Article

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Prasugrel and clopidogrel are inhibitors of the ADP-P2Y12 platelet receptor used in acute coronary syndrome patients. They require bioactivation via isoenzymes such as cytochrome P450 (CYP) 3A4, CYP2C19 and CYP2B6. Ritonavir and cobicistat are potent CYP3A inhibitors, prescribed as pharmacokinetic (PK) enhancers in the treatment of human immunodeficiency virus (HIV) infection.

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ORIGINAL RESEARCH ARTICLE

Impact of Boosted Antiretroviral Therapy on the Pharmacokinetics and Efficacy of Clopidogrel and Prasugrel Active Metabolites

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Abstract

Background and objectives Prasugrel and clopidogrel are inhibitors of the ADP-P_2Y_{12} platelet receptor used in acute coronary syndrome patients. They require bioactivation via isoenzymes such as cytochrome P450 (CYP) 3A4, CYP2C19 and CYP2B6. Ritonavir and cobicistat are potent CYP3A inhibitors, prescribed as pharmacokinetic (PK) enhancers in the treatment of human immunodeficiency virus (HIV) infection.

Methods In this study, the impact of boosted antiretroviral therapies (ARTs) on the PK of clopidogrel and prasugrel active metabolites (AMs), and on the efficacy of prasugrel and clopidogrel, were evaluated in a randomized crossover clinical trial.

Results A significantly lower exposure to clopidogrel AM [3.2-fold lower area under the concentration–time curve (AUC) and maximum plasma concentration (C_{max})] and prasugrel AM (2.1-fold and 1.7-fold lower AUC and C_{max}) were demonstrated in HIV-infected patients treated with boosted ARTs compared with healthy controls; however, a differential impact was observed on platelet inhibition between clopidogrel and prasugrel. Clopidogrel 300 mg induced adequate (although modest) platelet inhibition in all healthy subjects, while platelet inhibition was insufficient in 44% of HIV patients. On the contrary, prasugrel 60 mg induced a potent platelet inhibition in both healthy and HIV-infected subjects.

Conclusion Prasugrel appears to remain an adequate antiplatelet agent in HIV-infected patients and could be preferred to clopidogrel in this context, regardless of the metabolic interaction and inhibition of its bioactivation pathways.

Key Points

Exposure to the active metabolites of the antiplatelet agents clopidogrel and prasugrel is reduced by boosted human immunodeficiency virus (HIV) antiretroviral therapies, but the impact on platelet inhibition is more pronounced for clopidogrel than prasugrel.

Prasugrel remains an adequate antiplatelet agent in HIV patients and should be preferred to clopidogrel in this context.

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1 Introduction

Platelets play a key role in the pathogenesis and complications of atherosclerotic lesions; thus, antiplatelet drugs are part of the first-line treatment of atherothrombosis. Thienopyridines such as clopidogrel and prasugrel are irreversible inhibitors of ADP-P_2Y_{12} platelet receptors and are used in acute coronary syndrome (ACS) patients and for the secondary prevention of recurrent atherothrombotic events. Thienopyridines are prodrugs; approximately 15% of clopidogrel is bioactivated mainly via cytochromes P450 (CYP) 3A and CYP2C19, as well as CYP2B6 to a lesser extent. Prasugrel is rapidly hydrolyzed by carboxylesterase to a thiolactone intermediate metabolite that is almost completely transformed to its pharmacologically active metabolite (AM). CYP isoenzymes responsible for prasugrel bioactivation are mainly CYP3A and, to a lesser extent, CYP2B6, CYP2C19 and CYP2C9 [1]. Although clopidogrel and prasugrel AMs have comparable platelet inhibition potencies, a significantly higher level of platelet inhibition is achieved after administration of prasugrel compared with clopidogrel. Many large-scale, randomized trials outlined the higher efficacy of prasugrel compared with clopidogrel, and patients treated with prasugrel demonstrated greater platelet inhibition and lower rates of recurrent atherothrombotic events. This is potentially due to its more efficient bioactivation and higher plasma concentrations of the AM compared with clopidogrel. However, major bleeding events tend to be more frequent in patients treated with prasugrel [2–4].

