Research Article

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Patients Living with HIV and Coronary Disease: Are we Using Appropriate Anti platelets as Part of Dual Antiplatelet Therapy?

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ABSTRACT

Background: *People living with HIV (PLHIV) have a higher incidence of cardiovascular disease and complications after intervention, including in-stent thrombosis. The frequency of potential drug-drug interactions in the setting of acute coronary syndrome (ACS) with antiretroviral therapy (ART) and dual-antiplatelet therapy (DAPT) regimens remains unclear. We sought to determine the frequency of potential drug-drug interactions in a cohort of people living with HIV who were investigated for coronary disease and initiated on DAPT as per Australian ACS Guidelines.*

Methods: *A retrospective audit was performed in a single tertiary hospital in PLHIV presenting with symptomatic coronary artery disease (CAD) receiving DAPT. Patients were grouped based on exposure to a protease inhibitor or efavirenz and etravirine, given that these were found to have the greatest potential interactions with DAPT.*

Results: *Fifty-three patients received DAPT, of which 31 (58%) had a potential drug-drug interaction. Clopidogrel was the most frequent $P2Y_{12}$ inhibitor prescribed, accounting for 47 (87%) of the interactions. Twenty-six patients were on a protease inhibitor, of which 21 (81%) had a potential drug-drug interaction. There were 11 instances of efavirenz and 3 of etravirine use, of which all resulted in potential drug-drug interactions (100%, respectively).*

Conclusion: *Potential drug-drug interactions were very common in PLHIV needing DAPT. The widespread use of clopidogrel in DAPT regimens resulted in a high rate of drug-drug interactions. An awareness of interactions and guidelines around $P2Y_{12}$ inhibitor selection may help reduce the rate of in-stent thrombosis for PLHIV and improve clinical outcomes.*

Keywords

Anti-platelets, Coronary disease, Drug interactions, HIV.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the Western world, contributing to over one-third of all deaths [1] and is responsible for up to 12% of healthcare expenditure in Australia [2]. This burden of CVD disproportionately affects socioeconomically disadvantaged patients and those with chronic diseases, including people living with HIV (PLHIV) [3,4].

The widespread use of antiretroviral therapy (ART) in Australia has substantially reduced cardiac morbidity and mortality for PLHIV, with life expectancies approaching the general population [5,6]. However, individuals with HIV have a two-fold higher risk of CVD compared to the general population, due to a complex

interplay between the chronic inflammatory state of HIV infection, higher than average number of traditional cardiovascular risk factors and the effects of ART [7-9]. On average, PLHIV present with their first acute coronary syndrome (ACS) a decade younger than the general population and have higher rates of ACS after their index acute myocardial infarction [10,11]. PLHIV are considered a high-risk group post intervention, with higher rates of in-stent thrombosis [12]. Management of PLHIV is further complicated by the potential for drug-drug interactions, specifically within certain classes of ART and widely used cardiovascular medications.

The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (NHF-CSANZ) have published risk management guidelines aimed at reducing CVD and ACS [13]. Central to these guidelines is the use of antiplatelet therapy post ACS and stent insertion [14]. Dual-antiplatelet therapy (DAPT) comprises of aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) and is a standard part of managing ACS, regardless of revascularisation outcome [13].

These agents are potentially compromised by the use of ART, which itself induces changes in the metabolism of $P2Y_{12}$ inhibitors. Both non-nucleoside reverse transcriptase inhibitors (NNRTI), such as efavirenz and etravirine, and protease inhibitors (PI), such as ritonavir, can significantly increase or decrease the availability of active metabolite of the $P2Y_{12}$ inhibitors, thus, reducing their efficacy and/or increasing potential for toxicity [15].

The aim of this study was to assess the ART regimens of a cohort of PLHIV who were high-risk for CAD and were initiated on antiplatelet therapy as per NHF-CSANZ guidelines. The objective of this study was to assess the number of PLHIV who were prescribed a combination of ART and $P2Y_{12}$ inhibitor with the potential for a drug-drug interaction.

