Impact of Individual Antiretroviral Drugs on the Risk of Myocardial Infarction in Human Immunodeficiency Virus–Infected Patients

A Case-Control Study Nested Within the French Hospital Database on HIV ANRS Cohort CO4

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Background: The role of exposure to specific antiretroviral drugs on risk of myocardial infarction in human immunodeficiency virus (HIV)–infected patients is debated in the literature.

Methods: To assess whether we confirmed the association between exposure to abacavir and risk of myocardial infarction (MI) and to estimate the impact of exposure to other nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and non-NRTIs on risk of MI, we conducted a case-control study nested within the French Hospital Database on HIV. Cases (n=289) were patients who, between January 2000 and December 2006, had a prospectively recorded first definite or probable MI. Up to 5 controls (n=884), matched for age, sex, and clinical center, were selected at random with replacement among patients with no history of MI already enrolled in the database when MI was diagnosed in the corresponding case. Conditional logistic regression models were used to adjust for potential confounders.

Results: Short-term/recent exposure to abacavir was associated with an increased risk of MI in the overall sample (odds ratios [ORs], 2.01; 95% confidence interval [CI], 1.11-3.64) but not in the subset of matched cases and controls (81%) who did not use cocaine or intravenous drugs (1.27; 0.64-2.49). Cumulative exposure to all PIs except saquinavir was associated with an increased risk of MI significant for amprenavir/fosamprenavir with or without ritonavir (OR, 1.53; 95% CI, 1.21-1.94 per year) and lopinavir with ritonavir (1.33; 1.09-1.61 per year). Exposure to all non-NRTIs was not associated with risk of MI.

Conclusion: The risk of MI was increased by cumulative exposure to all the studied PIs except saquinavir and particularly to amprenavir/fosamprenavir with or without ritonavir and lopinavir with ritonavir, whereas the association with abacavir cannot be considered causal.

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CUMULATIVE EXPOSURE TO protease inhibitors (PIs) has been associated with risk of myocardial infarction (MI) in human immunodeficiency virus (HIV)–infected patients,[1-4] but the risk associated with individual PIs has not been widely reported, to our knowledge. More recently, specific nucleoside reverse transcriptase inhibitors (NRTIs), particularly abacavir, were incriminated.[5,6] However, Brothers et al[7] found no increase in the risk of MI associated with abacavir use in a pooled analysis of 12 randomized clinical trials. The results have raised a lot of debate because abacavir is 1 of the 2 most-used NRTIs to initiate therapy in the developed world in the recent period.[8,9] Since then, many studies[10-13] have explored the potential mechanisms for such an effect, with conflicting results. After the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study results were presented at the Conference on Retroviruses and Opportunistic Infections in 2008, the European Medicines Agency asked us whether the ongoing case-control study, nested within the French Hospital Database on HIV (FHDH) Agence Nationale de Recherches sur le SIDA et les hépatites (ANRS CO4), could help settle the issue of abacavir. We therefore wrote an analysis plan to evaluate the association between the risk of MI and cumulative exposure to NRTIs and recent or past exposure to NRTIs. In addition, we explored the role of specific non-NRTIs (NNRTIs) and PIs.

METHODS

STUDY POPULATION

The HIV-infected patients were selected from the FHDH, an ongoing, prospective, observational, nationwide, hospital-based cohort. The only FHDH inclusion criteria are HIV type 1 or 2 infection and written informed consent. Data are collected prospectively by trained research assistants using standardized forms. Clinical events are coded using the *International Statistical Classification of Diseases, 10th Revision*.[14] A follow-up form is completed at least every 6 months or at each visit or hospital admission during which a new illness is diagnosed, a new treatment is prescribed, or a noteworthy change in biological markers is noted. In July 2007, the database contained information on 74 958 patients who had been seen at least once between January 1, 2000, and December 31, 2006, which is 57% of all HIV-infected patients under care in France,[15] corresponding to a total follow-up duration of 298 156 patient-years.

