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Title: **Pharmacokinetic parameters and weight change in HIV patients newly switched to dolutegravir-based regimens in SIMPL'HIV clinical trial**

Running title: **Dolutegravir pharmacokinetics and weight change**

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Ethics committee approval: the study was conducted with the understanding and the consent of each participant. The study protocol was approved by both the Meaning and local ethics committees in Switzerland (CCER Number : 2016-02210), in accordance with the Helsinki Declaration and Good Clinical Practice.

Author contributions:

Study design: AC, LAD.

Recruitment of participants: AC, DS, GW, MS, EB, DB, MC, PS, PV, HG

Laboratory work: SAS, LAD.

Analysis and interpretation of data: PC, CB, MG.

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What is already known about this subject ?

- Weight gain in people with HIV receiving antiretroviral treatments is well documented, with a higher risk for those receiving integrase inhibitors, and especially dolutegravir.
- Some antiretrovirals including dolutegravir demonstrate a concentration-effect relationship for adverse events such as neuropsychological disorders.

What this study adds ?

- In this population of people with HIV newly switched to dolutegravir, we do report a significant 2.4 kg weight gain between baseline and week 48.
- We did not find evidence for an association between dolutegravir pharmacokinetic parameters and weight gain within this particular population.

Abstract

This study aims to evaluate the association between dolutegravir (DTG) pharmacokinetic parameters and weight changes in treatment-experienced people with HIV (PWHIV) from the Simpl'HIV study newly switched to a dual DTG-based regimen.

We used multivariable linear regressions to evaluate the association between DTG pharmacokinetic parameters at week 48 (derived using an established model) and weight change between week 0 and week 48. We adjusted our model for potential confounders including CD4 nadir, female sex, African origin, age, weight at week 0 and presence of an NNRTI-based regimen before switch to DTG.

The analysis included data from 39 PWHIV. An average significant weight gain of 2.4 kg was observed between baseline and week 48. DTG plasma exposure was not significantly associated with weight gain, even after adjusting for potential confounders (p=0.9).

We found no significant association between DTG pharmacokinetic parameters and weight gain amongst PWHIV newly switched to a DTG-based dual regimen.

Introduction

HIV infection related inflammation [1 2] and the widespread use of combined antiretroviral therapy (cART) in people with HIV (PWHIV) have been associated with a higher cardiovascular risk in some studies, changes in glucose and lipid metabolism, and weight gain [3 4].

Weight gain in PWHIV receiving cART is well documented. A number of recent studies have established a link between HIV disease (e.g. low CD4 nadir, high HIV RNA), female gender, African origin, older age and higher weight at baseline with weight gain during follow-up [4-10]. Furthermore, certain antiretroviral classes have been associated with weight gain. Evidence suggests that integrase strand transfer inhibitors (INSTIs) are associated with a higher risk of weight gain compared to other antiretroviral classes [4 11-15]. This weight gain is even more pronounced in PWHIV who received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing antiretroviral regimen prior switching to an INSTI-based regimen [16 17]. Among the INSTIs, dolutegravir (DTG) has been associated with a higher weight gain when compared to other INSTIs such as raltegravir and elvitegravir [14 18 19], and with a similar weight gain compared to bictegravir [20]. In ADVANCE study, the impact of tenofovir alafenamide on the dolutegravir-containing arm rate of weight gain was significant, suggesting an additive or synergistic effect when both drugs are used concomitantly [10].

While the association between weight gain and a number of factors have been extensively investigated, only one study have evaluated its association with DTG plasma concentrations [17]. We aimed to evaluate the association between DTG pharmacokinetic parameters and weight change in treatment-experienced PWHIV newly switched to a DTG-based dual regimen in the scope of a randomized clinical trial in Switzerland.

Methods

Study design and participants

Data was collected amongst PWHIV participating in the multicentre, non-inferiority, open-label, randomized, factorial design trial, called SIMPL'HIV, which was conducted within the Swiss HIV Cohort Study from May 2017 to May 2018 [21]. The SIMPL'HIV study demonstrated the non-inferiority of DTG plus emtricitabine in terms of maintaining viral suppression through 48 weeks of follow-up compared to standard triple therapy [22].The trial has been fully described elsewhere [23]. The study protocol was approved by the central ethics committee (Geneva, Switzerland) (CCER Number : 2016-02210), as well as by study sites in Switzerland (Ticino, Basel, Bern, Zurich) in accordance with the Helsinki Declaration and Good Clinical Practice. Briefly, PWHIV were eligible if they received any cART regimen

recommended by the European AIDS Clinical Society (EACS) [24] and were virologically suppressed (HIV-RNA<50 copies/mL) for at least 24 weeks prior to enrolment. Consenting participants were randomly assigned to either switch to DTG (50 mg once daily) plus emtricitabine dual maintenance therapy or to continue their cART. Post-hoc analysis of the association between DTG pharmacokinetic parameters and body weight change was conducted amongst all participants who were newly switched to DTG at their inclusion in the study, except for PWHIV suspected of non-adherence (DTG plasma concentration<100 ng/mL) (Supplement, Part 1).

