Impact of Nucleoside Reverse Transcriptase Inhibitors on Coronary Heart Disease

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The nucleoside and nucleotide reverse transcriptase inhibitor (N[t]RTI) drug class remains an integral component of effective antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection. However, these drugs are associated with toxicities, through their off-target effects, that may significantly contribute to a number of long-term comorbidities, including coronary artery disease (CAD) and myocardial infarction (MI), recognized to occur with increased frequency in those with HIV undergoing treatment with ART. The contribution of N(t)RTI to CAD and MI may arise either indirectly through induction of metabolic toxicities such as dyslipidemia and insulin resistance, or directly through impact on pathologic pathways involved in development of MI, such as altered platelet responsiveness or endothelial dysfunction. This review focuses on the available data relating to use of individual N(t)RTI drugs and the drug class as a whole and CAD, with a focus on MI.

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KEY WORDS

Antiretroviral therapy • Human immunodeficiency virus • Coronary heart disease • Nucleotide reverse transcriptase inhibitors • Cardiovascular disease

espite the success of antiretroviral therapy (ART) in reducing mortality from illnesses arising as a result of chronic human immunodeficiency virus (HIV) infection and AIDS, people living with HIV and on ART still have excess mortality, particularly those with lower recovery of CD4+ T-cell counts on ART.¹

Not unlike the general population, in whom cardiovascular disease (CVD) such as coronary heart diseases ranks as the leading cause of death in both the United States and Europe,^{2,3} CVD has also been observed as the most common cause of death in those with HIV who are on effective ART with suppressed plasma HIV RNA levels.¹ In a combined analysis of two large strategic trials involving 3280 ART-treated, virally suppressed subjects with HIV, CVD or sudden death accounted for 31% of deaths, whereas AIDS illnesses accounted for only 3% of observed mortality.¹

Although many studies have examined the incidence and prevalence of CVD and coronary artery disease (CAD) in people with HIV, arguably the best analysis to date derives from a health care registry analysis of US veterans (the Veterans Aging Cohort Study Virtual Cohort), which enabled analysis of incident acute myocardial infarction (MI) in veterans with and without HIV infection from similar demographic backgrounds, controlling for several CVD risk factors, including age, sex, hypertension, dyslipidemia, and smoking status. In this large, diverse cohort of 82,459, those with HIV had excess MI events, with an approximate 50% increase in risk of MI after adjustment for other CVD risk factors.⁴

Various factors have been implicated in the excess risk of CVD and CAD observed in those with HIV.5 There is a greater prevalence of some conventional CVD risk factors, such as smoking, in those with HIV,6 although elevated CVD risk remains even with adjustment for these factors.⁴ Indeed, not all CVD risk in HIV can be explained by the prevalence or severity of conventional CVD risk factors. A large, prospective cohort study of people with HIV, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, designed to determine predictors of MI in those with HIV, found MI risk to be over and above that predicted by modeling of conventional CVD risk factors alone.⁷ Several factors may explain this increased risk; HIV is associated with a proinflammatory state combined with persistent immune activation, both of which have been

implicated in CVD risk,⁸⁻¹⁰ with viremia arising from untreated HIV also associated with increased CVD risk.¹¹ In addition, much interest has focused on the potential for ART itself to contribute to CAD in those with HIV, through either direct or indirect mechanisms.

This article addresses the potential contribution from the nucleoside and nucleotide reverse transcriptase inhibitor (N[t]RTI) class of antiretroviral drugs to CVD in those living with HIV.

ART for HIV Infection

There are currently five principal classes of antiretroviral agents commonly recommended for use in first- or second-line ART: N(t)RTIs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, entry inhibitors (CCR5 inhibitors), and integrase strand transfer inhibitors. Their use in combination

termination of HIV RNA to DNA transcription and prevention of the establishment of effective cellular infection by the HIV virus. Seven nucleoside reverse transcriptase inhibitors (NRTIs; abacavir, didanosine, lamivudine, emtricitabine, zidovudine, stavudine, and zalcitabine) and one N(t)RTI (tenofovir disoproxil fumarate) are currently licensed for treatment of HIV infection.13 Conventional ART comprises two N(t)RTIs targeting different endogenous nucleotides (Table 1) used as a "backbone" in combination with other ART drug classes such as non-nucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitors, or protease inhibitors.