CASES

Cases were patients who had a first prospectively reported MI between January 1, 2000, and December 31, 2006. Patients with a history of MI were excluded. The *International Statistical Classification of Diseases, 10th Revision* code used to define MI was I21. The diagnosis of MI was confirmed by a cardiologist masked to antiretroviral treatment (ART) history who was provided with cardiac signs and symptoms; troponin, creatine kinase, or both levels; and electrocardiographic findings as recorded in the medical records. We used the American College of Cardiology/European Society of Cardiology definition.[16] Only definite and probable cases of MI and possible death from MI were included. The index date was the date of MI diagnosis.

CONTROL SUBJECTS

Control subjects were HIV-infected patients with no history of MI and no diagnosis evoking MI who had already been enrolled in the database when MI was diagnosed in the corresponding case (±6 months). They were matched with cases for age (±3 years) at MI diagnosis, sex, and clinical center. In a previous article,[17] a nested case-control study using incidence density sampling with the same matching factors provided results similar to those of the published cohort analysis.[3] We used a case-control approach rather than a cohort approach for the efficiency of this design because we needed to collect cardiovascular risk factors in the medical records for cases and controls. With the goal of having 3 controls per case and using incidence density sampling, we randomly selected up to 5 controls per case from the list of patients fulfilling the matching criteria. Cases were eligible as controls up to the onset of MI.

DATA COLLECTION

We collected the cardiovascular risk factors listed in the French National Guidelines published in 2005,[18] namely, age older than 50 years in men and 60 years in women, family history of premature coronary artery disease before age 55 years in the father or age 65 years in the mother, current smoker or smoking cessation within the previous 3 years, and hypertension, diabetes mellitus, or hypercholesterolemia. We also recorded current use of cocaine, intravenous drugs, or both as stated in the medical records[19] and body mass index[20] because these also affect cardiovascular risk. These data were extracted from the medical records by trained research assistants experienced in HIV infection using a predefined case report form. Data on HIV infection, plasma HIV type 1 RNA load, CD4 and CD8 cell counts, the CD4 nadir, a detailed history of prescribed ART, and AIDS status[21] before the index date were validated. All biological measurements were collected within 3 months of the index date.

STATISTICAL ANALYSIS

Conditional regression models (TPHREG, SAS version 9.1; SAS Institute Inc, Cary, North Carolina) were used to quantify the relation between exposure to each ART drug and risk of MI. Lipid variables and diabetes mellitus, which may lie on the causal pathway between exposure to some ART drugs and risk of MI, were excluded from the main analysis. Smokers included current smokers and smokers who had quit less than 3 years before the index date. Obesity was defined by a body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared). Hypertension was defined as use of an antihypertensive medication or as hypertension reported with a diagnosis date in the medical record. We also studied the potential effect of HIV-related variables on risk of MI. The continuous variables were modeled in class or after log transformation. When there was missing data, a "missing" category was created so that all the patients were included in the analyses.

The first model included cumulative exposure to each ART drug. Ritonavir used as another PI booster was counted with the other PIs, whereas ritonavir alone was counted for itself. The second model included exposure to each ART drug plus, for each NRTI, a 3-class variable consisting of no exposure, recent exposure (current or in the previous 6 months), and past exposure (>6 months previously). In these 2 models, potential confounding factors were included one by one to determine whether they changed the odds ratio (OR) for any drug by at least 10% in any of the models. Subsequent models were adjusted on the selected confounders: hypertension; smoking status; family history of premature coronary artery disease; cocaine, intravenous drug use, or both; plasma HIV type 1 RNA level of 50 copies/mL or less or not; CD4 to CD8 cell ratio less than 1 or at least 1; and exposure to each ART drug. The ORs are reported for ART drugs to which at least 100 patients were exposed.

