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Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients

The SMART/INSIGHT and the D:A:D study groups*

*Members of writing committee and of the two study groups are listed in the appendix.

Abstract

Background—Two nucleoside-reverse-transcriptase-inhibitors (NRTIs)-abacavir and didanosine-may each be associated with excess risk of myocardial infarction (MI). The reproducibility of this finding in an independent data set was explored and plausible biological mechanisms were sought.

Methods—Biomarkers, ischemic changes on the electrocardiogram, and rates of various pre-defined types of cardiovascular disease (CVD) events according to NRTIs used were explored in the SMART study. Patients receiving abacavir and not didanosine were compared with those receiving didanosine, and to those receiving NRTIs other than abacavir or didanosine (“other NRTIs”). Patients randomly assigned to the continuous ART arm of SMART was included in all analyses(N=2752); for the study of biomarkers, patients from the ART interruption arm was also included.

Results—Current use of abacavir was associated with an excess risk of CVD compared to other NRTIs. Adjusted hazard ratios for clinical MI (n=19), major CVD (MI, stroke, surgery for coronary artery disease (CAD), and CVD death;n=70), expanded CVD (major CVD plus congestive heart failure, peripheral vascular disease, CAD requiring drug treatment, and unwitnessed deaths;n=112) were 4.3 (95% confidence interval (CI):1.4–13.0), 1.8(1.0–3.1), and 1.9(1.3–2.9). At baseline in a subset of patients with biomarker data, high sensitivity-C reactive protein and interleukin-6 were 27% (p=0.02) and 16% (p=0.02) higher for patient receiving abacavir (N=175) compared to other NRTIs (N=500). Didanosine was not associated with altered risk of CVD nor with altered levels of biomarkers.

Conclusion—Abacavir was associated with an increased risk of CVD. The drug may cause vascular inflammation, which may precipitate a CVD event.

Introduction

Traditional risk factors have a similar impact on cardiovascular disease (CVD) in HIV-infected persons as they do in the general population^{1,2}. However, in HIV-infected persons, both HIV replication and antiretroviral therapy (ART) may contribute independently to cardiovascular risk^{1,3–6}.

To date, only one randomized clinical trial has been designed to include CVD as a pre-specified study endpoint⁸. Thus, much of our current understanding of the impact of ART on the risk of CVD is derived from observational research. Recently, an observational study, D:A:D, detected

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Conflict of interest statement

No member of the Writing Group for this report has any financial or personal relationships with people or organizations that could inappropriately influence this work, although most members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

a 90% (95% CI: 47%-145%) increase in the risk of myocardial infarction (MI) in patients who were currently receiving or who had recently received abacavir compared to patients who had not recently received this drug⁹. In the same report, a less statistically robust finding of a 49% (95% CI: 14% to 95%) increased risk of MI associated with current use of didanosine was also reported⁹.

These findings were unexpected, since abacavir is not known to adversely affect lipids and glucose metabolism, factors that are normally considered to be pro-atherogenic. These metabolic abnormalities likely contribute to the mechanism by which HIV protease inhibitors (PIs) increase the risk of MI^{4,6,10,11}; the adverse effect of PIs is gradual with longer exposure to drugs in this class, suggesting a gradual worsening of the underlying atherosclerotic process. In contrast, the MI risk associated with abacavir use was characterized epidemiologically as emerging quickly once the drug was initiated (within the first year of use), did not appear to be affected by duration of use of the drug, and was no longer present in patients who had ceased to take the drug for some months. These findings suggest that the mechanism by which abacavir might increase the risk of MI is more likely through an increased propensity for subclinical atherosclerosis to manifest itself as an MI, than a direct effect on the underlying atherosclerotic process *per se*.

Analyses of the SMART study were conducted to evaluate - in this independent dataset - whether the findings from D:A:D were reproducible and, if so, whether a possible biological mechanism to explain any increased CVD risk could be identified.

Methods

Design

The design and methods used in the SMART study have been described previously⁸. Two strategies of using ART were compared in 5472 patients: (i) the drug conservation (DC) strategy, where ART was only initiated once the CD4 count had decreased to < 250 cells/ μ L and was then interrupted once the CD4 count increased to > 350 cells/ μ L, and (ii) the viral suppression (VS) strategy, where ART was used continuously in order to maximally suppress viral replication. The trial was modified on 11th January 2006, when it was observed that the DC strategy lead to an excess risk of both serious AIDS and serious non-AIDS events (cardiovascular, renal, hepatic disease and non-AIDS defining cancers). The cohort was followed for an additional 18 months after this modification¹².