Ritonavir is a protease inhibitor widely used in combination with other antiretroviral therapies (ARTs) for the treatment of patients infected by human immunodeficiency virus (HIV). It is also a potent inhibitor of CYP3A and a moderate inhibitor of CYP2D6 [5–8]. It is largely prescribed as a pharmacokinetic (PK) enhancer to increase plasma concentrations of other ARTs through inhibition of their metabolism and boosting their bioavailability [8]. Cobicistat is also a potent CYP3A inhibitor prescribed as a PK enhancer in HIV-infected patients. Ritonavir and cobicistat have comparable CYP3A inhibition potencies. Cobicistat is a weak inhibitor of CYP2D6 and does not modulate other CYP activities, and is thus less subject to off-target metabolic drug–drug interactions (DDI) [9, 10]. Antiplatelet agents and ARTs are frequently coadministrated because of cardiovascular complications in HIV patients. Several studies have highlighted an increased risk of cardiovascular events in HIV-infected patients compared with uninfected people [11–14]. This is partly due to metabolic side effects of ARTs such as dyslipidemia and insulin resistance, as well as the chronic inflammatory state, classical risks factors (such as smoking and hypertension), and immune activity in such patients. Hence, studies assessing DDIs between antiplatelet agents and ARTs are needed in order to guarantee an optimal efficacy and safety for cardiovascular therapies in HIV-infected patients. The aim of the present study was to assess the impact of boosted ARTs on the PK and efficacy of clopidogrel and prasugrel AMs.

2 Patients and Methods

2.1 Study Population

Male subjects older than 18 years of age were eligible to participate in this study; women were not included in the study in order to reduce the sources of PK variability. HIV-infected patients with undetectable viremia, no comorbidities, and with stable antiretroviral treatment containing ritonavir or cobicistat as PK boosters were eligible for participation. Healthy volunteers were not allowed to take any medication and were asked to abstain from drinking grapefruit juice for at least 10 days before the start of the study. Volunteers with known renal or liver diseases, as well as those with a familial history of bleeding or known hemorrhagic diseases, were not included in the study. The study protocol was reviewed and approved by the independent Ethics Committee of Geneva, as well as the Swiss agency for therapeutic drugs (Swissmedic). All participants provided written informed consent prior to enrollment in the study. Protocol conception and trial conduct were performed in accordance with the Declaration of Helsinki ethical principles and Good Clinical Practice (GCP) guidelines of the International Council of Harmonization (ICH). This trial is registered at http://www.clinicaltrials.gov (trial identifier: NCT03054207).

2.2 Study Design and Treatments

This was an open-label trial with a randomized crossover design. Subjects received clopidogrel 300 mg or prasugrel 60 mg in two different sessions where the order of treatment attribution was randomly assigned (Fig. 1). The loading doses were chosen as they correspond to doses prescribed in common clinical practice. The response to antiplatelet treatments was measured by the point-of-care VerifyNow® assay following administration of clopidogrel or prasugrel in HIV patients treated with ritonavir- or cobicistat-boosted ART and in healthy controls. Furthermore, PK profiles of clopidogrel and prasugrel AMs, as well as their correlation with observed platelet inhibitions, were evaluated. The study was conducted at the Clinical Research Centre of Geneva University Hospitals. Two sessions were separated by a washout period of at least