We conducted sensitivity analyses to assess the robustness of the results. We made an analysis restricted to patients who received their first ART regimen after inclusion in the cohort to detect a potential selection bias. We also examined whether the impact of PIs was the same when they were boosted or not with ritonavir. We also included in the models hypercholesterolemia, defined as a low-density lipoprotein cholesterol level of at least 160 mg/dL (to convert to millimoles per liter, multiply by 0.0259) or as the use of lipid-lowering drugs (statins or fibrates); hypertriglyceridemia, defined as triglyceride levels of at least 150 mg/dL (to convert to millimoles per liter, multiply by 0.0113); high-density lipoprotein cholesterol level, defined by a 4-category variable (<40 mg/dL, 40 to <60 mg/dL, ≥60 mg/dL, and value missing) (to convert to millimoles per liter, multiply by 0.0259); and diabetes, defined as use of an antidiabetic drug or as fasting glucose levels greater than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or diagnosis of diabetes reported with a diagnosis date in the medical record to determine whether these variables lay on the causal pathway linking ART to risk of MI. To explore a potential channeling bias, we compared cases exposed to short-term/recent abacavir therapy with the other cases and in view of the results conducted an analysis restricted to patients who did not use cocaine or intravenous drugs.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

Of 74 958 patients, 423 MI cases were identified in the database; 38 of these cases (9.0%) were excluded from the analysis because MI was not confirmed, 31 because they did not meet the inclusion criteria, and 32 because they had a recurrent MI. In addition, 39 cases were excluded because their medical records were unavailable. Six cases corresponded to patients who were selected as controls but whose medical records mentioned an MI. Based on the 360 cases (including 289 cases in the case-control study: 32 patients with recurrent MI and 39 patients with missing medical records), the incidence of MI in the database was estimated to be 1.24 per 1000 patient-years (95% confidence interval [CI], 1.11-1.36). Overall, 289 cases and 884 controls were included in the analysis; 246 cases had 3 controls, 29 had more than 3, and 14 had fewer than 3. The diagnosis was definite in 74.4% of cases and probable in 16.6%, and 9.0% had a possible death due to MI.

Cases and controls were well matched for age and sex (**Table 1**). All the cardiovascular risk factors except obesity were more frequent in cases than in controls, and cases therefore had more cardiovascular risk factors ($P < .001$). Cases were less likely to have a controlled viral load ($P = .006$) and a normal CD4 to CD8 cell ratio ($P = .001$). The CD4 cell counts on the index date were not different in cases and controls. At enrollment in the cohort, 76% of patients had never received ART. On the index date, 95% of patients had been exposed to ART, and only 5% of cases and 7% of controls were not receiving therapy. The median length of ART exposure was 6.6 years in cases and 7.0 years in controls, and the median number of different ART drugs received was 7 in cases and 6 in controls. The proportions of patients exposed to each ART drug are given in **Table 2**. Most patients had been exposed to thymidine analogues (92.6%) and to PIs (77.7%).

ART AND THE RISK OF MI

Impact of NRTI Exposure

In model 1, no association was found between cumulative exposure to abacavir and risk of MI (**Table 3**). In model 2 (Table 3), which also included for each NRTI a 3-class exposure variable (none, recent, and past), there was evidence of an interaction between recent/past exposure and cumulative exposure to abacavir. Whereas the OR for cumulative exposure to abacavir decreased from 0.97 in model 1 to 0.88 in model 2, the OR for recent exposure was 1.60 and for past exposure was 1.62. This interaction was not observed to that extent with any other NRTIs (Table 3). This finding prompted us to build an additional model in which exposure to abacavir was defined using a 5-class variable in which duration of exposure was combined with time of use (no exposure, <1 year of exposure and recent use [ie, short-term/recent exposure], <1 year of exposure and past use; >1 year of exposure and recent use, and >1 year of exposure and past use). **Table 4** gives the results of univariate and multivariate analyses of this final model. Patients with short-term/recent exposure to abacavir had a significantly increased risk of MI (OR, 2.01). Although not significant, the risk of MI tended to increase with cumulative exposure to zidovudine (OR, 1.09 per year of exposure) and stavudine (1.11 per year of exposure). In a post hoc analysis, cumulative exposure to thymidine analogues (zidovudine and stavudine) was associated with an increased risk of MI (OR, 1.09 [95% CI, 1.00-1.19] per year). No effect was found with didanosine, lamivudine, tenofovir, or zalcitabine.