Any available ART could be used for patients in SMART. Thus, the VS arm of SMART represents a large cohort within which observational analyses of different ART and risk of CVD can be carried out.

Outcomes assessed

In SMART, cardiovascular events were collected and adjudicated by an Endpoint Review Committee using pre-specified criteria for each event^{4,8}. Three different CVD events were considered: 1) clinical MI as considered in DAD; 2) a composite of major CVD events as pre-specified in the SMART protocol and previously reported^{4,8} (clinical and silent MI, stroke, surgery for coronary artery disease (CAD), and CVD death); 3) an expanded composite CVD outcome, also considered by Phillips *et al*⁴, that includes major CVD plus peripheral vascular disease, congestive heart failure, drug treatment for CAD, and unwitnessed deaths.

Electrocardiograms (ECGs) were recorded at baseline and annually thereafter; these were collected electronically and read centrally as described previously¹³. Abnormalities considered to be evidence of ischemic changes on ECG were as follows: Q-wave changes

(Minnesota codes 1.1, 1.2. and 1.3), ST segment depression (codes 4.1, 4.2, 4.3), T-wave inversions (codes 5.1, 5.2, 5.3, and 5.4), bundle branch block, and QT-interval > 112%.

Four inflammatory markers (high sensitivity-C reactive protein [hsCRP], interleukin-6 [IL-6], amyloid A, and amyloid P) and two coagulation markers (D-dimer and prothrombin fragment 1+2 [F1.2]), were measured at baseline for cases of CVD, opportunistic disease, death, end stage renal disease or cirrhosis that occurred before the protocol change on the 11th of January 2006, and for two controls for each case matched on age, gender, site and date of randomization (561 controls)¹⁴. In addition, these markers were measured at baseline for a random sample of 499 patients. For the present set of analyses, patients in the random sample and control patients were included if they used an NRTI at study entry – a total of 791 patients fulfilled these criteria. Biomarker levels for cases were not included.

The conduct of these analyses

The first four research questions below were pre-specified in the analysis plan. The fifth research question was undertaken after reviewing the findings from the first 4 questions.

1. How different was the cardiovascular risk profile at study entry among patients on ART depending on whether abacavir, didanosine or other NRTIs were used?
2. Did the levels of any of the 6 inflammatory and coagulation markers vary at study entry according to NRTIs used?
3. For patients randomized to the VS arm, was the rate of developing new ECG abnormalities (with specific focus on ischemic abnormalities) during the study period different, depending on current use of NRTI?
4. For patients randomized to the VS arm, was the rate of CVD, defined in multiple ways as in previous SMART reports⁴ different depending on current use of NRTI?
5. For patients randomized to the VS arm, was the excess risk of CVD associated with current abacavir use confined to certain subgroups of patients?

In analyses responding to questions 4 and 5, only patients from the VS group were included, as inclusion of patients from the DC group may compromise our ability to address these questions, since interruption of ART may adversely affect inflammation and coagulation processes within the body¹⁴ and may elevate risk of CVD^{4,14}.

Statistical analyses

Baseline characteristics, including CVD risk factors, were compared for 3 groups of SMART study participants, defined by the type of NRTI used at study entry; (1) abacavir, not didanosine; (2) didanosine (with or without abacavir); and (3) nucleoside reverse transcriptase inhibitors (NRTIs) other than abacavir or didanosine (henceforth referred to as other NRTIs).

Additionally, groups (1) and (2) were compared to group (3) for the subgroup of patients in whom the six biomarkers had been measured at baseline. Differences in biomarker levels were assessed on the natural log scale ($\log_e$) since the distribution of the biomarkers was highly skewed. With use of the $\log_e$ transformation the percentage difference between groups can be obtained by $100(e^{\text{difference}} - 1)$. Adjusted differences were obtained using analysis of covariance and the covariates used were age, gender, race, smoking, CVD history, diabetes, total/HDL cholesterol, use of blood pressure or lipid-lowering medication, CD4+ cell count, HIV RNA level, hepatitis status, body mass index, and use of NNRTIs and PIs.

