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Recent Abacavir Use and Incident Cardiovascular Disease in Contemporary Treated People Living with HIV

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Abstract

Objective: Assessing whether the previously reported association between abacavir (ABC) and cardiovascular disease (CVD) remained amongst contemporarily treated people living with HIV (PLWH).

Design: Multinational cohort collaboration.

Methods: RESPOND participants were followed from latest of 01/01/2012 or cohort enrolment until the first of a CVD event (myocardial infarction [MI], stroke, invasive cardiovascular procedure [ICP]), last follow-up or 31/12/2019. Logistic regression examined odds of starting ABC by 5-year CVD or chronic kidney disease (CKD) D:A:D risk score. We assessed associations between recent ABC use (use within past six months) and risk of CVD with negative binomial regression models, adjusted for potential confounders.

Results: Of 29,340 individuals, 34% recently used ABC. Compared to those at low estimated CVD and CKD risks, the odds of starting ABC were significantly higher among individuals at high CKD risk (odds ratio 1.12 [95% confidence interval, 1.04-1.21]) and significantly lower for individuals at moderate, high or very high CVD risk (0.80 [0.72-0.88], 0.75 [0.64-0.87], 0.71 [0.56-0.90], respectively).

During 6.2 years median follow-up (interquartile range; 3.87-7.52), there were 748 CVD events (incidence rate [IR] 4.7/1000 persons-years of follow up [4.3-5.0]). The adjusted CVD IR ratio was higher for individuals with recent ABC use (1.40 [1.20-1.64]) compared to individuals without, consistent across sensitivity analyses. The association did not differ according to estimated CVD (interaction p=0.56) or CKD (p=0.98) risk strata.

Conclusion: Within RESPOND's contemporarily treated population, a significant association between CVD incidence and recent ABC use was confirmed and not explained by preferential ABC use in individuals at increased CVD or CKD risk.

Keywords: abacavir; antiretroviral therapy; antiretroviral drugs; cardiovascular disease; CVD

INTRODUCTION

With the introduction of combination antiretroviral (ARV) therapy and the subsequent prolonged life expectancy of people living with HIV (PLWH), the prevalence of several non-AIDS comorbidities, including cardiovascular disease (CVD), has significantly increased.[1-3] Causes of CVD in PLWH are multifactorial and include traditional CVD risk factors, such as family history, diabetes, hypertension, dyslipidemia, chronic kidney disease (CKD) and smoking. Additionally, associations between CVD and certain ARVs are well-described.[4] In 2008, the D:A:D study showed that participants under follow-up from 1999 until 2005 recently receiving abacavir (ABC) had a 90% increased incidence of myocardial infarction (MI) compared to those not recently using ABC,[5] with similar findings from other settings including the INSIGHT study.[6-8] Other studies, varying considerably in size and methodology, reported a non-significant association between recent ABC use and incident MI or no association at all.[9-13] A follow-up D:A:D analysis including events from 2008 to 2013 showed a similar association as previously reported, but further suggested that after 2008, individuals at >10% estimated 10-year CVD risk were less frequently using ABC.[14]

Several studies have suggested increased platelet reactivity[15-17] as a possible explanation for the association between ABC and CVD, potentially with simultaneous formation of coronary noncalcified/mixed atherosclerotic plaques.[18] Others have speculated that those initiating ABC had a higher underlying CVD risk, i.e., due to individuals with CKD preferentially using ABC over tenofovir disoproxil fumarate (TDF).

While the International Antiviral Society-USA panel no longer considers ABC as part of their first-line treatment regimens,[19] ABC remains a recommended first-line treatment option in Europe with a consideration to use other ARVs with lower CVD risk for those at >10% estimated 10-year CVD risk.[20] This analysis aimed to investigate whether the association between CVD and recent ABC use described in D:A:D remained in a more contemporary ART setting. We further aimed to explore if preferential initiation of ABC in individuals with renal impairment impacted associations between ABC and CVD incidence and whether the observed associations differed across estimated CKD and CVD risk strata.