Use of N(t)RTIs has been associated with a number of short- and long-term toxicities, primarily related to off-target effects of these drugs interfering with the func-

The N(t)RTI class is made up of analogues of endogenous nucleotides that, after undergoing intracellular phosphorylation to their active triphosphate form, compete with endogenous nucleotides for incorporation into growing DNA strands.

results in effective, prolonged suppression of HIV replication within target cells (predominantly CD4+ T cells) for the majority of those treated, with resulting improvements in CD4+ T-cell counts and reductions in morbidity and mortality.¹²

The N(t)RTI class is made up of analogues of endogenous nucleotides that, after undergoing intracellular phosphorylation to their active triphosphate form, compete with endogenous nucleotides for incorporation into growing DNA strands. The drugs lack a 3-prime hydroxyl moiety that prevents further addition of nucleotides, resulting in chain termination of DNA replication. In HIV, the incorporation of the nucleotide analogues derived from these results in

tion of endogenous nucleotides or other endogenous enzymes utilizing nucleotides.14 Toxicities associated with N(t)RTI use and the specific NRTI most commonly associated with relevant toxicities include renal failure as a consequence of renal tubular dysfunction (tenofovir disoproxil fumarate); abnormalities in adipose tissue metabolism, including lipodystrophy characterized by peripheral lipoatrophy (zidovudine, stavudine) and central lipohypertrophy; peripheral neuropathy (didanosine, stavudine); pancreatitis (didanosine, stavudine); insulin resistance (stavudine); dyslipidemia (abacavir, stavudine, zidovudine); and cytopenias (zidovudine, didanosine) such as anemia, leucopenia, and bone marrow suppression.15

TABLE 1

Nucleoside/Nu	ucleotide Reve	rse Transcript	tase Inhibitors	
Class	Pu	rine	Pyrim	idine
Endogenous nucleotide	Adenosine	Guanosine	Cytosine	Thymidine
Synthetic N(t)RTI analogue	Didanosine	Abacavir	Zalcitabine	Zidovudine
	Tenofovir disoproxil fumarate		Lamivudine	Stavudine
			Emtricitabine	
n addition to individua	al NRTIs fixed dose	NRTL combination	s are also available	including abacavi

In addition to individual NRTIs, fixed-dose NRTI combinations are also available, including abacavir/ lamivudine, tenofovir disoproxil fumarate/emtricitabine, and abacavir/lamivudine/zidovudine. NRTI, nucleoside reverse transcriptase inhibitor; N(t)RTI, nucleoside and nucleotide reverse transcriptase inhibitor.

Associations Between N(t)RTI and MI

Overall, effective ART reduces risk of CVD in those with HIV, amply demonstrated by the Strategies for Management of Antiretroviral Therapy (SMART) Study, in which CD4+ T-cell-guided ART interruption resulted in significantly increased risk of non-AIDS morbidity and mortality, including

Figure 1. Potential contribution to CVD risk of exposure to nucleoside and nucleotide reverse transcriptase inhibitors. NRTI may affect CVD and MI risk through both direct and indirect routes, with abacavir implicated in increased MI rates through a direct mechanism, whereas thymidine NRTI (zidovudine and stavudine) may affect CVD risk indirectly by inducing metabolic toxicities such as dyslipidemia and insulin resistance. In addition, renal dysfunction has also been associated with increased MI risk in HIV, although whether TDF will contribute to MI risk over the long term through increasing potential for renal dysfunction remains to be determined. ?, potential; ART, antiretroviral therapy; CVD, cardiovascular disease, HDLc, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; MI, myocardial infarction; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate. \uparrow = increased. Data from Bedimo RJ et al.²⁹

ART Naive		emia (low HDLc), ir ↑C	VD risk	on, immu		
	Abacavir	Didanosine	Thymid	ine NRTI	ד	DF
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Medium Term			Dyslipic	trophy demia & esistance		
Long Term			↑cv	D risk	Impact or	y ysfunction CVD risk rtain

CVD.¹⁶ However, given the spectrum of toxicities related to N(t)RTI exposure, including dyslipidemia, insulin resistance, and adipose tissue dysfunction, mainly related to exposure to the thymidine NRTI zidovudine and stavudine, many suspected that development of these toxicities would result in an increased risk of CAD, and MI in particular (Figure 1).