The association of abacavir with CVD outcomes was assessed using Cox models. All patients randomized to the VS group in SMART, the group assigned to receive continuous ART, were included, with follow-up through July 2007. For the main analyses, a participant's current

NRTI use at any time during follow-up was categorized as: (1) abacavir, but not didanosine; (2) didanosine, with or without abacavir; (3) other NRTIs; and (4) not taking NRTIs or any ART. Cox models included the participants' current NRTI use as three separate time-updated indicator variables (with category 3 as reference) with adjustment for the same baseline covariates mentioned above, thus allowing the estimation of adjusted hazard ratios (HRs). The analyses were repeated, as sensitivity analyses, for 1) recent use of abacavir, defined as in D:A:D (current use or use in the past 6 months rather than current use only⁸; 2) current use of abacavir versus tenofovir (without abacavir); and 3) abacavir use according to whether or not it was used as part of a NRTI-only regimen. As exact duration of individual drug exposure prior to study entry was not collected in SMART, analyses assessing the influence of cumulative exposure to the drugs could not be conducted.

Cox models were also used to study the association of abacavir with new ischemic events on the ECG. For these analyses the same NRTI group and covariates were used. Analyses were restricted to the 1592 VS patients without ischemic abnormalities at baseline and with at least one follow-up ECG. For these Cox analyses, follow-up was censored at the last ECG obtained.

HRs for CVD (expanded definition) comparing current use of abacavir but not didanosine versus other NRTIs were estimated in subgroups of patients. Too few patients developed an MI or major CVD events to consider subgroups for those outcomes. Subgroups were defined at study entry, by the presence of ischemic abnormalities and the number of CVD risk factors present at entry. These subgroups were evaluated using logistic models to take account of the matched case-control design. Homogeneity of HRs and ORs across subgroups was assessed by including an interaction term between the subgroup and the time-updated NRTI use indicators.

Results

Baseline characteristics

At study entry, of the 4544 patients receiving a NRTI, 1019 (22.4%) were receiving abacavir but not didanosine, 643 (14.2%) were receiving didanosine (of whom 99 received this together with abacavir), and 2882 (63.4%) were receiving other NRTIs (including 643 who were receiving tenofovir but neither abacavir nor didanosine) (Table 1). Patients receiving other NRTIs were more frequently women and used blood-pressure and cholesterol lowering drugs less frequently. Otherwise, the cardiovascular risk profile was similar irrespective of use of type of NRTI. The percent of patients with 5 or more CVD risk factors was 18%, 17%, and 14% for those receiving abacavir, didanosine and other NRTIs, respectively.

Biomarker analyses at study entry

hsCRP and IL-6 levels were higher in patients receiving abacavir at study entry compared to those using NRTIs other than abacavir or didanosine at study entry (Table 2); these differences were statistically significant after controlling for cardiovascular risk factors and other covariates at entry. Differences in levels of amyloid A, amyloid P, D-dimer and F1.2 were not significant. Baseline use of didanosine was not associated with elevated levels of any of these biomarkers.

Risk of developing CVD after study entry in the VS arm

In the multivariable analysis, current use of abacavir was associated with an increased risk of each of the predefined CVD outcomes (Table 3) compared with patients receiving any NRTI other than abacavir or didanosine. Conversely, use of didanosine was not associated with a significantly increased risk of any of the outcomes.

In a sensitivity analysis in which patients receiving tenofovir were treated as the reference group (rather than those receiving any NRTIs other than abacavir or didanosine), the excess risks of each cardiovascular outcome associated with current use of abacavir were comparable to those presented in Table 3 (see Table 3 footnote — interestingly, this is now longer than the table itself!). Analyses defining current use of NRTIs as in D:A:D (current use or use in the past 6 months rather than current use only) were also carried out and the results were very similar. Finally, subgroup analyses that considered whether abacavir was being used with an NNRTI or PI or in a totally NRTI-based regimen were considered and HR estimates were similar (data not shown).

Risk of developing ischemic abnormalities on the ECG after study entry among patients in the VS arm who did not have ECG evidence of ischemia at entry

470 of 1592 VS patients without evidence of ECG ischemia at baseline developed ECG abnormalities associated with ischemia during follow-up. The risk of developing ischemic abnormalities on ECG did not vary according to current NRTI use. Univariable and multivariable HRs for abacavir versus other NRTIs were 1.01 (95% CI: 0.82 to 1.26) and 0.99 (95% CI: 0.80 to 1.23), respectively. For didanosine versus other NRTIs the univariable and multivariable HRs were 0.81 (95% CI: 0.59 to 1.11) and 0.81 (95% CI: 0.59 to 1.12).