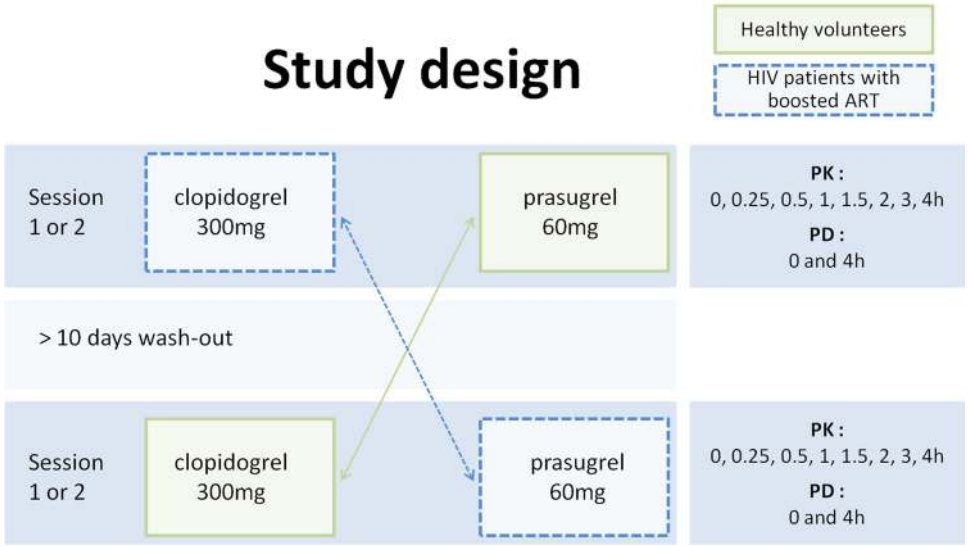

Fig. 1 Study design: open-label trial with a randomized crossover design. Subjects (healthy volunteers and HIV patients treated with ritonavir- or cobicistat-boosted ART) received clopidogrel 300 mg or prasugrel 60 mg in two different sessions where the order of treatment attribution was randomly assigned. *HIV* human immunodeficiency virus, *ART* antiretroviral therapy, *PK* pharmacokinetics, *PD* pharmacodynamics

10 days. Volunteers attended two half-day visits (approximately 4 h) for blood sampling. HIV patients continued their ARTs as usual. After an overnight fast, volunteers took a tablet of clopidogrel 300 mg or prasugrel 60 mg. Blood samples were collected before and 4 h after clopidogrel or prasugrel intake, in citrate-containing Vacutainer® tubes (Becton–Dickinson, Franklin Lakes, NJ, USA) for the assessment of platelet reactivity by the VerifyNow® P_2Y_{12} assay. Additional blood samples were collected in EDTA-containing tubes (Vacutainer®) prior to and 0.25, 0.5, 1, 1.5, 2, 3, and 4 h after the administration of prasugrel or clopidogrel, for PK analysis. Immediately after blood collection, 30 µL of 2-bromo-3-methoxyacetophenone (BMAP) 500 mM was added into blood tubes. This pretreatment allowed the unstable thiol group in AMs to form a disulfide bond with BMAP. Samples for PK analysis were centrifuged at 890*g* for 10 min and were stored at −80 °C until analysis.

2.3 Data Analysis

To detect a difference of platelet reactivity units (PRUs) of at least 30% (± 20%), with a power of 90% and α error of 5%, 9 volunteers were needed in each group. Therefore, a minimum of 18 subjects (9 HIV patients and 9 healthy volunteers) were needed for the overall study. The values were expressed by geometric means ($IC_{95\%}$) and the difference between treatment groups was estimated by two-sided Student's test. A p value <0.05 and <0.01 were defined as significant and highly significant, respectively. PK parameters of prasugrel and clopidogrel AMs were calculated by non-compartmental analysis using WinNonLin® software version 6.2 (Phoenix, a Certara company, Princeton, NJ, USA). The data and the statistical analysis comply with the recommendations on experimental design and analysis in pharmacology [15].

2.4 Pharmacokinetic (PK) Assessments of Active Metabolites (AMs)

Plasma samples (50 µL) were extracted by protein precipitation using 200 µL of acetonitrile. The analysis of samples was performed using fully validated methods using liquid chromatography coupled with a triple-quadrupole mass spectrometer. Details of quantification method validation and instruments are presented in electronic supplementary material 1.

2.5 Platelet Reactivity Assessment Using the VerifyNow® P_2Y_{12} Assay

Tubes were gently mixed after collection, stored at room temperature, and analyzed within 4 h. The VerifyNow® P_2Y_{12} assay was performed using single-use cartridges, and the VerifyNow® P_2Y_{12} system (Accrivia, San Diego, CA, USA) was used for measuring platelet aggregation via light transmittance variations. Results were displayed as an absolute PRU and an inhibition percentage calculated as [(baseline value − PRU)/baseline value] × 100. Various cut-off values are available for PRUs in the literature, ranging from 206 to 240 [16–20]. The cut-off of PRU ≥ 216 was used in this study as it was the most conservative value and because it had previously demonstrated the optimal detection of higher on-treatment platelet reactivity (HPR) [16].

3 Results

Twelve healthy volunteers and nine HIV-infected patients without cardiovascular diseases, with a mean age (range) of 42 (31–63) and 48 (29–66) years, respectively ($p = 0.28$), were included in the study. Their mean weight (range) was 74 (46–91) and 68 (57–83) kg, respectively ($p = 0.19$), and body mass index [BMI] (range) was 23.3 (18.8–27.1) and 23.1 (18.3–29.3), respectively ($p = 0.85$). Healthy volunteers took no medication. ART regimens for each HIV-infected patient are presented in Table 1. All HIV patients had undetectable viremia at the time of the study and presented no other relevant comorbidities. Administered drugs were well tolerated and no serious adverse events were reported during the study.

