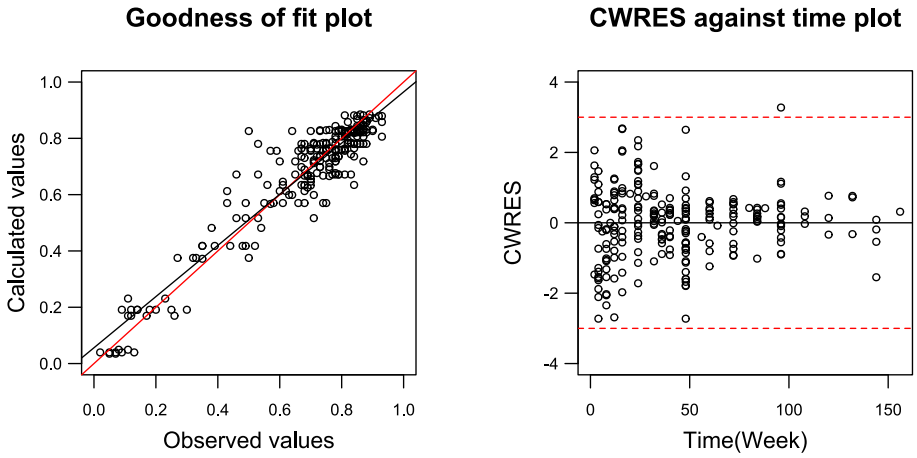

Fig. 3. Goodness of fit and CWRES plots associated with the base population model. Black and red lines represent regression and 1:1 correspondence lines, respectively.

Summarizes the results of covariate screening. Introduction of either *BSL* or *CD4* to k_0 provided significant decrease in the objective function value (OFV), where *CD4* was more effective. The covariate model comprising both *BSL* and *CD4* was not significantly different from that of *CD4* alone. Table 3 summarizes the parameter estimates for the *CD4* model. As discussed with the base model, a larger θ_1 for the DTG-based regimen reflects its faster-acting drug effect. The θ_2 was greater than unity, suggesting that appearance of drug effect be slower in severe patients having smaller baseline CD4 count.

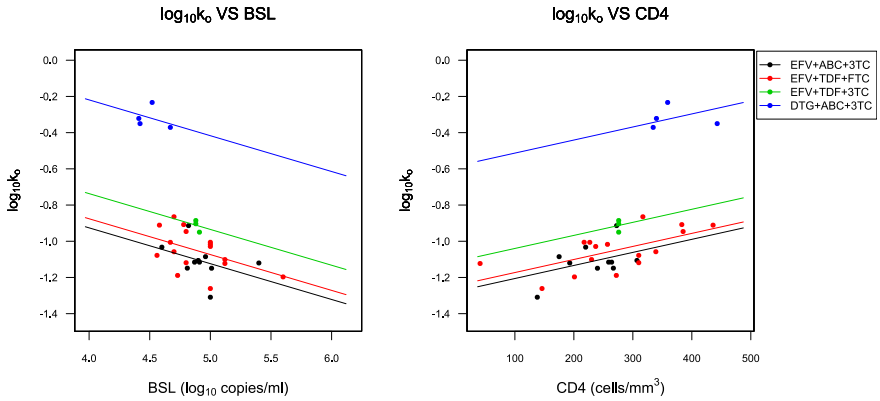

Fig. 4. Plots of regimen-stratified regression analysis for the onset rate constant ($\log_{10} k_o$). $\log_{10} k_o$ was estimated by Bayesian post hoc analysis.

Table 2
Regimen-stratified regression analysis for the onset rate constant ($\log_{10} k_o$).