Impact of NNRTI Exposure

In the final model, no association was found between risk of MI and cumulative exposure to efavirenz (OR, 1.01) or nevirapine (1.00).

Impact of PI Exposure

In the final model, the ORs of MI were 1.07 per year of exposure to indinavir with or without ritonavir ($P = .32$) and 1.10 per year of exposure to nelfinavir ($P = .15$). The risk was significant with lopinavir with ritonavir (OR, 1.33 per year) and with amprenavir/fosamprenavir with or without ritonavir (1.53 per year). There was no increased risk associated with exposure to saquinavir with or without ritonavir. In a post hoc analysis, cumulative exposure to any PI except saquinavir was associated with an increased risk of MI (OR, 1.15 [95% CI, 1.06-1.26] per year).

Sensitivity and Supportive Analyses

Similar results were obtained when the analysis was restricted to patients who were naive at inclusion in the cohort (ie, 61% of the full sample), with a slight difference, however, for abacavir. For short-term/recent abacavir use, the univariate OR was estimated to be 3.77 (95% CI, 1.86-7.64) and the adjusted OR to be 1.79 (95% CI, 0.74-4.27). Ritonavir boosting did not significantly change the association between PI exposure and risk of MI (eTable 1; http://www.archinternmed.com). The association between PI exposure and the risk of MI was not changed when metabolic variables were considered (eTable 2).

The 31 cases with short-term/recent exposure to abacavir were not significantly different from the other cases except for cocaine or intravenous drug use, time receiving ART, and AIDS status before MI (**Table 5**). In view of this result, we conducted an analysis that included only cases (n = 250) and their matched controls (n = 704) who were not cocaine or intravenous drug users (eTable 3). The OR for short-term/recent exposure to abacavir was 1.27 (95% CI, 0.64-2.49). In contrast, for the other associations, the ORs remained similar (eTable 3). There were not enough patients to repeat this analysis in cocaine or intravenous drug users.

COMMENT

We conducted a case-control study nested within a large database of HIV-infected patients to study the association

Table 1. Characteristics of the Study Patients on the Index Date[a]