3.1 PK Assessments of AMs

As expected, a 3.2-fold lower area under the concentration–time curve (AUC) ($p = 0.02$) and maximum plasma concentration (C_{max}) of clopidogrel AM ($p = 0.03$) were observed in healthy subjects compared with HIV patients. Similarly, mean 2.1-fold and 1.7-fold lower AUC ($p < 0.001$) and C_{max} ($p = 0.02$) of prasugrel AM were observed in HIV patients compared with healthy subjects. PK parameters for clopidogrel and prasugrel AMs are summarized in Table 2, and observed mean concentration–time profiles of clopidogrel and prasugrel AMs in healthy volunteers and HIV patients are illustrated in Fig. 2.

3.2 Platelet Reactivity Assessment by VerifyNow® P_2Y_{12} Assay

PRUs measured by the VerifyNow® assay were significantly different in healthy subjects compared with HIV patients following administration of either clopidogrel 300 mg or prasugrel 60 mg. Thirty-five percent lower PRUs were observed in healthy controls compared with HIV patients ($p = 0.04$) following clopidogrel intake. All healthy subjects had PRU below the cut-off value at 4 h after clopidogrel intake, while 44% of HIV patients had PRU values above the 206 cut-off value. On the contrary, all subjects responded well to prasugrel treatment, with mean PRU values of 0 and 2, respectively ($p = 0.21$). In terms of platelet inhibition, 90% higher platelet inhibition was observed in healthy controls compared with HIV patients ($p = 0.04$) following clopidogrel intake ($p = 0.03$). Detailed platelet reactivity results are outlined in Table 3. Individual PRU values observed after administration of clopidogrel and prasugrel are depicted in Fig. 3a, b, respectively.

Generally, a good consistency was observed between platelet inhibition and the AUC of clopidogrel AM (Spearman's correlation coefficient = 0.683, $p = 0.001$), as well as C_{max} (Spearman's correlation coefficient = 0.657, $p = 0.002$). Prasugrel intake led to almost complete platelet inhibition in all subjects, thus no significant correlation could be observed. The patient under cobicistat-boosted treatment showed no particular PK or platelet activity profile compared with those patients under ritonavir-boosted therapy.

Table 1 ART regimens of HIV-infected patients

Subject number	ART regimen
1	Tenofovir, emtricitabine, atazanavir, ritonavir
3	Darunavir, ritonavir, lamivudine
5	Darunavir, ritonavir, lamivudine, abacavir
21	Nevirapine, darunavir, ritonavir, tenofovir
22	Efavirenz, atazanavir, ritonavir, abacavir
23	Darunavir, ritonavir
24	Elvitegravir, cobicistat, emtricitabine, tenofovir
26	Darunavir, ritonavir, emtricitabine, tenofovir
27	Ritonavir, abacavir, lamivudine

ART antiretroviral therapy, *HIV* human immunodeficiency virus

4 Discussion

In the current clinical study, the impact of boosted ART on the PK and efficacy of clopidogrel and prasugrel AMs following administration of single loading doses of clopidogrel 300 mg and prasugrel 60 mg were assessed in both HIV-infected patients receiving potent CYP450 inhibitors and healthy male subjects. The originality of the present work relies on the assessment of PK profiles of clopidogrel and prasugrel AMs in both groups. As expected, a threefold lower AUC and C_{max} of clopidogrel AM were observed in healthy subjects compared with HIV patients. Similarly, an almost twofold lower AUC and C_{max} of prasugrel AM were observed in HIV patients compared with healthy subjects. These PK differences provide a mechanistic explanation pertaining to the pharmacodynamic (PD) findings. Regarding platelet inhibition following clopidogrel treatment, all healthy subjects had PRUs below the cut-off value 4 h after clopidogrel intake, while 44% of HIV patients had PRU values above the cut-off value. On the contrary, all subjects responded well to prasugrel treatment. In a general manner, a slightly higher interindividual variability was observed in HIV patients in terms of platelet inhibition compared with healthy subjects, which was in line with the higher variability observed in terms of PK of clopidogrel and prasugrel AMs.