Methods

Study population

A retrospective audit was performed on two previously collected datasets that looked at a group of PLHIV receiving ART who presented to St Vincent's Hospital in Sydney between 2002 and 2018. Study one aimed to angiographically characterise the extent of CAD for PLHIV who experienced ACS in an urban hospital setting [16]. Study two assessed cardiovascular risk factors management of PLHIV by surveying primary care physicians with a special interest in HIV infection [17]. Patients were pooled and identified in the medical record to verify both ART and DAPT regimens at the time of discharge.

Inclusion Criteria

Inclusion criteria included the presence of obstructive coronary artery disease (CAD) that necessitated the use of DAPT as per NHF-CSANZ guidelines [13]. Obstructive CAD was defined as either acute coronary syndrome (non-ST elevation and ST elevation ACS) or anyone receiving percutaneous coronary intervention (PCI) and coronary artery stenting.

Analysis

All patients who fit the above criteria had their ART regimen recorded with a view to assess the presence of a drug-drug interaction. An interaction was defined as an ART-DAPT combination that has the pharmacokinetic potential to either increase or decrease plasma concentrations of active $P2Y_{12}$ inhibitor metabolite. PIs and the NNRTIs efavirenz and etravirine pose the greatest risk of interaction, and patients receiving either class were further grouped to assess for interactions. The NNRTI nevirapine was not included as it is not associated with clinically significant effects with $P2Y_{12}$ inhibitors.

The specific regimens that were deemed to have negative interactions were any PI containing regimen combined with clopidogrel or ticagrelor, or, an NNRTI regimen containing either efavirenz or etravirine combined with clopidogrel. This determination was made due to the risk of clinically significant drug interactions being higher in PIs and NNRTIs versus other classes of ART such as NRTIs, integrase inhibitors, cobicistat and CCR5 receptor antagonists [15]. Data were compiled in Microsoft Excel.

The study protocol was independently reviewed and approved by St Vincent's Hospital Sydney's Human Research Ethics Committee (LNR/18/SVH/159) with cross-institutional approval from the University of Notre Dame Australia (018140S). All data were deidentified and pooled for presentation.

Results

Baseline Data

53 subjects received DAPT with a mean age of 60 (± 9) years were identified and included in the study. No female subjects were identified. The mean years since diagnosis of HIV were 18 (± 8) years. HIV viral loads were available for 43 patients; 41 had had undetectable viraemia (< 50 copies/L). Baseline characteristics are shown in table 1.

Table 1: Baseline Characteristics, including ART and presentation type.

Age	60	(9)	*years*
Years since diagnosis of HIV	18	(9)	*years*
CD4+ count	578	(272)	*cells/mm³*
Viral Load < 50 copies/L*	43	(81)	*%*
ART use	53	(100)	*%*
PI exposure	26	(49)	*%*
NNRTI	19	(36)	*%*
NRTI	44	(85)	*%*
Acute Coronary Syndrome (ACS)	20	(37)	*%*
Percutaneous coronary intervention	23	(43)	*%*
ACS	10	(19)	*%*
Symptomatic IHD	13	(25)	*%*
Coronary Artery Bypass Surgery or other	30	(57)	*%*

Continuous variables represented as mean and SD; categorical data presented as percentage; ART = antiretroviral therapy; PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; * data missing for 10 patients.

Overall, 23 patients (43%) received a coronary stent whilst 30 patients (57%) underwent coronary artery bypass grafts (CABG) or received medical therapy. Within this cohort, 20 patients (37%) presented with ACS; 10 patients (50%) received a coronary stent and 10 patients (50%) received medical management or CABG.

Discharge Medications

All patients were receiving ART at discharge. 40 patients were found to be taking an ART medication that had the potential to interact with a $P2Y_{12}$ inhibitor; 26 patients regimens included a protease inhibitor (49%), 11 patient regimens included efavirenz (28%) and 3 patients regimens included etravirine (8%).

Clopidogrel was the $P2Y_{12}$ inhibitor most frequently used, in 46 patients (87%), with four patients prescribed ticagrelor (8%) and three prescribed prasugrel (6%).