Regimen	BSL		CD4	
	Equation	Adjusted R^2	Equation	Adjusted R^2
DTG + ABC+3TC	$log_{10}k_o = -0.198 \times BSL + 0.572$	0.884	$log_{10}k_o = 7.21 \times 10^{-4} \times CD4 - 0.585$	0.901
EFV + ABC+3TC	$log_{10}k_o = -0.198 \times BSL - 0.135$		$log_{10}k_o = 7.21 \times 10^{-4} \times CD4 - 1.28$	
EFV + TDF + FTC	$log_{10}k_o = -0.198 \times BSL - 0.0845$		$log_{10}k_o = 7.21 \times 10^{-4} \times CD4 - 1.24$	
EFV + TDF+3TC	$log_{10}k_o = -0.198 \times BSL - 0.0544$		$log_{10}k_o = 7.21 \times 10^{-4} \times CD4 - 1.11$	

Table 3
Parameter estimates for each regimen based on a final population model.

Parameters	Parameter estimates			
	DTG + ABC+3TC	EFV + ABC+3TC	EFV + TDF + FTC	EFV + TDF+3TC
E_{max}	0.833 ± 0.014	0.909 ± 0.054	0.959 ± 0.017	0.909 ± 0.073
θ_1	0.416 ± 0.079	0.0779 ± 0.0076	0.0861 ± 0.0064	0.122 ± 0.017
θ_2[a]	11.9 ± 6.3			
η_{ko}[a]	0.0387 ± 0.0155			
$k_d (\times 10^{-3})$	0.845 ± 0.358	3.93 ± 1.43	2.75 ± 0.48	1.70 ± 0.24
η_{kd}[a]	0.153 ± 0.076			
t_{lag}[a]	1.55 ± 0.07			
ε	1.96 ± 0.36			

[a] θ_2 of k_o, t_{lag}, inter-individual variation of k_o and k_d (η_{ko} and η_{kd}), and intra-individual variation (ε) were assumed to be constant irrespective to any of regimens, in order to inflation of number of parameters to be estimated by curve-fit.

4. Discussion

This is the first MBMA that modeled and quantitatively compared the time course of drug effect from DTG-based and EFV-based regimens in HIV-infected patients. MBMA presents two major advantages over conventional meta-analyses; that is, it allows to deal with the longitudinal kinetics and to enlarge available data sources. Quantitative characterization of the kinetics of onset and decay of drug effect provides additional information on drug products or regimens. Richer data enable us to gain a more reliable and accurate account of their comparative efficacy.

Simple consecutive first-order reaction kinetics were adopted to describe the time course of drug effect from each regimen. Since the drug effect was defined with the proportion of participants with viral load less than of <50 copies/mL in plasma, E_{max} should not exceed unity. Indeed, EFV + TDF + FTC has the highest E_{max} (0.950). However, the regimen did not necessarily provide the highest drug effect. The highest peak of observed drug effect was with DTG + ABC+3TC with a E_{max} of 0.900, which was due to higher k_o and lower k_d. Comparative superiority among the regimens must be evaluated comprehensively with all the three parameters. It should also be noted that the decay rate constant k_d does not simply reflect weakening of the effect (*e.g.*, viral drug resistance) but also tapering and premature discontinuation of participants in clinical trials.

Among the 3 EFV-based regimens, EFV + ABC+3TC showed the most inferior performance (the lowest E_{max}, lowest k_o and highest k_d). WHO recommends TDF + FTC or TDF+3TC as NRTI combinations of EFV-based regimens, because these two combinations have offered the opportunity to harmonize regimens across different populations. TDF + FTC and TDF+3TC have been preferred for people co-infected with HIV and HBV, in addition to being effective for people co-infected with tuberculosis and pregnant women [49]. In addition, several clinical trials have indicated that EFV + ABC+3TC are more likely to cause adverse events than EFV + TDF + FTC [19,22]. A higher k_d value of EFV + ABC+3TC might be due to the adverse event-associated discontinuation of participants in clinical trials. Thus, the result of the present analysis supports that EFV + TDF + FTC or EFV + TDF+3TC might be superior to EFV + ABC+3TC.