Table 2 Observed PK of clopidogrel and prasugrel active metabolites following administration of clopidogrel 300 mg and prasugrel 60 mg single doses in healthy male volunteers and HIV-infected patients

	Healthy volunteers	HIV patients	*p* value[a]
Clopidogrel AM			
AUC_4 (ng h mL^{-1})	80.5 (59.4–109)	25.1 (13.8–45.7)	0.02[b]
C_{max} (ng mL^{-1})	55.9 (37.9–82.3)	17.3 (9.39–32.0)	0.03[b]
T_{max} [h; median (range)]	1.01 (0.83–1.23)	0.86 (0.69–1.06)	0.19
$t_{½}$ (h^{-1})	0.72 (0.49–1.07)	0.65 (0.58–0.72)	0.40
Prasugrel AM			
AUC_4 (ng h mL^{-1})	414 (361–475)	200 (148–270)	< 0.001[c]
C_{max} (ng mL^{-1})	362 (272–484)	207 (147–291)	0.02[b]
T_{max} (h; median (range)]	0.69 (0.49–0.96)	0.56 (0.37–0.86)	0.64
$t_{1/2}$ (h^{-1})	0.76 (0.64–0.91)	0.96 (0.77–1.20)	0.16

Data are expressed as geometric means (95% confidence interval) unless otherwise specified

AM active metabolite, AUC_4 area under the concentration–time curve from time zero to 4 h, C_{max} maximum plasma concentration, T_{max} time to achieve maximum plasma concentration, $t_{½}$ elimination half-life, *PK* pharmacokinetics, *HIV* human immunodeficiency virus

[a] *p* values were calculated based on the two-sided Student's test

[b] A p value < 0.05 was considered significant

[c] A p value < 0.01 was considered highly significant

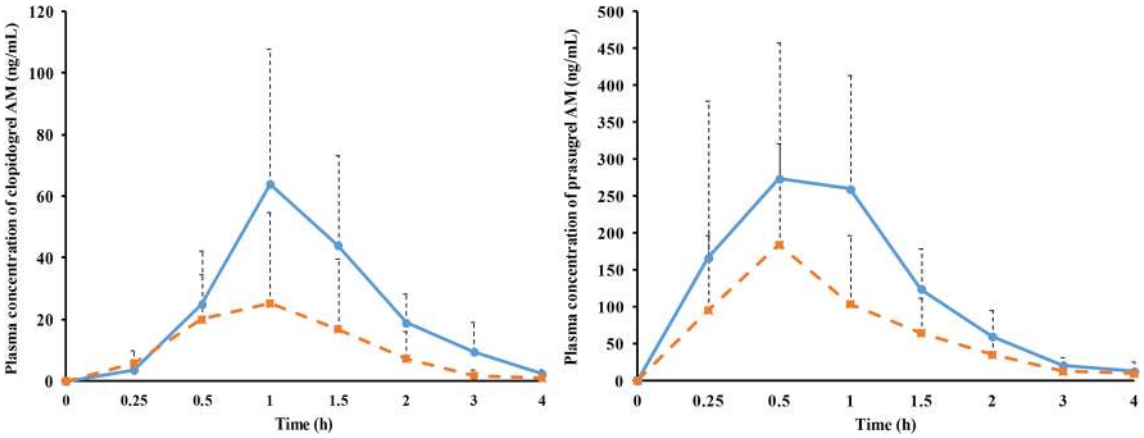

Fig. 2 Observed mean concentration–time profiles of clopidogrel AM (left) and prasugrel AM (right) following administration of single loading doses of clopidogrel 300 mg and prasugrel 60 mg in healthy male volunteers (solid lines) and HIV patients (dashed lines). *AM* active metabolite, *HIV* human immunodeficiency virus

In a previous in vitro experiment, we showed that ritonavir extensively inhibited prasugrel bioactivation in human liver microsomes, raising the hypothesis of a clinically relevant DDI between ritonavir and prasugrel via CYP3A inhibition [21]. This PK interaction was subsequently confirmed by a clinical study where single doses of ritonavir 100 mg and prasugrel 60 mg were coadministered in healthy volunteers. A 38 and 45% decrease in the AUC and C_{max} of prasugrel AM were observed when prasugrel was coadministered with ritonavir [22]. In a recent cross-sectional clinical study by Hauguel-Moreau et al. the residual platelet reactivity following dual antiplatelet therapy (DAPT), including clopidogrel, prasugrel or ticagrelor and aspirin, was compared between ACS patients with and without HIV infection [23]. In the latter study, the platelet reactivity was moderately higher in HIV patients compared with the control group after DAPT, and they had significant HPR compared with uninfected patients. However, other concomitant drugs such as statins, calcium channel blockers, and proton pump inhibitors were also present in subjects' treatments and could have affected the overall antiplatelet–ART DDI outcome. In our study, prasugrel induced a potent platelet inhibition in both groups, regardless of the potential DDI with ritonavir and the reduced exposure of HIV patients to prasugrel AM. On the contrary, the administration of clopidogrel led to a modest platelet inhibition in both groups, which was in line with observations by Hauguel-Moreau et al. [23]. Long-term administration of ritonavir or cobicistat in HIV patients leads to competitive and mechanism-based inhibition of