Potential DAPT Interactions and ART

Thirty-one patients (58%) were deemed to have an interaction. Drug-drug interactions were recorded in 21 of 28 patients (81%) who received a protease inhibitor. 11 instances of interactions were recorded in 10 patients receiving efavirenz (11 patients; one interaction was accounted for with concurrent PI use). All patients on etravirine (3 patients) also received a PI and were considered to have a drug-drug interaction, and therefore did not contribute to the overall number of interactions (Table 2).

Table 2: DAPT by type, ART of interest and drug-drug interactions.

Dual antiplatelet therapy	53	
Clopidogrel	46	87%
Ticagrelor	4	8%
Prasugrel	3	6%
Drug-drug interactions (patients)	31	58%
ART interactions (by medication) *Protease inhibitor*	21/26	81%
Efavirenz	11/11^	100%
Etravirine	3/3#	100%

^ 1 patient registered an interaction with a concurrent PI

All patients registered an interaction with a concurrent PI

Discussion

In this retrospective audit, a high proportion of PLHIV who received DAPT as per NHF-CSANZ guidelines had a potential drug-drug interaction. Significantly, three in five patients were prescribed a drug combination that reduced the efficacy of the $P2Y_{12}$ inhibitor clopidogrel. The highest proportion of interactions occurred in patients on a regimen that included a ritonavir-boosted PI (49%).

Although PI and NNRTI based regimens are now less commonly initiated as first-line regimens in treatment naïve patients, PI based regimens are still considered a valid alternative first-line regimen in certain patient groups in both the USA and the Australasian guidelines [18]. World Health Organisation (WHO) guidelines do still list Efavirenz as part of an alternative first line regimen, and protease inhibitors as a second-line therapy [19]. Despite a reduced prescribing frequency of PIs and NNRTIs in first-line regimens, a large number of patients remain on these medications as part of long-term treatment due to the past treatment failure, anti-retroviral resistance, or stability on a regimen initially prescribed at a time when PIs and NNRTIs were used as a backbone of therapy. Given these reasons, many of the patients who remain on regimens with potential interactions are likely to be an older cohort with increased risks of comorbidities, and a higher cardiovascular risk profile.

PIs, including ritonavir, are strong inhibitors of CYP3A enzymes and reduce the activation of clopidogrel and prasugrel to their active metabolite. This theoretically increases the potential of thrombus formation and in-stent thrombosis. The $EVERE_2$ST-HIV study drew strong conclusions supporting this, demonstrating increased platelet reactivity with ART regimens that combined PIs with these $P2Y_{12}$ inhibitors [20]. Although significant heterogeneity existed in the $EVERE_2$ST-HIV study population, the authors concluded that protease inhibitor use was associated with the highest increase in platelet reactivity.

Interestingly, the $EVERE_2$ST-HIV also study found significantly reduced $P2Y_{12}$ mediated platelet activity with concurrent exposure to NNRTIs, including efavirenz and etravirine. This biological finding contradicts the theorised reduced efficacy of clopidogrel with NNRTI co-administration [15]. The clinical significance of NNRTI drug-drug interactions remains unclear as the $EVERE_2$ST-HIV authors could not draw definitive conclusions, calling for well-designed RCTs to address this.

Taken together, the pro-coagulant effect of PI use and the potential anti-coagulant effects of NNRTI use necessitate judicious assessment of a patient's ART regimen. This includes pharmacological review to effectively balance thrombosis prevention and bleeding risk in the secondary prevention settings.

Recommendations

DAPT is the standard management strategy in a patient presenting with ACS to help prevent in-stent thrombosis after PCI [13]. Questions exist regarding the theoretical clinical effects of drug-drug interactions between ART and $P2Y_{12}$ inhibitors due to the lack of high-quality RCTs but concern remains as PIs have been implicated with in-stent thrombosis following PCI [21,22]. Clinicians should be mindful of the potential interactions with DAPT and ART, particularly in patients with complex ART requirements who may not be able to be transitioned onto newer regimens that have less potential for interactions.

The $P2Y_{12}$ inhibitor prasugrel has the least potential interaction with most ART combinations. The inhibitory effect of protease inhibitors is somewhat mediated by its greater potency than clopidogrel and is recommended for use in PI and NNRTI containing regimens [15]. Clopidogrel and ticagrelor are not recommended with PI or NNRTI regimens. Importantly, ticagrelor is contraindicated with the use of ART combinations of the strong CYP3A inhibitors ritonavir and cobicistat. Ticagrelor differs

Table 3: Key antiretroviral drug-drug interactions with antiplatelet medications.