Risk of CVD associated with NRTIs after study entry in the VS group according to whether patients had 5 or more CVD risk factors or ischemic abnormalities at study entry

For this analysis (table 4), we considered the expanded definition of CVD shown in table 3. The risk of CVD associated with current use of abacavir compared with NRTIs other than abacavir and didanosine tended to be higher (p-value for interaction: 0.10) in patients with 5 or more CVD risk factors when entering SMART compared with those entering SMART with fewer or no CVD risk factors (Table 4). Patients with evidence of ischemic abnormalities on their entry electrocardiograph had similar trends, although less pronounced (p-value for interaction: 0.50). These trends were not observed for the analyses focusing on the effect of didanosine.

Discussion

The analyses reported in this manuscript were conducted in response to recent observations from the D:A:D study⁹ suggesting an increased risk of MI in patients currently receiving abacavir. The findings are broadly consistent with that report, and suggest that the risk of CVD is approximately doubled in patients currently receiving abacavir compared with patients currently receiving NRTIs other than abacavir or didanosine.

In D:A:D⁹, current use of abacavir was associated with a 90% increase in the rate of MI. In the dataset used in the analyses reported in this paper, only 19 patients experienced a clinical MI, limiting the use of this endpoint to confirm the D:A:D findings. However, our analyses of this outcome as well as those incorporating broader definitions of CVD suggested increased rates that were similar to, and within the range observed in the D:A:D study. Of note, the excess risk associated with use of abacavir was also observed when use of abacavir was compared to use of tenofovir, suggesting that tenofovir is not associated with adverse effects on the arterial vasculature compared to other NRTIs (primarily zidovudine and stavudine containing regimens in SMART). However, it should be noted that as the power of our analyses was limited, and as D:A:D did not have sufficient power to address this question, the potential impact of tenofovir on the risk CVD should be confirmed in other datasets.

When stratifying the group according to whether 5 or more CVD risk factors were present at study entry or not, the excess risk of CVD associated with current use of abacavir tended to be

higher in those with such increased underlying risk of CVD. In D:A:D, the excess risk associated with recent abacavir use (in relative terms) did not appear to be greater in those with higher underlying CVD risk⁹. Rather, a marginally significant interaction was observed in the opposite direction when comparing the risk among patients at low and medium/high cardiovascular risk. More studies are required to shed further light on this issue. Of note, both the analyses and the definition of underlying CVD risk differed between the two studies, in part due to differences in availability of data to estimate underlying risk.

The identification of a biological mechanism that may explain the increased risk of CVD in those receiving abacavir is important for two reasons. Firstly, such a mechanism would provide biological plausibility for associations that are derived from observational data. Secondly, understanding of any biological mechanism may permit the identification of patient subgroups who may be at particularly high or low risk of this event, thus allowing the drug to be used in a more targeted way.

The present set of analyses provides one suggestion of a plausible biological mechanism. At study entry, patients on abacavir had higher levels of hsCRP and IL-6 compared with patients receiving other NRTIs. Conversely, for the four other biomarkers considered, all of which have previously been associated with CVD, significant differences were not observed.

Based on the biomarker findings, abacavir may have proinflammatory properties. Abacavir causes hypersensitivity reactions in patients with HLA B*5701 and, as such, has already been demonstrated to have proinflammatory properties in genetically predisposed persons¹⁵. However, since the abacavir-associated hypersensitivity reaction is observed within the first 6-8 weeks after the drug is started, and most patients in SMART had been on the drug for considerably longer periods at entry in the trial, it is unlikely that a hypersensitivity reaction, *per se*, can explain our findings. Consistent with this, the D:A:D study found a continuously elevated risk of MI associated with abacavir irrespective of duration of exposure⁹. However, approximately one third of patients with HLA B*5701 do not develop a hypersensitivity reaction after starting abacavir¹⁵ and it is possible that ongoing subclinical inflammatory reactions in these patients may contribute to our findings, or that abacavir may stimulate inflammation by other mechanisms.