Characteristic	Cases (n=289)	Controls (n=884)	*P* Value[b]
General characteristics			
Male sex, No. (%)	257 (89)	788 (89)	
Age, median (IQR), y	47 (41-54)	46 (40-54)	
BMI ≥30, No. (%)	10 (3)	39 (4)	.80[c]
Current smoker, No. (%)[d]	186 (64)	356 (40)	<.03[c]
Smoking cessation ≤3 y, No. (%)	24 (8)	32 (4)	
Cardiovascular disease			
Family history of premature CAD, No. (%)[d]	53 (18)	59 (7)	<.001[c]
Hypertension or hypertension treatment, No. (%)[d]	59 (20)	103 (12)	.001[c]
Current cocaine or intravenous drug use, No. (%)	38 (13)	83 (9)	.04
Diabetes or diabetes treatment, No. (%)[d]	45 (16)	91 (10)	.04[c]
Glucose, median (IQR), mg/dL	95 (88-108)	92 (85-103)	.12
Latest lipid measurements, use of lipid-lowering medication			
Hypercholesterolemia or hypercholesterolemia treatment, No. (%)[d]	150 (52)	288 (33)	<.001[c]
Hypertriglyceridemia, No. (%)[d]	164 (57)	423 (48)	.08[c]
Cholesterol, median (IQR), mg/dL			
Total	208 (173-255)	205 (170-236)	.001
LDL	127 (93-162)	124 (93-154)	.43
HDL	39 (31-50)	42 (35-54)	.02
Triglycerides, median (IQR), mg/dL	168 (115-292)	150 (97-221)	<.001
No. of cardiovascular risk factors, No. (%)[e]			
0	5 (2)	170 (19)	<.001
1 or 2	171 (59)	553 (63)	
≥3	113 (39)	161 (18)	
Characteristics linked to HIV infection			
Plasma HIV type 1 RNA, median (IQR), copies/mL	127 (50-3900)	50 (50-1368)	.02
Plasma HIV type 1 RNA ≤50 copies/mL, No. (%)	125 (43)	457 (52)	.006
CD4 cell nadir, median (IQR), cells/mm^3	135 (41-238)	177 (68-309)	.001
CD4 cell count, median (IQR), cells/mm^3	427 (256-638)	451 (291-634)	.48
CD4 to CD8 cell ratio ≥1, No. (%)[d]	19 (7)	116 (13)	.001[c]
CD8 cell count, median (IQR), cells/mm^3	1049 (710-1372)	929 (639-1246)	.59
Delay between HIV diagnosis and index date, median (IQR), y	10.1 (6.4-14.6)	8.9 (4.8-13.3)	.001
AIDS before index date, No. (%)	126 (44)	289 (33)	.001
No treatment before index date, No. (%)	11 (4)	55 (6)	.13
No treatment at index date, No. (%)	15 (5)	61 (7)	<.001
Time receiving ART, median (IQR), y	6.6 (3.9-8.9)	7.0 (4.1-10.1)	.003
No. of different therapeutic lines, median (IQR)	5 (2-8)	4 (2-7)	<.001
No. of different antiretroviral drugs, median (IQR)	7 (5-10)	6 (4-8)	<.001
First ART after inclusion in the cohort, No. (%)	210 (73)	677 (77)	.32

Abbreviations: ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein; NA, not applicable.

SI conversion factors: To convert cholesterol (total, LDL, and HDL) to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] The index date is the date of myocardial infarction diagnosis.

[b] Univariate conditional logistic regression.

[c] *P* value is calculated including missing data.

[d] Information on smoking was available for 276 cases and 789 controls; family history of premature CAD, 199 cases and 333 controls; hypertension, 285 cases and 877 controls; diabetes, all cases and 882 controls; hypercholesterolemia, 284 cases and 882 controls; hypertriglyceridemia, 280 cases and 868 controls; and CD4 to CD8 cell ratio, 278 cases and 873 controls.

[e] Cardiovascular risk factors were age older than 50 years in men or 60 years in women, current smoker or smoking cessation in the previous 3 years, family history of premature CAD, hypertension, hypercholesterolemia, diabetes, and cocaine or intravenous drug use.

between ART and risk of MI. We found that the risk of MI was increased by cumulative exposure to any studied PI except saquinavir and particularly to lopinavir with ritonavir and amprenavir/fosamprenavir with or without ritonavir. Cumulative exposure to thymidine analogues was also associated with an increased risk of MI. Abacavir initiation was associated with an increased risk of MI, whereas longer exposure to abacavir was not. These associations persisted when the analysis was restricted to nonusers of cocaine and intravenous drugs, except for abacavir. All NNRTIs and NRTIs other than abacavir and thymidine analogues were not associated with risk of MI.