To address this question, the D:A:D study was designed to explore factors associated with MI in people living with HIV, including associations between exposure to NRTI and MI risk. In the first analysis, comprising 23,468 subjects, cumulative exposure to ART was associated with an increased risk of MI. In addition, both dyslipidemia and type 2 diabetes (common in those with established metabolic toxicities associated with NRTI) were also associated with increased risk of MI, although presence of lipodystrophy was not.¹⁷ This suggested that NRTI may have, at least indirectly, contributed to MI risk through development of metabolic toxicities contributing to dyslipidemia and insulin resistance.

In a further D:A:D analysis of 517 MIs occurring in 33,347 subjects, providing more than 157,000 personyears of follow-up, surprisingly no association was found between cumulative exposure to zidovudine and stavudine, the NRTI most associated with the potential to induce dyslipidemia, insulin resistance, and MI.18 However, the analysis revealed an unexpected association between exposure to abacavir and didanosine and subsequent MI (relative risk [RR] 1.90; 95% confidence interval [CI], 1.47-2.45 and RR 1.49; 95% CI, 1.14-1.95, respectively). The characteristics of this association differed from others previously observed in the D:A:D study in that, rather than being related predominantly to cumulative drug exposure, it was strongest with recent exposure (ie, the risk was present in those who were currently on the drug or had been exposed to it within the previous 6 mo). The risk persisted with correction for major CVD risk factors, suggesting that the effect was not mediated through indirect effects of exposure to either abacavir or didanosine on other CVD risk factors such as lipids.

In a subsequent updated D:A:D analysis of 580 MIs over 178,835 person-years of follow-up that also examined exposure to tenofovir disoproxil fumarate (for which concerns for increased CVD and MI risk related to the potential for renal dysfunction with exposure), CD4+ T-cell-guided treatment interruption; an analysis of 2752 ART-treated subjects revealed an association between abacavir use and increased CVD endpoints, including MI (hazard ratio [HR] 4.3; 95% CI, 1.4-13.0) at the time of the event,²¹ although the analysis was based on only 19 MI cases. An association between abacavir and MI was also observed in a Canadian retrospective nested case-control study; those with HIV and MI were found more likely to be on abacavir (odds ratio [OR] 1.79; 95% CI, 1.16-2.76), although this analysis did not adjust for potential confounders such as smoking status.²² However, similar results were observed in an Australian retrospective case-

The findings from the D:A:D study of an association between exposure to abacavir and MI were unexpected given that abacavir was associated with less potential for metabolic toxicity when compared with other NRTIS...

no association was observed with either recent or cumulative tenofovir disoproxil fumarate exposure and MI; however, the association between recent exposure to abacavir or didanosine persisted, albeit with a slightly reduced risk (RR 1.70; 95% CI, 1.17-2.47 and RR 1.41; 95% CI, 1.09-1.82, respectively).¹⁹

Abacavir and MI: Conflicting Clinical Data

The findings from the D:A:D study of an association between exposure to abacavir and MI were unexpected given that abacavir was associated with less potential for metabolic toxicity when compared with other NRTIs²⁰; this stimulated further exploration in several additional, primarily smaller cohort studies as well as analyses within a number of randomized controlled trials.