Absolute weight change was defined as the difference between weight at week 48 and baseline weight (before DTG initiation). A 2.7 ml blood sample was collected at week 48, under steady-state conditions, along withinformation about date and accurate time of last drug intake. Blood was stored at -80°C and all samples were analysed at the end of the study. DTG plasma concentrations were determined in the laboratory of Clinical Pharmacology in the Lausanne University Hospital, using a previously developed method adapted and validated to include DTG [25]. The method showed acceptable inter-day and intra-day precision (2.4%–5.7% CV and 0.3%–1.3% CV, respectively) and trueness (−7.4% to 7.1% bias). Lower limit of quantification was 40 ng/mL. Our laboratory participates to inter-laboratory (external) QC proficiency programs for dolutegravir [26] which confirms analytical accuracies and precisions.

Pharmacokinetic analyses

Since plasma DTG concentrations were measured at unselected times following drug intake, they could not be directly used to compare drug exposure between patients. Individual pharmacokinetic parameters at standardised times after drug intake (*i.e.* residual plasma concentration C_{min} and maximum plasma concentration C_{max}) and all over the dosing interval (*i.e.* area under the curve from 0 to 24h $AUC_{0\text{-}24}$, representing the total exposure) were therefore derived using the base (without covariates) population pharmacokinetic model of a previously published paper [27] along with the measured concentrations through a Bayesian approach (NONMEM version 7.4) [28]. The appropriateness of the model for the purpose of this study was evaluated through calculations of model prediction bias and precision [29]. A significant but acceptable bias of -9% (95% confidence interval, -15% to -3%) for individual prediction with a precision of 26% similar to the proportional part of the model residual error supported the good predictive performances of the selected model.

Statistical analyses

Linear regression was performed to assess the association between DTG pharmacokinetic parameters and weight gain, adjusting for potential confounders including CD4 nadir, female gender, African origin, baseline age (at week 0), baseline weight and presence of a NNRTI-based regimen before switch to DTG. The only missing CD4 nadir value was replaced by the median in the study population. Since all participants were virologically supressed at their inclusion of the study, the effect of baseline HIV-RNA was not evaluated. A sensitivity analysis was carried out by removing PLWH who were receiving an INSTI-based regimen before switching to DTG. DTG pharmacokinetic parameters (*i.e.* C_{min}, C_{max}, AUC_{0-24}) were log-transformed for normalization. Continuous variables (*i.e.* CD4 nadir, age, baseline weight and log-transformed AUC_{0-24}, C_{min} and C_{max}) were centred on their median value. For each analysis, a *p*-value ≤0.05 was considered statistically significant.

Results

Study population

Amongst the 41 PWHIV included to the "new to DTG arm", two were excluded from the analysis due to undetectable (n=1) or low DTG plasma concentration (<100 ng/mL, n=1) (supplement, Part 1). Thus, a total of 39 PWHIV were included, of whom 82% were male and 77% Caucasian. Five participants (13%) were of African origin, of those 3 were females. Median [interquartile range IQR] age and baseline weight were 45 years [40-51] and 74 kg [69-81], respectively. Median CD4 nadir and baseline CD4 were 259 cells/µL [130-321] and 648 cells/µL [518-944], respectively. Twenty-one PWHIV (54%) were on an NNRTI-based regimen, 10 (26%) on an INSTI (raltegravir or elvitegravir), and 8 (20%) on a PI, prior to switching to DTG as part of this study.

Concerning DTG pharmacokinetics, the median AUC_{0-24} was 56 613 ng.h/mL [47 805-64 496], median C_{min} 1 372 ng/mL [1 039-1 679], and median C_{max} 3 533 ng/mL [3 189-3 846]. Body weight at week 48 significantly influenced DTG AUC_{0-24} (*p*=0.02), as previously reported [27 30].

An average significant weight gain of 2.4 kg ($CI_{95\%}$ 1.3-3.5) was observed between baseline and week 48. Individual values ranged between -2.0 kg and +11.5 kg (Figure 1). The highest weight gain within the 48 weeks following SIMPL'HIV inclusion (+11.5 kg) was attributed to menopause in a Caucasian woman who also suffered from depression. Characteristics of PWHIV with the highest weight gain are presented in the Supplement, Part 2.