The use of a nested design allowed us to avoid the main drawback of the case-control design, namely, classification bias on exposure, while allowing us to fully validate the treatment histories prospectively recorded in the database. We did not include recurrent MI because it would have been difficult to control for the selection bias by analysis for these cases given that the ART drug prescribed to them was likely to have been chosen differently. We also excluded 39 potential cases whose medical records were lacking. Although this could represent a small selection bias, it would have been impossible to adjust for confounding for these cases. Three-quarters

Table 2. Treatment History of Patients Exposed to Each Antiretroviral Drug and Cumulative Exposure

Variable	Cases (n=289)		Controls (n=884)	
	Cases Exposed, No. (%)	Cumulative Exposure, Median (IQR)[a]	Controls Exposed, No. (%)	Cumulative Exposure, Median (IQR)[a]
NRTIs				
Abacavir	127 (43.9)	1.43 (0.35-3.02)	283 (32.0)	1.77 (0.53-3.64)
Didanosine	186 (64.4)	2.06 (0.85-3.75)	505 (57.1)	2.20 (0.94-4.00)
Lamivudine	269 (93.1)	3.72 (2.23-5.19)	774 (87.6)	3.55 (1.94-5.35)
Stavudine	199 (68.9)	3.15 (1.68-4.58)	519 (58.7)	3.02 (1.62-4.38)
Tenofovir	65 (22.5)	1.34 (0.55-2.17)	173 (19.6)	1.00 (0.53-1.91)
Zalcitabine	92 (31.8)	1.02 (0.53-1.84)	222 (25.1)	0.91 (0.52-1.84)
Zidovudine	256 (88.6)	2.65 (1.55-4.70)	742 (83.9)	2.77 (1.38-4.83)
Any thymidine analogue	276 (95.5)	5.15 (3.27-7.36)	810 (91.6)	4.89 (3.01-6.80)
NNRTIs				
Efavirenz	109 (37.7)	1.42 (0.61-2.52)	295 (33.4)	1.69 (0.72-3.01)
Nevirapine	111 (38.4)	1.14 (0.66-2.40)	269 (30.4)	1.49 (0.67-3.13)
PIs				
Amprenavir/fosamprenavir ± ritonavir–	46 (15.9)	1.28 (0.64-2.69)	71 (8.0)	0.80 (0.45-1.49)
Amprenavir/fosamprenavir + ritonavir	38 (13.1)	1.20 (0.51-3.03)	61 (6.9)	0.69 (0.37-1.59)
Amprenavir/fosamprenavir	20 (6.9)	0.85 (0.25-1.34)	17 (1.9)	0.64 (0.42-0.90)
Indinavir ± ritonavir–	146 (50.5)	1.77 (0.85-2.97)	351 (39.7)	1.79 (0.73-3.16)
Indinavir + ritonavir	39 (13.5)	0.95 (0.30-1.40)	98 (11.1)	0.61 (0.34-1.24)
Indinavir	130 (45.0)	1.66 (0.76-2.89)	312 (35.3)	1.78 (0.90-3.08)
Lopinavir + ritonavir	94 (32.5)	1.62 (0.65-2.78)	196 (22.2)	1.09 (0.45-2.11)
Nelfinavir	131 (45.3)	1.29 (0.81-2.44)	322 (36.4)	1.52 (0.83-2.49)
Saquinavir ± ritonavir–	92 (31.8)	1.31 (0.65-2.15)	232 (26.2)	1.46 (0.79-2.33)
Saquinavir + ritonavir	51 (17.6)	1.61 (0.62-2.46)	125 (14.1)	1.33 (0.79-2.40)
Saquinavir	60 (20.8)	0.84 (0.45-1.30)	146 (16.5)	1.00 (0.66-1.69)
Any PIs except saquinavir	239 (82.7)	3.27 (1.56-5.05)	625 (70.7)	2.84 (1.46-4.44)

Abbreviations: IQR, interquartile range; –, without a booster; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

[a] Cumulative exposure for patients exposed to the antiretroviral drug per year.