In the SMART study, subjects were randomized to remain on continuous ART or undergo control study of 68 HIV-positive patients with CAD that did adjust for traditional CVD risk factors (OR $(2.10)^{23}$ and in a large, multicenter, retrospective study exploring the association of an unfavorable genetic background defined by 23 CAD-associated single-nucleotide polymorphisms with first CAD event in HIV-positive patients compared with sex-matched control subjects.²⁴ A Danish cohort study of 2952 subjects with HIV examining 67 hospitalizations for MI also found higher rates of hospitalizations for MI in those on abacavir versus those not on abacavir (RR 2.00; 95% CI, 1.10-3.64),²⁵ whereas an analysis from the Swiss HIV Cohort Study also determined a consistent risk of MI in cohort subjects with exposure to abacavir.26 Interestingly, in the latter study, exploratory modeling of the association suggested that the cardiovascular adverse effect of abacavir does not occur immediately; rather,

there is a "lag" period (1-6 mo) before abacavir exposure increases the risk for a CVD event (ie, current risk of a cardiovascular event cumulates with abacavir exposure over 5-20 mo).26 In addition to these cohort data, one randomized clinical trial, the Simplification of Antiretroviral Therapy with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) study, examined virologically suppressed subjects with HIV undergoing a switch to either abacavir or tenofovir disoproxil fumarate as part of NRTI fixed-dose combinations; it detected significantly more cardiovascular events in the abacavir group (2.2 vs 0.3 events per 100 patient-years).27

Although these data fit well with the original D:A:D observations, other studies have failed to show any association between abacavir exposure and CAD and MI. In a large French cohort (74,958 participants), although preliminary analyses of 360 MI cases did show an association between recent exposure to abacavir and MI (OR 2.01; 95%, CI, 1.11-3.64), there were more illicit drug users (intravenous [IV] drug and cocaine use) in those with recent abacavir use. Examining the same cohort, a subsequent case-control analysis of 250 cases of MI matched with control subjects (excluding those who used IV drugs or cocaine) failed to show a persistent association between abacavir exposure and MI,²⁸ suggesting that perhaps illicit drug use may explain the increased risk of MI in those on abacavir. Similarly, in an analysis of a large US Veterans health care registry, an association between abacavir exposure and MI was not consistently observed when the analysis was controlled for renal dysfunction, which did significantly contribute to increased MI risk.29 The authors speculated that subjects

with renal dysfunction were more likely to be treated with abacavir rather than tenofovir disoproxil fumarate, the use of which has been associated with nephrotoxicity, thereby creating a channeling bias that could explain increased MI rates in abacavir recipients. However, another analysis of predominantly ART-experienced US veterans who initiated ART containing either abacavir or tenofovir disoproxil fumarate did observe an association between recent abacavir use and a range of CVD events, systematic review has also confirmed an association between MI and abacavir use when examining observational data but not data from randomized clinical trials.³⁵

So why are the data so conflicting? Although a number of potential reasons may explain the difference, in addition to the potential for unmeasured confounding, the most obvious differences among the data from cohorts and those from randomized controlled trials are the considerable differences in the demographics and treatment characteristics of

Studies in which an association between abacavir and MI was observed were mainly composed of subjects with HIV who were already on ART at enrollment (eg, the D:A:D, SMART, and STEAL studies, and many of the cohort studies), whereas most of the meta-analyses that showed no abacavir association examined data derived from clinical trials of predominantly antiretroviral-naive patients commencing ART.

including MI (HR 1.64; 95% CI, 0.88-3.08) and stroke (HR 2.05; 95% CI, 1.00-4.19), which was not significantly attenuated by adjustment for renal function.³⁰ These analyses demonstrate the inherent inability of most cohort studies to control for all bias, with the potential for unmeasured confounding to lead to unexpected results, such as the association between abacavir exposure and MI.

In addition to these cohort data, a combined analysis of prospective randomized trials from the Aids Clinical Trials Group (ACTG A5001) of participants initiating ART with and without abacavir,³¹ as well as three meta-analyses examining abacavir use in prospective clinical trials, have failed to reveal any association between abacavir exposure and MI,³²⁻³⁴ although these analyses were based on fewer MI cases: 36 events from 17,404 person-years of follow-up in the ACTG A5001 analysis³¹ and 46 incident MIs from 26 different studies in one review.³⁴ A further

those under study (Table 2). Studies in which an association between abacavir and MI was observed were mainly composed of subjects with HIV who were already on ART at enrollment (eg, the D:A:D, SMART, and STEAL studies, and many of the cohort studies), whereas most of the meta-analyses that showed no abacavir association examined data derived from clinical trials of predominantly antiretroviral-naive patients commencing ART. If, as previously mentioned, HIV viremia itself may be associated with increased CVD risk, then reductions in CVD risk accompanying reduced viremia with effective ART may mask any potential increases in CVD risk arising from exposure to specific drugs such as abacavir. Additional potential reasons for differences in observations between studies include differences in age of study participants, with cohort studies representing generally older populations than those observed in clinical trials, length of follow-up, reduced power to detect associations