How could elevated levels of IL-6 be linked with excess risk of CVD? Elevated levels of IL-6 are recognized to be associated with an increased risk of CVD^{16,17}. The mechanism may be that elevated IL-6 levels reflect an ongoing vascular inflammatory reaction in the arterial wall resulting in instability of existing plaques and thereby increasing the risk that pre-existing subclinical atherosclerosis will manifest itself clinically as CVD¹⁶⁻¹⁸. IL-6 may also directly exacerbate the aggregation potential of platelets¹⁹, thereby increasing this risk. Of note, IL-6 may be elevated due to many different factors, and no prior studies have assessed what contribution drug-induced production may have to the circulating pool of IL-6, compromising the interpretation of further detailed comparisons of prior findings to our results.

In the present set of analysis, abacavir was not associated with altered risk for the development of ischemic abnormalities from central coding of serial ECG determinations. This apparent lack of impact on the atherosclerotic process is consistent with the epidemiological characterization of the abacavir signal⁹ (summarized in the introduction).

Based on the data from D:A:D and presented here, the proposed underlying mechanism by which abacavir increases the risk of CVD is through an increased propensity for subclinical atherosclerosis to manifest itself clinically; the increased propensity is caused by the proinflammatory potential of the drug.

The excess risk of CVD associated with current use of abacavir could be due to a channeling effect; i.e. patients at an a priori excess underlying risk of CVD may have been preferentially placed on abacavir as discussed previously⁹; the fact that two observational studies come to the same result could be due to the possibility of similar confounding that is operating in both observational datasets. Only randomized controlled trials can effectively eliminate this possibility. Similarly, we cannot exclude the possibility that patients on abacavir had elevated hsCRP and IL-6 for reasons other than use of abacavir. Only prospective assessment of levels of these biomarkers before and after initiating abacavir will be able to clarify this association. In SMART, there is insufficient power to assess this. Additionally, comparisons of IL-6 levels between the two arms of the study is confounded by the fact that interruption of ART leads to loss of HIV control which by itself induced IL-6¹⁴). Rather, analyses of stored biobank material from studies designed to randomly compare virological outcome of abacavir to other NRTIs are more suitable sources of this information.

The present analyses did not identify a significant association between current use of didanosine and an increased risk of CVD or elevated biomarker levels. In analyses focusing on clinically detectable MI, an excess risk of this outcome was indeed found in patients currently taking didanosine, but this was not statistically significant and was not seen when assessing other CVD outcomes. In all of these analyses, confidence intervals around the estimate of hazard ratios were wide, as a consequence of the low number of patients on didanosine and the low number of cardiovascular endpoints. In the D:A:D study, a statistically significant increased risk of MI associated with recent didanosine was observed, although it was less marked in size and less robust in various types of sensitivity analyses compared with the findings concerning abacavir use. Additional analyses in other datasets are required to assess whether current use of didanosine is indeed associated with excess risk of CVD.

In SMART, abacavir was used more often without an NNRTI or PI than in D:A:D. Also, the reference group of patients on NRTIs other than abacavir and didanosine includes relatively more patients on tenofovir than were included in D:A:D. Nevertheless, our findings concerning abacavir use were remarkably similar to those reported from D:A:D. This independent confirmation of the findings from D:A:D, derived from a population with a somewhat different pattern of use of the drug, strengthens the evidence that the association maybe causal.

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Appendix

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The role of member of the writing committee: The D:A:D steering committee approached the INSIGHT executive committee and requested collaboration in February 2008. A writing committee with membership from both groups was formed. An analysis plan was drafted by JDL and JDN prior to the conduct of any analyses, and revised based on comments from other members of the writing committee. DD and RJP lead the plans for the analysis of the ECG's.

RT performed the biomarker measurements. The statistical analyses were carried out by the Statistical and Data Management Center for INSIGHT at the University of Minnesota (JN, BG, JDN). All members contributed to the interpretation of these analyses, as well as to the revisions of a draft manuscript produced by JDL and JDN.

SMART study group: Participating staff are listed elsewhere⁸.

D:A:D Study Group: Participating staff are listed elsewhere⁹.