Table 3 Observed antiplatelet activity following administration of clopidogrel 300 mg and prasugrel 60 mg single doses in healthy male volunteers and HIV-infected patients using the VerifyNow® assay

	Healthy volunteers	HIV patients	*p*-Value[a]
Clopidogrel			
PRU (T_{4h})	97 (54–175)	150 (81–274)	0.04[b]
Inhibition%	42% (32–55%)	4% (0–66%)	0.03[b]
Prasugrel			
PRU (T_{4h})	0 (0–1)	2 (1–5)	0.21
Inhibition%	99% (99–100%)	98% (95–100%)	0.10

Data are expressed as geometric means (95% confidence interval) unless otherwise specified

PRU platelet reactivity units

[a] *p* values were calculated based on the two-sided Student's signed rank test

[b] A p value < 0.05 was considered significant

CYP3A and lessens the formation of latter AMs. This could explain why lower platelet inhibition was observed by Hauguel-Moreau et al. in HIV patients compared with non-HIV patients.

Potent inhibition of the CYP3A enzyme by ritonavir has been the subject of numerous in vitro and in vivo studies [6, 7, 24, 25]. A few studies suggested that ritonavir could also induce CYP3A when administered at steady state, but all these studies were conducted in rats [25–27]. Altogether, existing clinical studies suggest a lower magnitude of CYP3A inhibition at ritonavir steady state compared with single-dose administration; however, no absolute CYP3A induction effect was outlined in any of the studies. On the other hand, ritonavir was shown to be a moderate inducer of CYP2B6, CYP2C9, CYP2C19, and CYP1A2 in various in vitro and in vivo studies [24–28]. The impact of CYP3A inhibition by ritonavir on clopidogrel and prasugrel bioactivations could therefore be somewhat reduced by the induction of these other isoenzymes. In a randomized clinical study in healthy volunteers, the effect of repeated administration of ritonavir and darunavir on the PK of artemether (a substrate of CYP3A, CYP2B6, CYP2C9, and CYP2C19) and lumefantrine (a substrate of CYP3A) was assessed. The AUC of artemether was reduced by 16%, while the AUC of lumefantrine was increased by 270% [29]. In another clinical study in healthy subjects, the impact of the potent CYP3A inhibitor ketoconazole on the PK and PD of clopidogrel and prasugrel AMs was assessed. In that study, although ketoconazole slightly decreased the C_{max} of prasugrel AM, no impact on its AUC or platelet inhibition was observed. With regard to clopidogrel AM, both AUC and platelet inhibition were reduced by approximately 30% [30].

In a substudy of the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–thrombolysis in myocardial infarction 38 (TRITON–TIMI 38) study, the relationship between exposure to prasugrel AM, clinical efficacy, and the incidence of major and minor bleedings were assessed using a population PK analysis [31]. In the latter study, higher prasugrel AM plasma concentrations were linked to a higher bleeding risk during maintenance therapy. Additionally, age ≥ 75 years and weight < 60 kg were two factors associated with a higher rate of bleeding events. Consequently, prasugrel is generally not recommended in such patients. However, since the PK of prasugrel is linear up to 60-mg daily doses, the authors suggested reducing the prasugrel dose to mitigate the bleeding risk in these patients. A maintenance daily dose of 5 mg instead of 10 mg was recommended in