arising from smaller number of MI events within the clinical trials versus the cohort studies, and differences in the methods for detection or definition of CAD or MI events between the various studies; D:A:D was specifically designed with CVD and MI as a robust endpoint, whereas many of the clinical trials would have relied on investigator adverse event reporting.

Taking all of these issues into account, the observational cohort data are limited by the potential for unmeasured bias confounding the results, whereas the clinical trials with less robust endpoint detection, lower event rate, and shorter follow-up are equally limited in their ability to refute the cohort findings. Nevertheless, any observation of serious adverse safety outcomes with use of a drug deserves thorough investigation, as no other N(t)RTI has been consistently associated with MI-particularly commonly used drugs from this class such as tenofovir disoproxil fumarate and zidovudine, both of which would have the potential to indirectly influence CVD risk through drug-specific toxicities such as renal dysfunction and metabolic toxicities, respectively (Figure 1). In the absence of a definitive, prospective clinical trial to address the issue, which is arguably unlikely given the required size, length of follow-up required, cost, and possible challenges of recruitment, data to provide a robust and valid mechanism to explain how recent abacavir exposure could reversibly lead to increased potential for MI are one of the few remaining investigative options.

Abacavir and MI: Potential Mechanisms

Given that the association between abacavir exposure and MI is limited to recent more than cumulative

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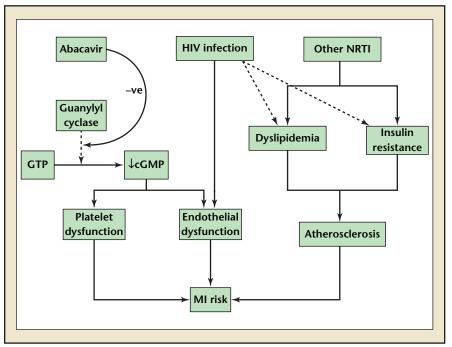
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exposure, research into potential mechanisms has focused more on thrombosis occurring around acute MI events rather than on underlying accelerated atherosclerosis, which would be expected to be less readily reversible upon drug discontinuation.

Inflammation, endothelial dysfunction, and altered coagulation can all contribute to the acute MI event. HIV infection is characterized by a proinflammatory state, with monocyte activation, in particular, consistently observed and associated with markers of subclinical CVD.^{10,36}

In the pathogenesis of MI, inflammation and altered coagulation are pathologically linked and both have been proposed as potential mechanisms to explain the association between abacavir exposure and MI, particularly as both can be reversibly affected, thereby potentially explaining an altered MI risk that occurs only during or recently after exposure to a drug. Although changes in markers of inflammation with abacavir initiation have not consistently been observed in clinical studies,^{37,38} in vitro studies have shown that abacavir exposure both increases platelet reactivity, potentially through inhibition of guanylyl cyclase,³⁹ and alters leukocyte-endothelial interactions through leukocyte activation.40 Guanylyl cyclase is involved in the synthesis of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate, fitting with the concept of an off-target toxicity from abacavir, which is a guanosine analogue. Consistent findings have also been demonstrated when these pathways have been examined in vivo. Several studies have observed increased platelet reactivity in HIV-positive subjects treated with abacavir.^{41,42} One cross-sectional study demonstrated significantly increased platelet aggregation in response to a number of platelet agonists in blood drawn from abacavir-treated subjects compared with non-abacavir-treated subjects,⁴¹ and a more recent

Figure 2. Potential mechanisms underlying associations between nucleoside and nucleotide reverse transcriptase inhibitors and coronary heart disease. cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; HIV, human immunodeficiency virus; MI, myocardial infarction; NRTI, nucleoside reverse transcriptase inhibitor.