References

1. D:A:D Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* Nov 20;2003 349(21):1993–2003. [PubMed: 14627784]
2. Mensah GA, Brown DW, Croft JB, et al. Major Coronary risk factors and death from coronary heart disease. *Am J Prev Med* 2005;29:68–74. [PubMed: 16389129]
3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *JCEM* 2007;92:2506–2512. [PubMed: 17456578]
4. Phillips AN, Andrew Carr, Jacquie Neuhaus. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antiviral Therapy* 2008;13:177–187. [PubMed: 18505169]
5. Currier J, Taylor A, Boyd F, et al. Coronary Heart Disease in HIV-infected individuals. *JAIDS* 2003;33:506–512. [PubMed: 12869840]
6. Klein, D.; Hurley, L.; Silverberg, M., et al. Surveillance Data for Myocardial Infarction Hospitalizations among HIV⁺ and HIV⁻ Northern Californians: 1994 – 2006. 14th CROI; Los Angeles. 2007; et al Abstract 807
7. Obel N, Thomsen HG, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *CID* Jun 15;2007 44(12):1625–31.
8. SMART Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283–96. [PubMed: 17135583]
9. D:A:D study group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* Apr 26;2008 371(9622):1417–26. [PubMed: 18387667]
10. Iloeje UH, Yuan Y, L'italien G, et al. Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005;6:37–44. [PubMed: 15670251]
11. D:A:D study group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* Apr 26;2007 356(17):1723–35. [PubMed: 17460226]
12. El-Sadr, W.; SMART Study Group. Re-initiation of ART in the CD4-guided ART Interruption Group in the SMART Study Lowers Risk of Opportunistic Disease or Death 15th Conference on Retroviruses and Opportunistic Infections; 2008; abstract 36
13. Carr A, Grund B, Neuhaus J, et al. Asymptomatic myocardial ischaemia in HIV-infected adults. *AIDS* 2008;22(2):257–67. [PubMed: 18097228]
14. Kuller, L.; SMART Study Group. Elevated Levels of Interleukin-6 and D-dimer Are Associated with an Increased Risk of Death in Patients with HIV 15th Conference on Retroviruses and Opportunistic Infections; 2008; abstract 139
15. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* Feb 7;2008 358(6):568–79. [PubMed: 18256392]
16. Woods A, Brull DJ, Humphries SE, Montgomery HE. Genetics of inflammation and risk of coronary artery disease: the central role of interleukin-6. *Eur Heart J* 2000;21:1574–83. [PubMed: 10988009]
17. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* Apr 8;2008 5(4):e78. [PubMed: 18399716]
18. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685–95. [PubMed: 15843671]

19. Oleksowicz L, Mrowiec Z, Zuckerman D, Isaacs R, Dutcher J, Puszkin E. Platelet activation induced by interleukin-6: evidence for a mechanism involving arachidonic acid metabolism. *Thromb Haemost* 1994;72:302–8. [PubMed: 7831669]

Table 1

Clinical and cardiovascular risk factors among 4544 SMART participants receiving NRTI according to type of NRTI used at study entry¹

	Abacavir, not didanosine	Didanosine	No abacavir or didanosine ²	Total
N	1019	643	2882	4544
Characteristics at study entry:				
Age (median, IQR)	45 (39-51)	44 (38-49)	44 (38-50)	44 (38-50)
% female	23	23	28	27
%HIV-RNA≤400 copies/mL	82	78	84	83
CD4 count (median, IQR), cells/μL	639 (495- 836)	596(475-794)	630(486-814)	630(487-819)
% prior CV disease	4	5	3	4
% current smokers	38	41	39	39
% any ischemic abnormality ³	36	35	36	36
% diabetes	7	6	7	7
% on BP lowering drugs	21	20	18	19
% lipid lowering drugs	21	21	15	18
Total/HDL cholesterol ratio (median, IQR)	4.6 (3.6-5.9)	4.7 (3.6-5.9)	4.6 (3.6-5.9)	4.6(3.6-5.9)
% with past or current abacavir use	100	28	7	31
% NRTI only	39	6	4	12
% using NNRTI	35	45	54	49
% using trizivir®	50	0	0	11
% using tenofovir	17	25	22	21
% using lopinavir/ritonavir	11	24	12	14
% 5 or more CVD risk factors ⁴	18	17	14	15

Abbreviations: BP=blood pressure; CV=cardiovascular; IQR=interquartile range; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; trizivir®=combination tablet containing zidovudine, lamivudine and abacavir.

¹ Patients randomized to the viral suppression arm (n=2265) has comparable profile to the overall results for both groups combined.

² The 2882 patients using an NRTI but not abacavir or didanosine include 643 patients using tenofovir, 1557 using zidovudine but not tenofovir, and 636 using stavudine and not tenofovir or zidovudine.