DTG + ABC+3TC yielded a much greater k_o than EFV-based regimens, resulting in faster-acting drug effect. Despite their

different mechanisms, both DTG and EFV inhibit the proliferation of HIV. The present result that DTG is more effective than EFV was consistent with the viral dynamics study [50] and experimental data in cell culture [51]. Another notable feature of the DTG-based regimen was that DTG + ABC+3TC provided an approximately three times lower k_d than EFV-based regimens. As mentioned above, the k_d could be affected by premature discontinuation of participants in clinical trials. Indeed, Patel et al. [11] revealed in their meta-analysis that patients receiving the DTG-based regimen are less likely to suffer from adverse events than those receiving the EFV-based regimen. The low k_d for DTG + ABC+3TC would be attributed to the lower incidence of adverse event-associated discontinuation than the EFV-based regimen. DTG has been known to have high genetic barrier and minimal cross-resistance [52,53]. In contrast, EFV is characterized by a low barrier to the development of resistance [53,54]. Walmsley et al. [18] has shown that no patients developed resistance mutation in DTG group whereas six patients developed NNRTI-resistance mutations in EFV group, indicating that DTG was less likely to cause virological failure. Difference in resistance profile of each drug might also be due to difference in k_d between DTG + ABC+3TC and EFV-based regimens.

The covariate model analysis revealed a positive relationship between baseline CD4 count and k_o regardless of the regimens. This means that the appearance of drug effect would be slower in patients with a smaller baseline CD4 count, as has been demonstrated in the meta-analysis of Skowron et al. [55]. However, it should be remembered that the therapeutic outcome of the regimens in clinical trials, *i.e.*, the proportion of participants with a minimal viral load, has been evaluated as a summary level. Lambert et al. [56] indicated that meta-analysis using summary-level data might be effective in estimating drug effects but not in investigating relationships between patient characteristics and drug effects. They suggested that individual-level data are generally required to discover any such relationships. The positive relationship between the speed of appearance of anti-HIV effect and baseline CD4 count still remains to be confirmed.

Limitations of this study include difference in demographic characteristics of HIV-infected patients between clinical trials and real world. According to UNAIDS data [1], approximately half of the HIV-infected adults are women, and more than 70% of HIV-infected patients are African. However, clinical trials have been conducted mostly with male Caucasians. It has been reported that gender difference in HIV disease progression exists, where females have lower risks of AIDS dementia complex, tuberculosis, Kaposi's sarcoma, lymphomas, and death without AIDS [57]. A major metabolizing enzyme of EFV is CYP2B6, which are polymorphic in different ethnicities [58]. Naidoo et al. [59] described that ethnic differences and the associated prevalence of CYP2B6 polymorphisms result in significant differences in the pharmacokinetics/pharmacodynamics of EFV, warranting dosage reduction in carriers of specific CYP2B6 polymorphisms. Such gender and ethnic difference might affect the result of meta-analyses. Future data on DTG-based regimens promises to gain more reliable analysis results.

In conclusion, the DTG-based regimen provided faster and more sustainable drug effect than the EFV-based regimen. MBMA would be a powerful tool for investigating the kinetics of drug effect, which can be applied by compiling pieces of data from different sources.

Conflicts of interest

The authors have no potential conflicts of interest to declare.

Acknowledgements

This work was financially supported in part by JSPS KAKENHI under grant numbers 25670073 (FY), 16K18938 (MT) and 18K06747 (MT).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.03.015.