METHODS

Study design and participants

The RESPOND consortium is a multinational collaboration of 17 European/Australian cohorts formed in 2017. Details on RESPOND have previously been published.[21] Annual data collection includes demographics, HIV-specific information, and clinical data, including validated and non-validated events. Ischemic CVD events and cerebral haemorrhages, occurring within 12 months of the last clinical visit before RESPOND enrolment and thereafter, are reported using study-specific forms. Moreover, the reported forms are centrally validated according to prespecified criteria building on the WHO's MONICA study definitions (for details, see RESPOND Manual of Operations).[22,23]

We followed participants >18 years from the latest of cohort enrolment or 1 January 2012 (baseline) to the earliest of first CVD event, last follow-up (FU) visit, or 31 December 2019. We excluded individuals with incomplete event data, missing gender, no follow-up data after the first visit and those that did not have a CD4 count and viral load measured 12 months prior to or within 3 months after baseline.

Individuals with a CVD event prior to baseline were included in the primary analysis for consistency with prior RESPOND and D:A:D analyses.[24,25] During FU, an incident CVD event was only counted if the type of event differed from the CVD event experienced prior to baseline (e.g. a stroke followed by a MI) and was not an invasive cardiovascular procedure (ICP; coronary angioplasty/stenting, coronary bypass surgery, carotid endarterectomy) performed in relation to a MI or stroke.

Statistical methods

The outcome was the first MI, stroke or ICP after baseline, calculated per 1000 person-years of follow-up (PYFU).

We used logistic regression to assess whether individuals at a higher estimated 5-year D:A:D risk of CVD or CKD[26,27], compared to those at low risk, were preferentially starting ABC. Risk categories are described in Figure 1.

For consistency with prior studies, recent ABC use was defined as current use or use within the previous six months.[5,6,14] Associations between incident CVD and recent ABC use were assessed using multivariable negative binomial regression models. A priori, the model was adjusted for factors previously linked with CVD, including sex, ethnicity, region, HIV acquisition risk, age, body mass index (BMI), current CD4 count, CD4 nadir, hypertension, dyslipidemia, diabetes, prior AIDS-defining conditions, prior CVD and prior CKD, all fitted at baseline. Smoking status and exposure to ARVs previously associated with risk of CVD events, including cumulative exposure to ritonavir-boosted lopinavir (LPV/r), boosted darunavir (DRV/b), indinavir (IDV), stavudine (d4T), didanosine (ddI), and integrase strand transfer inhibitors (INSTIs) were included as time-updated variables. INSTIs were included based on previous RESPOND findings of an association between the INSTI class and CVD incidence independent of estimated CVD risk strata.[25] We further explored the inclusion of antiplatelet medication use as a potential confounder. An unknown category accounted for missing data for categorical variables in the regression model. Variable fitting is shown in the legend of Figure 2.

In sensitivity analyses, adjustment was only made for the estimated 5-year D:A:D CVD and CKD risk scores, respectively, to investigate potential overfitting of the model. Further sensitivity analyses excluded individuals with CVD prior to baseline and included only centrally-validated CVD events. To be consistent with prior investigations, the analysis was repeated excluding ICPs and strokes from the composite CVD endpoint. [5,14] This analysis was adjusted for age, CD4 nadir, smoking status, and prior CVD due to lower statistical power.

Furthermore, we examined whether the association between CVD incidence and ABC varied depending on the estimated 5-year CVD and CKD risk score strata by including an interaction term between recent ABC use and CVD or CKD risk score in the primary model.

Analyses were performed using Stata/MP 16.1 (StataCorp LLC). All p-values are two-sided, and a p-value <0.05 was defined as statistically significant.

RESULTS

In this analysis, 29,340 (90.3%) of 32,487 RESPOND participants were included. Of the 3,147 excluded participants, 7 had missing data on gender, 1,512 incomplete event data and 1,714 individuals did not have a CD4 count or viral load measurement in the 12 months before or within 3 months after baseline. Further, 264 individuals did not have follow-up data after the first visit. Compared to those included, fewer excluded participants had comorbidities at baseline (42.7% vs 73.3%), while a higher proportion were ART-naive (53.3% vs 24.4%). Included participants were predominantly males (74.4%) of Western European origin (43.7%) and men having sex with men (45.1%). Median baseline age was 44 years (interquartile range [IQR] 36–51), median CD4 count was 524 cells/mm^3 (IQR 357–715) and 94 (12.6%) had a CVD event prior to baseline.

During 6.16 years median FU (interquartile range [IQR] 3.87–7.52; 160,252 PYFU), there were 748 CVD events (incidence rate [IR] 4.7/1000 PYFU (95% confidence interval, CI 4.3–5.0)): 299 MIs, 228 strokes, 221 ICPs. Participants developing CVD had a higher prevalence of traditional CVD risk factors compared to those without a CVD event, including dyslipidemia (84.6% vs 60.7%), hypertension (44.1% vs 18.7%), smoking (40.8% vs 27.6% current smokers), diabetes (13.2% vs 3.7%) and a BMI >25 (28.5% vs 22.7%), consequently increasing their estimated CVD risk at baseline (Supplementary table S1, http://links.lww.com/QAD/C627).