Association between dolutegravir pharmacokinetic parameters and weight gain

Neither the univariate analyses (Supplement, Part 3), nor the multivariable analysis, which adjusted for CD4 nadir, female sex, African ethnicity, age, baseline weight and presence of a NNRTI-based regimen before switch to DTG, showed a significant association between DTG pharmacokinetic parameters (DTG $AUC_{0\text{-}24}$, C_{min} orC_{max}) and weight change between baseline and weeks 48. Table 1 shows the non-significant results ($p \geq 0.9$) of the association between each DTG pharmacokinetic parameter and weight gain, after adjustment for potential confounders.

Results from the sensitivity analysis removing patients switched from an INSTI based therapy to DTG (n=29) also failed to demonstrate an association between DTG pharmacokinetic parameters and weight change in PLWH who were not receiving an INSTI-based regimen before switching to DTG (data not shown).

Discussion

We did not find evidence for an association between DTG pharmacokinetic parameters and weight gain within this particular population of PWHIV newly switched to DTG in the context of the SIMPL'HIV randomized clinical trial. This might arise from the moderate between-subject variability in DTG concentration-time profile, compromising our power to detect an effect of pharmacokinetic parameters on weight gain.

This result is in agreement with other studies. Two studies presented as conference abstracts and evaluating the association between weight gain and DTG pharmacokinetics, specifically plasma (n=96, DTG plasma exposure similar to the present study) and hair (n=177) concentrations, found no significant association [17 31]. Conversely, some ARVs demonstrated a concentration-effect relationship for other adverse events. Indeed, an influence of plasma concentration on neuropsychological disorders has been reported for DTG or efavirenz [32 33], suggesting that therapeutic drug monitoring could be useful for treatment individualization.

In this population of PWHIV newly switched to DTG, we do however report a significant 2.4 kg weight gain between baseline and week 48, comparable to that reported in other studies of virologically supressed PWHIV. Lake *et al*. reported a weight gain of 1.3 kg amongst 198 virologically suppressed PWHIV one year after switching to a DTG-based regimen [8], while the Swiss HIV Cohort Study reported a weight gain of 0.7 kg/year in a large cohort (n= 2186) of virologically suppressed PLWH switched to a DTG-containing regimen [34]. More pronounced weight gain has been observed in

studies focusing on ARV-naïve PWHIV, with values ranging from 4.3 to 7.1 kg, 96 weeks after treatment initiation [9 10]. This initial weight gain has historically been thought of as a "return-to-health" phenomenon [35 36]. As all PWHIV were virologically supressed for at least 24 weeks prior to inclusion in this study, it suggests that other mechanisms are implicated in the weight gain described in our population. Irrespective of the exact mechanisms, weight gain while on HIV-treatment has been linked with an increased risk of cardiovascular diseases [37 38], highlighting the importance of personalised medicine. A better understanding of factors influencing adverse events, including weight gain, amongst PWHIV on treatment is crucial to guide individualized selection of cART regimen in clinical practice. Long-term data will confirm a potential plateau effect in weight change over time, as suggested by preliminary results presented in part 2 of the supplementary material.

To our knowledge, this is one of the first studies to explore the association between DTG pharmacokinetic parameters and weight gain in PWHIV stable on ART and newly switched to a DTG based regimen. However, this analysis has a number of limitations. First, the study is based on a relatively small sample size (n=39), which limits the statistical power in particular because weight gain is multifactorial. However, the data was comprehensive and included information on a considerable number of known confounders which could be adjusted for in the statistical analyses, although not statistically significant in univariate analyses. Some other potential contributors for weight gain, such as patients' diet or physical exercise, were not evaluatedin our study. Second, the SIMPL'HIV trial was not designed to compare weight gain between multiple cART. Larger cohort studies are needed to confirm the directionality of the results reported here and to confidently assess the contribution of several factors to weight change, especially in subgroups of PWHIV at higher risk of weight gain.

Despite these limitations, we believe that this study contributes important data to the field. We did not find evidence for an association between DTG pharmacokinetic parameters and weight gain within this particular population of PWHIV newly switched to a DTG in the context of the SIMPL'HIV randomized clinical trial.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 [39].

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Table 1: Multivariable regression of the association between each DTG pharmacokinetic parameter and weight change.