³ Q-wave, ST depression, T-wave inversion, any bundle branch block or QTI>112%

⁴ Five or more of age >45, male gender, smoking, total/HDL cholesterol > 4, BP-lowering treatment, lipid-lowering treatment, prior CVD, diabetes, and ischemic changes on the ECG

Table 2
Median (IQR) levels of six pre-selected biomarkers at study entry and percent difference between the abacavir and didanosine groups and the other NRTI group: 791 patients on NRTI at study entry

Biomarker	(1) Abacavir, no didanosine (n=175)	(2) Didano- sine (n=116)	(3) Other NRTI (n=500)	% Diff. (1) vs (3) (p-value) Unadj. Adjusted	% Diff. (2) vs (3) (p-value) Unadj. Adjusted
hsCRP (µg/mL)	2.99 (1.27-6.46)	2.24 (1.01-4.81)	2.33 (0.96-5.31)	17.4 (0.14) 27.1 (0.02)	3.9 (0.77) 4.1 (0.73)
IL-6 (pg/mL)	2.52 (1.67-3.67)	2.33 (1.42-3.67)	2.23 (1.36-3.74)	15.0 (0.04) 16.2 (0.02)	0.0 (0.99) 1.0 (0.91)
Amyloid A (mg/L)	3.50 (1.80-6.90)	3.40 (2.05-6.67)	3.57 (1.90-6.77)	3.0 (0.71) 15.0 (0.14)	5.1 (0.65) 4.1 (0.72)
Amyloid P (µg/L)	67.6 (51.5-88.1)	62.5 (48.3-81.3)	64.5 (50.8-86.2)	4.1 (0.27) 7.3 (0.07)	6.8 (0.13) 6.8 (0.12)
D-dimer (µg/mL)	0.27 (0.17-0.61)	0.27 (0.17-0.51)	0.27 (0.15-0.49)	13.9 (0.12) 6.2 (0.49)	11.6 (0.27) 15.0 (0.17)
FL2 (pmol/L)	327 (243-513)	307 (221-475)	352 (256-527)	2.0 (0.77) 4.9 (0.41)	8.6 (0.16) 8.6 (0.21)

Abbreviations: NRTI=nucleos(t)ide reverse transcriptase inhibitor

Percent difference obtained by calculating differences after natural log (log_e) transformation, exponentiating, subtracting 1.0 and multiplying by 100. Comparisons are between abacavir and no didanosine and other NRTI and between didanosine and other NRTI group. Univariate and adjusted differences are shown. Adjustment is for age (46 years), gender (27% females), race, smoking (37% current smokers), CVD history (3% with such a history), diabetes (10% with such a history), total/HDL cholesterol (4.6), use of blood pressure (29%) or lipid-lowering medication (23%), CD4+ cell count (632 cells/µL), HIV RNA level (72% < 400 copies/mL), hepatitis status, body mass index, and use of NNRTIs (48%) and PIs (e.g. 13% on lopinavir). In parentheses after each variable presented for the entire cohort in Table 1 is indicated median levels or % for the 791 patients included in the present set of analyses.

Hazard ratio (HR) for developing each cardiovascular outcome for patients in the viral suppression arm of SMART, according to type of NRTI currently used

and

Table 3

Type of event	Number of events	Hazard ratio (95% CI) *			
		Abacavir no didanosine		Didanosine	
		Univariable	Multivariable ^{1,2}	Univariable	Multivariable ¹
CVD, major ³	70	1.63 (0.96-2.76)	1.80 (1.04-3.11)	0.98 (0.41-2.35)	1.06 (0.43-2.58)
Clinical MI	19	4.22 (1.41-12.6)	4.25 (1.39-13.0)	2.13 (0.41-11.0) ⁶	1.89 (0.35-10.2)
CVD, minor ⁴	58	2.83 (1.61-4.97)	2.70 (1.51-4.83)	0.98 (0.34-2.85)	1.03 (0.35-3.03)
CVD, expanded definition ⁵	112	1.84 (1.22-2.76)	1.91 (1.25-2.92)	0.83 (0.40-1.75)	0.86 (0.40-1.85)

Abbreviations: ART=antiretroviral therapy; CAD=coronary artery disease, CHF=congestive heart failure; CI=confidence interval; CVD=cardiovascular disease; MI=myocardial infarction.; NRTI=nucleos(t)ide reverse transcriptase inhibitor.