By the end of FU, 9848 (24.5%) individuals with 39192 PYFU recently used ABC, of which 32.1% (12250 PYFU) were also on a protease inhibitor (PI). Among those recently using ABC, there were 254 CVD events (IR 6.48/1000 PYFU [CI 5.71–7.33]); 109 MIs, 83 strokes, 63 ICPs.

The odds of starting ABC among participants with moderate (1 – <5%; odds ratio, OR, 0.80 [95% CI 0.72–0.88]), high (5 – <10%; 0.75 [0.67–0.87]), and very high (>10%; 0.71 [0.56–0.90]) estimated 5-year CVD risk were significantly lower than for those at low (<1%) risk. Compared to individuals at low (<0) CKD risk, the odds for starting ABC were significantly higher for individuals at high (>5; 1.12 [1.04–1.22]) estimated 5-year CKD risk (p<0.001 for all, Figure 1).

The crude CVD IR ratio (IRR) was higher for individuals with recent ABC use compared to those without (IRR 1.60 [95% CI 1.37–1.86], p<0.001). After adjustments for potential confounders, recent ABC use was associated with a 40% increased CVD rate (IRR 1.40 [1.20–

1.64], p<0.001, Figure 2). The association also remained after adjusting for use of antiplatelet medication (IRR 1.41 [1.21–1.65], p<0.001), albeit only 1097 persons (3.7%) were using such medication. All sensitivity analyses were consistent with the primary analysis (Figure 2).

There was no interaction between the observed ABC association with CVD, and the estimated CVD or CKD risk score (interaction p=0.56 and p=0.98, respectively), suggesting a similar CVD incidence rate for recent ABC exposure for individuals at both high and low estimated CVD or CKD risk.

DISCUSSION

Within RESPOND's heterogeneous population of contemporarily treated PLWH, recent ABC use remains associated with a 40% increased CVD incidence independently of other risk factors, including simultaneous PI use. The findings were consistent across several sensitivity analyses, with no evidence suggesting relative CVD rates differed according to estimated CVD or CKD risk strata.

It has previously been proposed that preferential treatment with ABC in individuals with increased CKD risk to avoid renal toxicities related to a TDF-containing backbone might explain the increased CVD rates seen with ABC.[28,29] Indeed, we also observed that participants with a high 5-year CKD risk were more likely to start ABC than those at low CKD risk. However, despite this evidence of channelling bias, the association between ABC and incident CVD was not significantly changed after adjustment for known CVD risk factors, including renal function, and across CKD risk strata. This suggests that renal impairment and channelling do not explain the association between ABC and CVD.

Individuals with a higher estimated 5-year CVD risk were less likely to initiate ABC, consistent with the European guidelines' recommendations to consider suitable alternatives to ABC for PLWH at higher (>10%) CVD risk in whom the absolute CVD risk associated with ABC use is greatest[20]. The association between ABC and CVD incidence was similar across CVD risk strata, suggesting underlying channelling related to CVD event risk is also not likely to explain the association seen.

Additionally, we accounted for exposure to any ARV previously shown to be associated with CVD as potential confounders, including INSTIs (as a group), cumulative exposure to LPV/r and DRV/b, and the older ARVs IDV, ddI and d4T.

Whilst causal inference cannot be made within the observational RESPOND study, there is a suggested causal mechanism linking ABC use to CVD, with several studies suggesting an ABC-induced increased platelet reactivity.[15-17] Based on the short lifespan of platelets, the suggested mechanism is consistent with the reversible nature of the association, as well as with investigations related to a temporary increase of platelet-activating-factor after ABC initiation.[30,31] Only a small proportion of participants in the current analysis (3.7%) were on

antiplatelet medication, and adjustment for use hereof did not change the observed association between ABC and incident CVD.

In 2008, the D:A:D study showed a 90% increase in the rate of MI with recent ABC use.[5] Due to lower analytical power in RESPOND at the time of this project, we used a composite CVD endpoint rather than using solely MIs. In a sensitivity analysis, we excluded strokes and ICPs, and the association was strengthened with an IRR of 1.64 (95% CI 1.29–2.07), albeit with wider confidence intervals. Using a composite endpoint including strokes and ICPs may have weakened the association slightly in RESPOND, as also suggested by the INSIGHT study.[6] Despite heterogeneity in endpoints and study populations, our results confirm an increased CVD incidence with recent ABC use.