	Estimate (kg)	Standard error	95% confidence interval	*p*-value
DTG AUC_{0-24}[a]				
Intercept	1.5	1.0	-0.5 to 3.6	0.1
DTG AUC_{0-24}[b,c]	0.3	2.8	-5.5 to 6.1	0.9
R-squared: 0.11				
DTG C_{min}[a]				
Intercept	1.5	1.0	-0.5 to 3.6	0.1
DTG C_{min}[b,c]	0.2	1.7	-3.3 to 3.7	0.9
R-squared: 0.11				
DTG C_{max}[a]				
Intercept	1.5	1.0	-0.5 to 3.6	0.1
DTG C_{max}[b,c]	0.4	4.6	-9.0 to 9.8	0.9
R-squared: 0.11				

[a]Adjusted for CD4 nadir, female gender, African origin, baseline age, baseline weight and presence of a NNRTI-based regimen before switch to DTG

[b]Continuous variables centred on median values.

[c]Data were log-transformed for analysis.

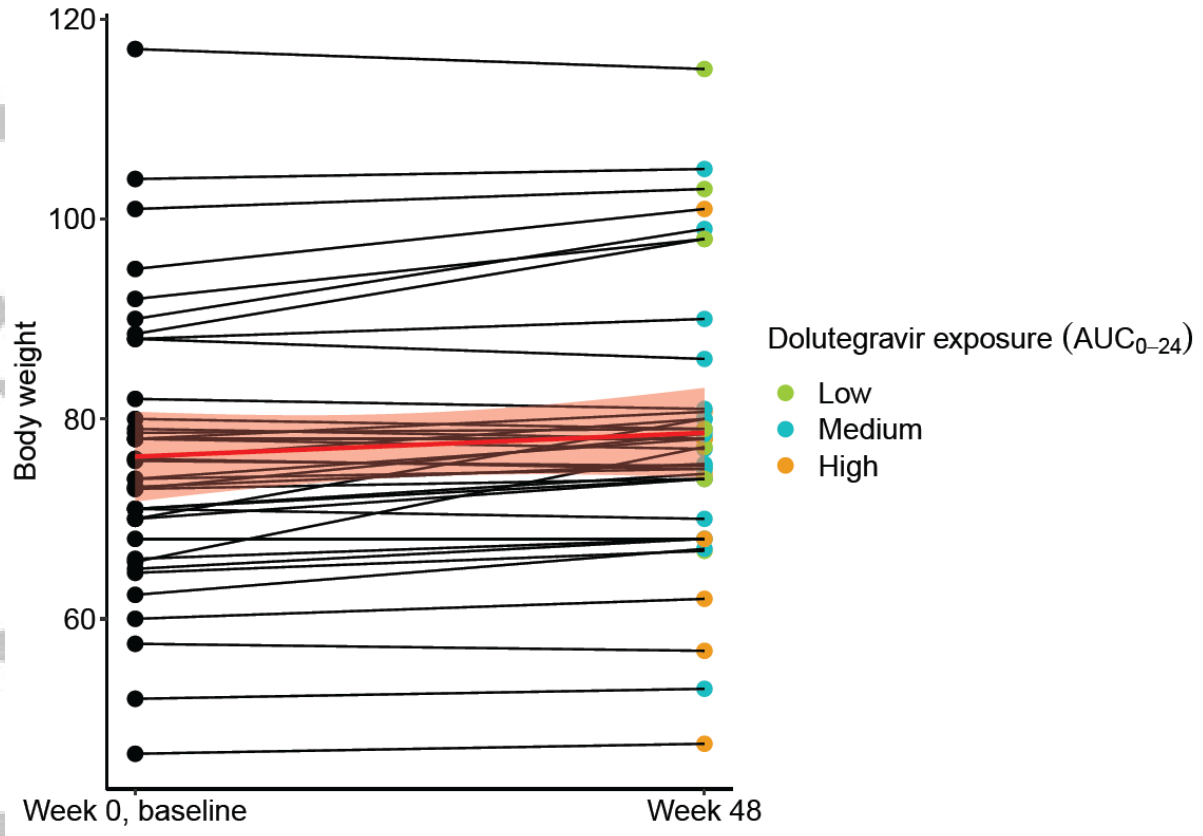

Figure 1: Weight change between baseline and week 48. Points at week 48 are colored according to DTG $AUC_{0\text{-}24}$ (green points, low exposure: $AUC_{0\text{-}24}$<percentile 25; blue points, medium exposure: percentile 25<$AUC_{0\text{-}24}$<percentile 75; orange points, high exposure: $AUC_{0\text{-}24}$>percentile 75). Measurements of weight for each individual are jointed with a black line. The non-adjusted regression line is shown in red with its 95% confidence interval (light red area). The regression line shows a slight increase in weight over the study period.