* compared with patients receiving other NRTIs than abacavir and didanosine

¹ Adjusted for age, gender, race, baseline HIV-RNA, smoking status, prior CVD, diabetes, blood-pressure lowering drugs, hepatitis B or C virus infection, baseline CD4 cell count, baseline use of NNRTI and baseline use of PI. The multivariable analyses include 67, 19, 57, and 108 events. Losses are due to missing covariate values.

² In four separate models using patients receiving tenofovir based NRTI but not abacavir or didanosine (as opposed to NRTI's other than abacavir and didanosine) as reference group, the HR (95% for the four types of events were: 1.50 (0.80-2.80), 8.90 (1.13-70.4), 2.20 (1.13-4.27), and 1.55 (0.97-2.50). For these same outcomes, the HR for tenofovir versus other NRTI (not abacavir, didanosine or tenofovir) were 1.18 (0.59-2.36), 0.34 (0.04-3.08), 1.71 (0.72-4.03) and 1.42 (0.81-2.46).

³ Includes MI, stroke, CAD requiring surgery or CVD death

⁴ Includes CHF, peripheral vascular disease or CAD requiring drug treatment

⁵ Includes MI, stroke, CAD requiring surgery, CVD suspected unwitnessed death, CHF, peripheral vascular disease or CAD requiring drug treatment

⁶ This model was re-run excluding any patient taking abacavir and the HR was 1.25 (95% CI: 0.15-10.7).

Hazard ratio (HR) for developing CVD (expanded definition, see legend to table 3 for definition) for patients in the viral suppression arm of SMART according to prevalence of 5 or more CVD risk factors and presence of ischemic abnormalities on an electrocardiograph at study entry, according to type of NRTI currently used

and

Table 4

Variable at study entry stratified for		Hazard ratio (95% CI) ¹			
		Abacavir, but no didanosine	Inter-action p-value	Didanosine	Inter-action p-value
% 5 or more CVD risk factors ²	Yes	3.06 (1.59-5.89)	0.10	0.85 (0.24-3.04)	0.59
	No	1.34 (0.74-2.41)		0.92 (0.35-2.40)	
Ischemic abnormality ³	Yes	3.11 (1.55-6.26)	0.50	1.40 (0.45-4.32)	0.60
	No	1.59 (0.87-2.90)		0.62 (0.19-2.06)	

Abbreviations: ART=antiretroviral therapy; CI=confidence interval; CVD=cardiovascular disease; NRTI=nucleos(t)ide reverse transcriptase inhibitor

¹ Compared with patients receiving other NRTIs than abacavir and didanosine after adjusted for age, gender, race, baseline HIV-RNA, smoking status, prior CVD, diabetes, blood-pressure lowering drugs, hepatitis B or C virus infection, baseline CD4 cell count, baseline use of NNRTI and baseline use of PI.

² Five or more of age >45, male gender, smoking, total/HDL cholesterol > 4, BP-lowering treatment, lipid-lowering treatment, prior CVD, diabetes, and ischemic changes on the ECG

³ A total of 103 events occurred in patients with ECG available at study entry for assessment of presence or absence of ischemic abnormalities.

Webtable 1

Cardiovascular profile at study entry for patients in the viral suppression arm of SMART experiencing CVD (expanded definition, see legend to table 3 for definition), according to which type of NRTI was used when the event occurred

	Treatment Just Prior to Event		
	On abacavir but not didanosine	On didanosine	On other NRTI than abacavir and didanosine
N	40	7	49
Characteristics at study entry (median, IQR) or %:			
Age (years)	49 (45-55)	48 (47-49)	50 (41-57)
% female	15	29	18
% current smoker	55	57	47
% with prior CVD	13	0	14
Total/HDL cholesterol ratio	5.7 (4.1-7.8)	4.5 (3.4-5.9)	5.8 (3.9-7.7)
Triglyceride level (mg/dL)	225 (140-383)	151 (106-192)	203 (131-376)
% on blood pressure lowering treatment	55	29	35
% on lipid lowering treatment	43	29	22
% diabetes	18	14	8
% on abacavir	63	29	4

Abbreviations: CVD=cardiovascular disease; IQR=interquartile range; NRTI=nucleos(t)ide reverse transcriptase inhibitor