Antiretroviral	Metabolism	Antiplatelet Effect	Recommendation
Protease Inhibitors			
Ritonavir	CYP3A4 inhibitor, P-gp, CYP2D6	↓ AUC of clopidogrel active metabolites w/ ketoconazole (400mg CYP3A4 inhibitor) → not clinically significant; case report of ↓ clopidogrel effectiveness ↓ AUC of prasugrel active metabolites Strong CYP3A inhibition ↑ risk of bleeding with ticagrelor	Prasugrel
Atazanavir, darunavir, lopinavir	CYP3A4 inhibition		
Cobicistat	CYP3A4 inhibitor	As per protease inhibitors	Prasugrel
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz	Inducer of CYP3A4 and CYP2B6 Inhibitor of CYP2C9 and CYP2C19	In vitro study showed ↓ AUC Possible ↓ bioactivation of clopidogrel with possible ↑ efavirenz exposure	Prasugrel or ticagrelor
Etravirine	Inducer of CYP3A4 Inhibitor of CYP2C19 (moderate), CYP2C9 (weak), P-gp (weak)	Possible ↓ bioactivation and ↓ AUC of clopidogrel's active metabolite Possible ↓ AUC of prasugrel / ticagrelor although unlikely to be clinically relevant	Prasugrel or ticagrelor
Nevirapine	Inducer of CYP3A4	Nil clopidogrel effect Possible ↓ AUC of prasugrel and ticagrelor although unlikely to be clinically significant	No limitation of $P2Y_{12}$ inhibitor selection
Rilpivirine	Weak inducer of CYP3A4 Inducer of CYP2C19	Unlikely clopidogrel interaction	No limitation of $P2Y_{12}$ inhibitor selection
Integrase Inhibitors			
Raltegravir, elvitegravir, dolutegravir	Inducer of CYP2C9 (elvitegravir only)	No expected interaction	No limitation of $P2Y_{12}$ inhibitor selection
CCR5 inhibitors			
Maraviroc		No expected effect	No limitation of $P2Y_{12}$ inhibitor selection

Adapted from Hauguel-Moreau, Boccara [20].

from both clopidogrel and prasugrel pharmacokinetically; both ticagrelor and its main metabolite are pharmacologically active. Strong CYP3A inhibition results in an excess of ticagrelor that significantly increasing bleeding risk [15,23]. The increasing use of ticagrelor therefore poses a potential concern for PLHIV. $P2Y_{12}$ inhibitor interactions with ART are summarised in table 3.

Limitations

There were many limitations with this study. Of most relevance, this study did not explore outcome data related to thrombotic and bleeding events. Despite this, the audit gives important feedback given that ART, although improving life expectancy, results in additional metabolic changes that necessitate polypharmacy. Secondly, the majority of subjects in this study presented before recommendations were available and therefore provide a historical perspective which may not reflect current practice. Future research would better reflect current practice and provide up to date feedback on prescription practices. Finally, subject selection relied heavily on a manual search of previous CTCA and PCI data from a single clinic. Prospective audits should seek to identify this cohort of subjects when they have either DAPT initiated or in the cardiac catheter lab at PCI. This approach would reduce sampling and recall bias which would allow for more detailed risk analysis. This approach would improve the generalisability of results and addresses patient factors such as gender and ethnicity. This approach would strengthen our practitioner's ability to tailor ART and improve prescription quality and efficacy.

Conclusion

A high rate of PLHIV were discharged on DAPT medications that potentially exposed them to increased morbidity and mortality. This was attributable to the widespread use of NNRTI and PIs that led to high rates of theorised drug-drug interactions in patients that received DAPT as per national guidelines. The high rate of theoretical interactions may underline the mechanism of increased stent thrombosis in PLHIV. A multidisciplinary approach is required to enhance appropriate $P2Y_{12}$ inhibitor selection or alteration of ART regimen to reduce cardiac morbidity and mortality for PLHIV.

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