References

[1] UNAIDS. UNAIDS DATA. 2018. http://www.unaids.org/en/resources/documents/2018/unaids-data-2018. [Accessed 23 March 2018].
[2] Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. PLoS One 2014;9:e97482. https://doi.org/10.1371/journal.pone.0097482.
[3] Maggiolo F. Efavirenz: a decade of clinical experience in the treatment of HIV. J Antimicrob Chemother 2009;64:910–28. https://doi.org/10.1093/jac/dkp334.
[4] Rathbun RC, Lockhart SM, Miller MM, Liedtke MD. Dolutegravir, a second-generation integrase inhibitor for the treatment of HIV-1 infection. Ann Pharmacother 2014;48:395–403. https://doi.org/10.1177/1060028013513558.
[5] Shah BM, Schafer JJ, Desimone Jr JA. Dolutegravir: a new integrase strand transfer inhibitor for the treatment of HIV. Pharmacotherapy 2014;34:506–20. https://doi.org/10.1002/phar.1386.
[6] The Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. https://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL003400.pdf. [Accessed 9 February 2019].
[7] European AIDS Clinical Society. The European guidelines for treatment of HIV infected adults in Europe. 2015., Version 8.0. http://www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf. [Accessed 9 February 2019].
[8] Clinton Health Access Initiative. reportHIV Market Report. https://clintonhealthaccess.org/content/uploads/2018/09/2018-HIV-Market-Report_FINAL.pdf [accessed 9 February 2019].
[9] World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1. [Accessed 9 February 2019].
[10] Rutherford GW, Horvath H. Dolutegravir plus two nucleoside reverse transcriptase inhibitors versus efavirenz plus two nucleoside reverse transcriptase inhibitors as initial antiretroviral therapy for people with HIV: a systematic review. PLoS One 2016;11:e0162775. https://doi.org/10.1371/journal.pone.0162775.
[11] Patel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One 2014;9:e105653. https://doi.org/10.1371/journal.pone.0105653.
[12] Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV 2016;3:e510–20. https://doi.org/10.1016/S2352-3018(16)30091-1.
[13] Mould DR. Model-based meta-analysis: an important tool for making quantitative decisions during drug development. Clin Pharmacol Ther 2012;92:283–6. https://doi.org/10.1038/clpt.2012.122.
[14] Gross JL, Rogers J, Polhamus D, Gillespie W, Friedrich C, Gong Y, et al. A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus. BMJ Open 2013;3. https://doi.org/10.1136/bmjopen-2012-001844. https://doi.org/10.1136/bmjopen-2012-001844.
[15] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097.
[16] Cochrane Handbook for systematic reviews of interventions. 2011., Version 5.1.0. http://handbook-5-1.cochrane.org/.
[17] Kryst J, Kawalec P, Pilc A. Efavirenz-based regimens in antiretroviral-naive HIV-infected patients: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2015;10:e0124279. https://doi.org/10.1371/journal.pone.0124279.
[18] Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir

Immune Defic Syndr 2015;70:515–9. https://doi.org/10.1097/QAI.0000000000000790.
[19] Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, et al. Abacavir–Lamivudine versus tenofovir–emtricitabine for initial HIV-1 therapy. N Engl J Med 2009;361:2230–40. https://doi.org/10.1056/NEJMoa0906768.
[20] Honda M, Ishisaka M, Ishizuka N, Kimura S, Oka S, Group JA-H-1 QDTS. Open-label randomized multicenter selection study of once daily antiretroviral treatment regimen comparing ritonavir-boosted atazanavir to efavirenz with fixed-dose abacavir and lamivudine. Intern Med 2011;50:699–705. https://doi.org/10.2169/internalmedicine.50.4572.
[21] Echeverria P, Negredo E, Carosi G, Galvez J, Gomez JL, Ocampo A, et al. Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (Lake Study). Antivir Res 2010;85:403–8. https://doi.org/10.1016/j.antiviral.2009.11.008.
[22] Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D, Fisher M, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr 2010;55:49–57. https://doi.org/10.1097/QAI.0b013e3181dd911e.
[23] Kumar P, DeJesus E, Huhn G, Sloan L, Small CB, Edelstein H, et al. Evaluation of cardiovascular biomarkers in a randomized trial of fosamprenavir/ritonavir vs. efavirenz with abacavir/lamivudine in underrepresented, antiretroviral-naive, HIV-infected patients (SUPPORT): 96-week results. BMC Infect Dis 2013;13:269–2334. 13–269, https://doi.org/10.1186/1471-2334-13-269.
[24] Bartlett JA, Johnson J, Herrera G, Sosa N, Rodriguez A, Liao Q, et al. Long-term results of initial therapy with abacavir and Lamivudine combined with Efavirenz, Amprenavir/Ritonavir, or Stavudine. J Acquir Immune Defic Syndr 2006;43:284–92. https://doi.org/10.1097/01.qai.0000243092.40490.26.
[25] Moyle GJ, DeJesus E, Cahn P, Castillo SA, Zhao H, Gordon DN, et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-infected adults: results of the Ziagen once Daily in Antiretroviral Combination Study. J Acquir Immune Defic Syndr 2005;38:417–25. https://doi.org/10.1097/01.qai.0000147521.34369.c9.
[26] DeJesus E, Herrera G, Teofilo E, Gerstoft J, Buendia CB, Brand JD, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004;39:1038–46. https://doi.org/10.1086/424009.
[27] Podzamczer D, Ferrer E, Sanchez P, Gatell JM, Crespo M, Fisac C, et al. Less lipoatrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. J Acquir Immune Defic Syndr 2007;44:139–47. https://doi.org/10.1097/QAI.0b013e31802bf122.
[28] Kravchenko A, Orlova-Morozova E, Nagimova F, Kozirev O, Shimonova T, Bichko V, et al. Safety and antiviral effect of Elpida (VM-1500), a novel NNRTI (+Truvada) in treatment-naive HIV-1-infected patients at 24- to 48-week therapy. J Int AIDS Soc 2016;19:36.
[29] Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J Acquir Immune Defic Syndr 2008;47:74–8. https://doi.org/10.1097/QAI.0b013e31815acab8.
[30] Rockstroh JK, DeJesus E, Lennox JL, Yazdanpanah Y, Saag MS, Wan H, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr 2013;63:77–85. https://doi.org/10.1097/QAI.0b013e31828ace69.
[31] Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet (London, England) 2011;378:238–46. https://doi.org/10.1016/S0140-6736(11)60936-7.
[32] Landman R, Koulla-Shiro S, Sow PS, Ngolle M, Diallo MB, Gueye NF, et al. Evaluation of four tenofovir-containing regimens as first-line treatments in Cameroon and Senegal: the ANRS 12115 DAYANA Trial. Antivir Ther 2014;19:51–9. https://doi.org/10.3851/IMP2675.
[33] Vernazza P, Wang C, Pozniak A, Weil E, Pulik P, Cooper DA, et al. Efficacy and safety of lersivirine (UK-453,061) versus efavirenz in antiretroviral treatment-naive HIV-1-infected patients: week 48 primary analysis results from an ongoing, multicenter, randomized, double-blind, phase IIb trial. J Acquir Immune Defic Syndr 2013;62:171–9. https://doi.org/10.1097/QAI.0b013e31827a2ba2.
[34] Cohen C, Elion R, Ruane P, Shamblaw D, DeJesus E, Rashbaum B, et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. AIDS 2011;25:F7–12. https://doi.org/10.1097/QAD.0b013e328345766f.
[35] ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet (London, England) 2014;383:1474–82. https://doi.org/10.1016/S0140-6736(13)62187-X.
[36] ENCORE1 Study Group. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. Lancet Infect Dis 2015;15:793–802. https://doi.org/10.1016/S1473-3099(15)70060-5.
[37] Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012;379:2439–48. https://doi.org/10.1016/S0140-6736(12)60917-9.