Given this study's observational nature, we cannot entirely rule out the impact of residual confounding, such as lifestyle modifications and familiar predisposition, missing data or channelling bias, as discussed above.

In conclusion, recent ABC use remained significantly and independently associated with a 40% increased relative CVD risk within a contemporary treatment setting, and did not differ according to estimated CVD or CKD risk, supporting current European guidelines.

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Authors contribution

NJ, supervised by JL, LR, LP, and BN, conceived the idea and developed the project proposal and a statistical analysis plan. All authors reviewed the proposal and analysis plan. LG, with the supervision of AM, performed the statistical analysis, which was reviewed by all authors. NJ developed the first draft of the manuscript and revised the subsequent drafts. NJ, LR, LP, BN, LG, and AM reviewed all versions of the manuscript and interpreted the data. JMM, KGP, GW, CS, SDW, FW, APM, CM, AC, CP, AMO, JV, AS, AVA, ACA, LBM, JL, HG, FR, RZ,

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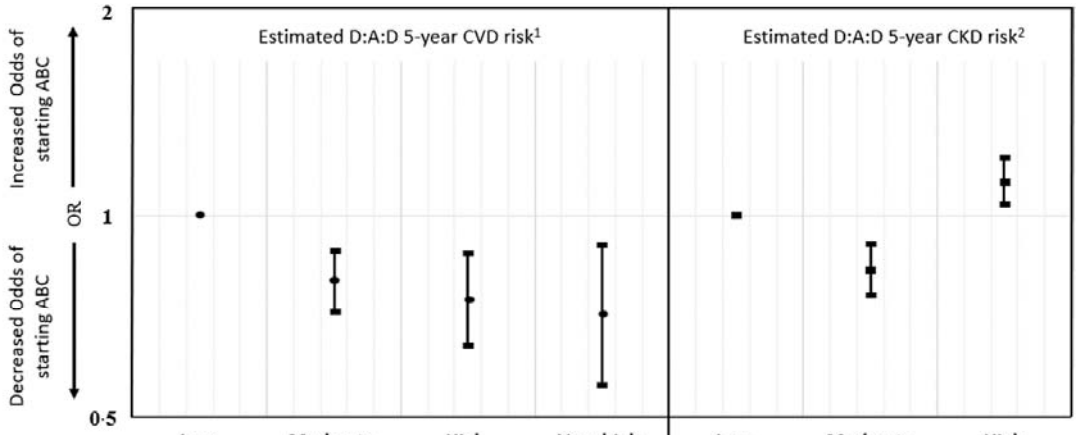
Legend for Figure 1

Odds ratios of initiating ABC by 5-year D:A:D CVD (left) and CKD risk score (right).



	Low (<1%)	Moderate (≥1 – <5%)	High (≥5 – <10%)	Very high (≥10%)	Low (< 0)	Moderate (≥0 – <5)	High (≥5)
Adjusted odds ratio* (95% CI)	**1**	**0.80** (0.72–0.88)	**0.75** (0.67–0.87)	**0.71** (0.56–0.90)	**1**	**0.83** (0.76–0.90)	**1.12** (1.04–1.21)
n	3502	8018	1834	579	8096	7755	8275

*p<0.001 for all; adjusted for baseline year

[1]Components of the D:A:D CVD risk score include: gender, age, smoking status, diabetes

(diagnosis or on antidiabetic treatment), family CVD history, systolic blood pressure, total cholesterol, HDL, CD4 cell count, cumulative PI exposure, cumulative NRTI exposure, current ABC use