of the cases and controls had never received ART before being enrolled in the cohort, a feature that would tend to limit the selection bias; the analysis restricted to these patients gave the same results as the main analysis. There was a small amount of missing data for the cardiovascular risk factors except for family history of premature coronary artery disease, in which the proportion of missing data was 31% for cases and 62% for controls, suggesting that the report of this item in the medical record may have occurred after the MI was diagnosed and most often was unknown by the physician when prescribing the treatment. Therefore, although it is a limitation of this study, it is unlikely to have played a major confounding role. Additional variables could have been accounted for as potential confounders, such as renal function.[22] However, no study to date, to our knowledge, has reported different results when accounting only for the main MI risk factors compared with when accounting for the main MI risk factors and renal function. Because creatinine level was not measured regularly for all the patients throughout the study period, we could not account for this variable in this study. Given the association between traditional cardiovascular risk factors and renal function, we do not believe that renal function could be a major confounder in this study population because most patients exposed to abacavir in this study were not naive patients but were highly preexposed patients. This situation is different from deciding which NRTI to prescribe to a naive patient nowadays, a decision that could certainly be influenced by renal function. Observational studies, such as this one, cannot demonstrate the causal nature of an association. However, the ORs for PIs and NNRTIs were very close in the univariate and multivariate models, indicating that the association observed with all the PIs except saquinavir with or without ritonavir is unlikely to be explained by remaining confounders.[23] The situation was different in the case of NRTIs, however, particularly for tenofovir and abacavir. For example, the univariate OR was 1.19 for tenofovir, whereas in the final model it was 1.00; in addition, the OR declined from 2.76 to 2.01 for short-term/recent abacavir exposure. In the analysis restricted to cases and their matched controls included as naive in the cohort, the OR declined from 3.77 to 1.79 for short-term/recent abacavir exposure, and in the analysis restricted to nonusers of cocaine and intravenous drugs, it declined from 2.00 to 1.27. It follows that the present results are likely to be more robust for PIs and NNRTIs than for NRTIs.[23]

In a previous analysis of the D:A:D study, the relative rate of MI per year of PI exposure was 1.16 (95% CI, 1.10-1.23), a value close to the estimated OR of 1.15 (1.06-1.26) in the present study. Similarly, as in a recent analysis of the D:A:D study,[24] we found no association between risk of MI and exposure to saquinavir with or without ritonavir, whereas we found that lopinavir with ritonavir increased the risk of MI. In both studies, the risk of

Table 3. Risk of Myocardial Infarction by Exposure to Specific Antiretroviral Drugs