[38] van Lunzen J, Antinori A, Cohen CJ, Arribas JR, Wohl DA, Rieger A, et al. Rilpivirine vs. efavirenz-based single-tablet regimens in treatment-naive adults: week 96 efficacy and safety from a randomized phase 3b study. AIDS 2016;30:251–9. https://doi.org/10.1097/QAD.0000000000000911.
[39] Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay AL, et al. A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. AIDS 2016;30:869–78. https://doi.org/10.1097/QAD.0000000000000988.
[40] Miro JM, Manzardo C, Ferrer E, Loncà M, Guardo AC, Podzamczer D, et al. Immune reconstitution in severely immunosuppressed antiretroviral-naive HIV-1-Infected patients starting efavirenz, lopinavir-ritonavir, or atazanavir-ritonavir plus tenofovir/emtricitabine: final 48-week results (the advanz-3 trial). J Acquir Immune Defic Syndr 2015;69:206–15. https://doi.org/10.1097/QAI.0000000000000567.
[41] Puls RL, Srasuebkul P, Petoumenos K, Boesecke C, Duncombe C, Belloso WH, et al. Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study. Clin Infect Dis 2010;51:855–64. https://doi.org/10.1086/656363.
[42] Markowitz M, Nguyen BY, Gotuzzo E, Mendo F, Ratanasuwan W, Kovacs C, et al. Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection. J Acquir Immune Defic Syndr 2009;52:350–6. https://doi.org/10.1097/QAI.0b013e3181b064b0.
[43] Elvucitabine/Efavirenz/Tenofovir vs. Lamivudine/Efavirenz/Tenofovir in HIV-1 infected, treatment naive subjects. 2016. https://clinicaltrials.gov/ct2/show/NCT00350272?term=NCT00350272&rank=1.
[44] Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. J Am Med Assoc 2004;292:191–201. https://doi.org/10.1001/jama.292.2.191.
[45] Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet (London, England) 2013;381:735–43. https://doi.org/10.1016/S0140-6736(12)61853-4.
[46] Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013;13:927–35. https://doi.org/10.1016/S1473-3099(13)70257-3.
[47] Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet (London, England) 2017;390:2063–72. https://doi.org/10.1016/S0140-6736(17)32299-7.
[48] Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falco V, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label. Lancet HIV 2017;4:e536–46. https://doi.org/10.1016/S2352-3018(17)30095-4.
[49] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. https://www.who.int/hiv/pub/arv/arv-2016/en/. [Accessed 23 March 2018].
[50] Wang X, Song X, Tang S, Rong L. Dynamics of an HIV model with multiple infection stages and treatment with different drug classes. Bull Math Biol 2016;78:322–49. https://doi.org/10.1007/s11538-016-0145-5.
[51] Donahue DA, Sloan RD, Kuhl BD, Bar-Magen T, Schader SM, Wainberg MA. Stage-dependent inhibition of HIV-1 replication by antiretroviral drugs in cell culture. Antimicrob Agents Chemother 2010;54:1047–54. https://doi.org/10.1128/AAC.01537-09.
[52] Canducci F, Ceresola ER, Boeri E, Spagnuolo V, Cossarini F, Castagna A, et al. Cross-resistance profile of the novel integrase inhibitor Dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. J Infect Dis 2011;204:1811–5. https://doi.org/10.1093/infdis/jir636.
[53] Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. Drugs 2012;72:e1–25. https://doi.org/10.2165/11633630-000000000-00000.
[54] Sluis-Cremer N, Tachedjian G. Mechanisms of inhibition of HIV replication by non-nucleoside reverse transcriptase inhibitors. Virus Res 2008;134:147–56. https://doi.org/10.1016/j.virusres.2008.01.002.
[55] Skowron G, Street JC, Obee EM. Baseline CD4(+) cell count, not viral load, correlates with virologic suppression induced by potent antiretroviral therapy. J Acquir Immune Defic Syndr 2001;28:313–9.

[56] Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. J Clin Epidemiol 2002;55:86–94. https://doi.org/10.1016/S0895-4356(01)00414-0.

[57] Jarrin I, Geskus R, Bhaskaran K, Prins M, Perez-Hoyos S, Muga R, et al. Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women. Am J Epidemiol 2008;168:532–40. https://doi.org/10.1093/aje/kwn179.

[58] Owen A, Pirmohamed M, Khoo SH, Back DJ. Pharmacogenetics of HIV therapy. Pharmacogenetics Genom 2006;16:693–703. https://doi.org/10.1097/01.fpc.0000236338.41799.57.

[59] Naidoo P, Chetty VV, Chetty M. Impact of CYP polymorphisms, ethnicity and sex differences in metabolism on dosing strategies: the case of efavirenz. Eur J Clin Pharmacol 2014;70:379–89. https://doi.org/10.1007/s00228-013-1634-1.