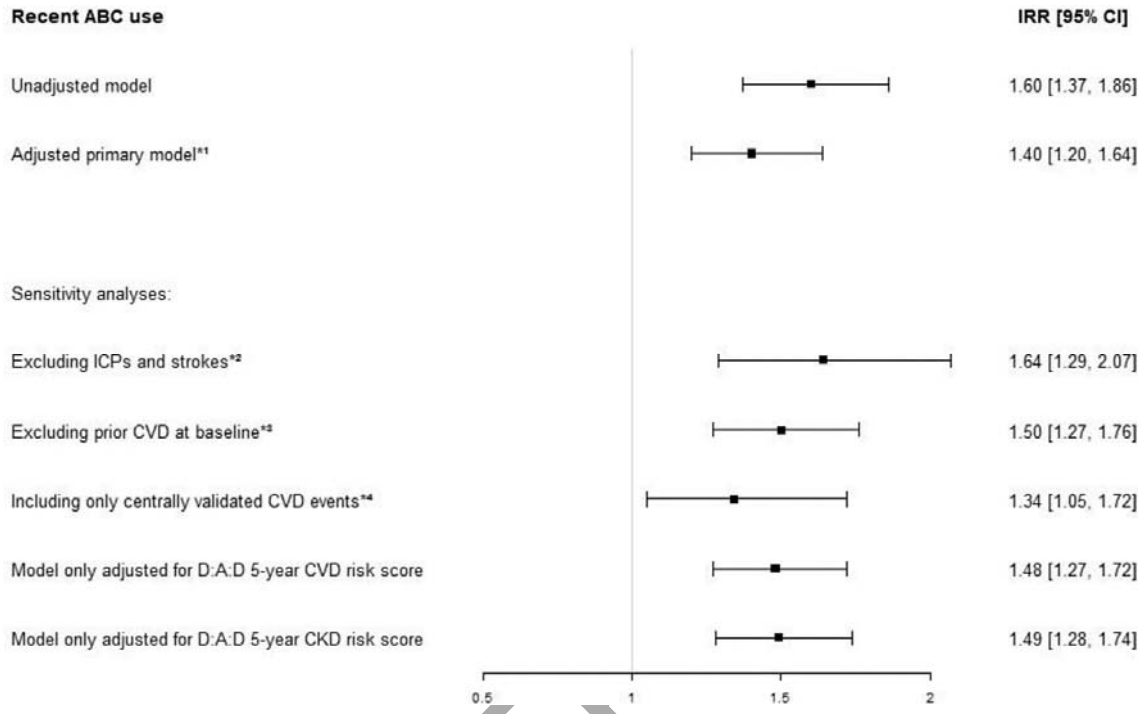
[2]Components of the summed D:A:D CKD risk score include: (+2)injecting drug use, (+1)

HCV antibody positive, (+4) aged 35-50, (+7) aged 50-60, (+10) aged >60, (+6) baseline eGFR <70, (-6) baseline eGFR >90, (+1) female, (+1) nadir CD4 <200/mm3, (+1) hypertensive, (+1) prior CVD, (+2) diabetic

Abbreviations: CVD: cardiovascular disease, CKD: chronic kidney disease, ABC: abacavir, HDL: high-density lipoprotein, PI: protease inhibitor, NRTI: nucleos(t)ide reverse transcriptase inhibitor, HCV: viral hepatitis C, eGFR: estimated glomerular filtration rate

Legend for Figure 2

Incidence rate ratios of CVD with recent ABC use, compared to no recent ABC use



*[1]Adjusted for age (per 10 years older), sex (male, female), ethnicity (Black, White, other), region (West Europe, South Europe and Argentina, North Europe and Australia, East Europe), BMI (kg/m; <18.5, 18.5-<25, 25-<30 and >30), HIV acquisition risk (MSM, heterosexual contact, IDU), CD4 cell count (per 100 cell/µL higher), hypertension (yes/no), diabetes (yes/no), prior AIDS (yes/no), prior CVD (yes/no), prior CKD (yes/no), dyslipidaemia (yes/no), all fixed at baseline. Calendar year, smoking and ARVs previously associated with CVD (cumulative exposure to LPV/r, DRV/b, IDV, d4T, DDI and INSTIs [0, 0-6, 6-12, 12-24, 24-36, >36 months]) were included in the model as time-updated variables

*[2]Only adjusted for age, CD4 nadir, smoking status, and prior CVD; n events = 300

*[3]n events = 642

*[4]Results were non-significantly different to the adjusted primary model; n events = 302

Abbreviations: MSM: Men who have sex with men, IDU: Intravenous drug use, BMI: Body mass index, CVD: Cardiovascular disease, CKD: Chronic kidney disease, LPV/r: Ritonavir boosted lopinavir, DRV/b: Cobicistat or ritonavir-boosted darunavir, IDV: Indinavir, d4T: Stavudine, DDI: Didanosine, INSTI: Integrase strand transfer inhibitor, PYFU: Person years of follow-up, IRR: Incidence rate ratio, ICP: Invasive cardiovascular procedure, ABC: Abacavir