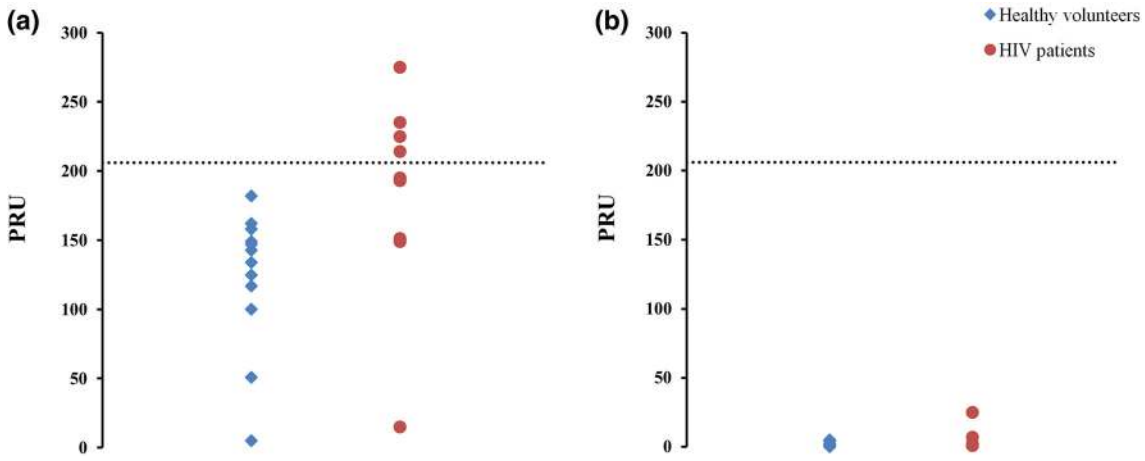

Fig. 3 PRUs observed in healthy subjects (filled diamond) and HIV patients (filled circle) following administration of single loading doses of **a** clopidogrel 300 mg and **b** prasugrel 60 mg, evaluated using the VerifyNow® assay. *Dashed lines* represent the non-response cut-off value. *PRUs* platelet reactivity units, *HIV* human immunodeficiency virus

such patients, which was also supported by the regulatory drug label in a few regions [31–33].

The main limitations of the current clinical study were its modest sample size, absence of female participants, and administration of single loading doses of antiplatelet agents, which may have masked the potential difference between both subject groups on long-term therapy. A more important difference in platelet inhibition between HIV-infected and uninfected patients can be expected following long-term treatment by antiplatelet agents and boosted ARTs [23]. Subjects included in this study had undetectable levels of viremia, thereby the results may not be transposable to patients with significant viral load. This study was not designed to evaluate clinical endpoints such as stent thrombosis or bleeding events. These findings should be followed up by appropriately designed longitudinal studies, as suggested by Gurbel et al. [34]. Finally, the design of the study did not allow controlling for the possible effects of HIV disease itself on the PK of the AMs and low platelet responses. Indeed, the contribution of HIV-related malabsoption problems and altered platelet responsiveness to our findings, although theoritical, cannot be excluded. Plasma concentrations of the parent clopidogrel and prasugrel were not measured in our study.

5 Conclusions

In summary, the coadministration of thienopyridine antiplatelet agents with ART boosters led to significantly lower exposure to their AMs in HIV patients compared with untreated healthy controls; however, the consequent differences in platelet inhibition were not of the same magnitude for both drugs. All in all, prasugrel seems to remain an adequate antiplatelet agent and should be preferred to clopidogrel regardless of the potential metabolic DDI and the expected inhibition of its bioactivation. Obviously, this choice is only appropriate if the bleeding risk is acceptable in such patients. In cases where prasugrel is associated with a higher risk of bleeding events, for instance in patients older than 75 years or with a body weight <60 kg, a reduced prasugrel dose can be used [31, 32]. On the other hand, the potent and reversible antiplatelet agent ticagrelor may be considered in HIV patients in the future. Indeed, in a recent clinical study, we demonstrated that the PK interaction between ritonavir and ticagrelor could be successfully counterbalanced by administration of a reduced oral dose of ticagrelor in healthy volunteers using physiologically-based PK modeling and simulation. Although ticagrelor is contraindicated in ritonavir-treated patients, this strategy could represent a promising approach in such patients once the model is validated in patients [35].

The PK of parent clopidogrel and prasugrel molecules or inactive metabolites would probably add valuable information, helping to exclude a decrease in the absorption of these antiplatelet drugs in HIV patients.

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Compliance with Ethical Standards

Conflict of Interest Niloufar Marsousi, Youssef Daali, Pierre Fontana, Jean-Luc Reny, Virginie Ancrenaz-Sirot, Alexandra Calmy, Serge Rudaz, Jules Alexandre Desmeules and Caroline Flora Samer declare no conflicts of interest relevant to the content of this article.

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