publication has also demonstrated increased platelet responsiveness in abacavir-treated subjects with in vitro findings again consistent with cGMP inhibition.42 Endothelial dysfunction has also been observed with abacavir exposure. In a crosssectional comparison of 61 virally suppressed HIV-positive subjects, those on abacavir had significantly lower brachial artery flowmediated vasodilatation, an effect that remained significant when controlled for traditional CVD risk factors.43 No similar studies have been performed relating to use of didanosine. These accumulating data point toward a potentially valid mechanism to explain how abacavir exposure could lead to a reversible alteration in coagulation, which explains how current or recent use of abacavir clinically could increase risk of MI, as observed in clinical cohort studies (Figure 2). Further translational studies are warranted to explore this phenomenon.

Conclusions

Lifelong treatment of HIV with ART necessitates a fuller understanding of the long-term effects of exposure to antiretroviral drugs. Without an effective therapeutic vaccine or HIV cure, and with the focus of HIV management shifting toward earlier treatment, to not only prevent morbidity but to control the epidemic, it is essential that focus is maintained on optimizing drug safety. It is clear that, for the majority of people living with HIV, the benefits in clinical outcome from effective treatment with currently recommended ART regimens outweigh the risks of toxicity. However, although the NRTI class remains central to effective ART strategies, a greater understanding through research of mechanisms underlying off-target toxicities is

necessary to ensure that the full benefits of ART are realized and the potential serious toxicities are either abrogated or avoided, particularly in an environment where universal treatment of HIV infection is being proposed.⁴⁴

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MAIN POINTS

- The nucleoside and nucleotide reverse transcriptase inhibitor (N[t]RTI) drug class remains an integral component
 of effective antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection; however, these
 drugs are associated with toxicities that may significantly contribute to a number of long-term comorbidities,
 including coronary artery disease (CAD) and myocardial infarction (MI).
- N(t)RTI may affect cardiovascular disease risk either directly, by affecting endothelial function, or indirectly, through driving toxicities such as dyslipidemia or insulin resistance.
- Studies in which an association between abacavir and MI was observed were mainly composed of subjects with HIV who were already on ART at enrollment, whereas most of the meta-analyses that showed no abacavir association examined data derived from clinical trials of predominantly antiretroviral-naive patients commencing ART.
- It is clear that, for the majority of people living with HIV, the benefits in clinical outcome from effective treatment with currently recommended ART regimens outweigh the risks of toxicity.

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Addendum

Recently presented data have provided additional insights into the clinical association among exposure to abacavir (ABC), the risk of myocardial infarction (MI), and potential pathogenic mechanisms. The initial associations between ABC and MI from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study were unexpected, leading to speculation that the observed associations may have arisen through channeling bias, with patients at potential increased risk of MI or with preexisting renal dysfunction (another independent risk factor for MI) being preferentially prescribed ABC1 as it was regarded as more metabolically friendly.

However, in the most recent analysis of the D:A:D study, which encompasses a total of 941 MI occurring over 367,559 patient-years of follow-up, associations between ABC and MI were analyzed over two time periods: before the first published observations in 2008 and after 2008. This analysis enabled the determination of changes in prescribing behavior since 2008 and observed a reverse channeling bias whereby those with higher risk of MI were actually less likely to be prescribed ABC in the post-2008 period. Despite this change in prescribing habits, the association between ABC and MI persisted, even in fully adjusted analysis that included creatinine measurements. In addition, the effect size changed little between the pre- and post-2008 observation periods {adjusted rate ratio (95% confidence interval [CI]) 1.97 [1.68-2.33] and 1.97 [1.43-2.72], respectively}.²

Additional data have also emerged regarding the association between ABC and platelet function. Results from a substudy of virally suppressed, HIV-positive patients on ABC-containing antiretroviral therapy who were randomized to either remain on ABC or switch to tenofovir disoproxil fumarate (TDF) also observed changes in a platelet biomarker (soluble glycoprotein VI [sGPVI]) in those who switched to TDF,³ again supporting a potential role for ABC altering platelet function as an underlying mechanism to explain increased MI risk.

Taken together, these data further support a role for ABC in modifying biological functions related to cardiovascular health that may explain how ABC exposure could increase risk of MI.

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