Variable	Exposed, No.		Model 1: Cumulative Exposure Only		Model 2: Cumulative, Recent, and Past Exposure	
	All	Cases	OR (95% CI)[a]	*P* Value	OR (95% CI)[a]	*P* Value
NRTIs						
Abacavir						
Cumulative exposure	410	127	0.97 (0.86-1.10)	.64	0.88 (0.74-1.04)	.12
No exposure	763	162	NA	NA	1 [Reference]	NA
Past exposure	120	39	NA	NA	1.60 (0.89-2.85)	.11
Recent exposure	290	88	NA	NA	1.62 (0.93-2.81)	.09
Didanosine						
Cumulative exposure	691	186	0.91 (0.82-1.01)	.06	0.88 (0.77-1.01)	.07
No exposure	482	103	NA	NA	1 [Reference]	NA
Past exposure	380	109	NA	NA	1.09 (0.64-1.85)	.76
Recent exposure	311	77	NA	NA	1.22 (0.65-2.30)	.54
Lamivudine						
Cumulative exposure	1043	269	0.96 (0.86-1.08)	.52	0.91 (0.80-1.04)	.18
No exposure	130	20	NA	NA	1 [Reference]	NA
Past exposure	225	71	NA	NA	1.30 (0.55-3.10)	.55
Recent exposure	788	198	NA	NA	1.42 (0.62-3.29)	.41
Stavudine						
Cumulative exposure	718	199	1.11 (0.99-1.24)	.07	1.14 (0.99-1.32)	.08
No exposure	455	90	NA	NA	1 [Reference]	NA
Past exposure	433	127	NA	NA	1.15 (0.64-2.08)	.63
Recent exposure	285	72	NA	NA	0.96 (0.47-1.99)	.92
Tenofovir						
Cumulative exposure	238	65	1.01 (0.79-1.30)	.95	1.20 (0.85-1.69)	.31
No exposure	935	224	NA	NA	1 [Reference]	NA
Past exposure	40	15	NA	NA	0.71 (0.25-1.95)	.50
Recent exposure	198	50	NA	NA	0.58 (0.28-1.20)	.14
Zalcitabine						
Cumulative exposure	314	92	0.99 (0.82-1.21)	.95	0.96 (0.71-1.31)	.80
No exposure	859	197	NA	NA	1 [Reference]	NA
Past exposure	293	87	NA	NA	1.11 (0.63-1.97)	.72
Recent exposure	21	5	NA	NA	0.84 (0.15-4.69)	.84
Zidovudine						
Cumulative exposure	998	256	1.09 (1.00-1.19)	.05	1.11 (1.00-1.23)	.05
No exposure	175	33	NA	NA	1 [Reference]	NA
Past exposure	518	135	NA	NA	0.83 (0.41-1.69)	.61
Recent exposure	480	121	NA	NA	1.04 (0.49-2.20)	.93
NNRTIs						
Efavirenz						
Cumulative exposure	404	109	1.01 (0.87-1.16)	.94	1.01 (0.87-1.17)	.94
Nevirapine						
Cumulative exposure	380	111	1.01 (0.88-1.15)	.95	0.99 (0.86-1.14)	.88
PIs						
Amprenavir/fosamprenavir ± ritonavir–						
Cumulative exposure	117	46	1.57 (1.24-2.00)	.001	1.56 (1.21-2.01)	.001
Indinavir ± ritonavir–						
Cumulative exposure	497	146	1.07 (0.95-1.21)	.29	1.06 (0.94-1.21)	.34
Lopinavir + ritonavir						
Cumulative exposure	290	94	1.37 (1.13-1.65)	.002	1.34 (1.09-1.64)	.005
Nelfinavir						
Cumulative exposure	453	131	1.09 (0.96-1.25)	.20	1.08 (0.94-1.24)	.28
Saquinavir ± ritonavir–						
Cumulative exposure	324	92	0.94 (0.81-1.09)	.39	0.93 (0.79-1.09)	.35

Abbreviations: CI, confidence interval; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; OR, odds ratio; PIs, protease inhibitors; –, without a booster.

[a] Adjusted for hypertension, smoking, family history of premature coronary artery disease, cocaine or intravenous drug use, plasma human immunodeficiency virus type 1 RNA level, CD4 to CD8 cell ratio, and exposure to the antiretroviral drugs listed in the table and to emtricitabine, atazanavir with or without ritonavir–, ritonavir alone, and tipranavir with ritonavir.

MI associated with PI exposure changed little regardless of whether the PIs were boosted by ritonavir or when lipid variables and diabetes were taken into account. Although this may be explained by uncertainties in lipid level measurement, it could also imply that mechanisms other than increased lipid levels, such as an effect on endothelial cells,[25] could be involved in the increased risk of MI associated with cumulative PI expo-

Table 4. Risk of Myocardial Infarction According to Exposure to Antiretroviral Drugs: Univariate and Adjusted Models

Variable	Exposed, No.		OR (95% CI)	
	All	Cases	Univariate Model	Final Model[a]
NRTIs				
Abacavir				
No exposure	763	162	1 [Reference]	1 [Reference]
Short-term, recent exposure	72	31	2.76 (1.67-4.55)	2.01 (1.11-3.64)
Long-term, recent exposure	218	57	1.34 (0.94-1.93)	1.05 (0.65-1.69)
Short-term, past exposure	76	24	1.66 (0.99-2.79)	1.31 (0.68-2.51)
Long-term, past exposure	44	15	1.94 (1.00-3.79)	1.48 (0.62-3.49)
Didanosine, cumulative exposure	691	186	1.02 (0.95-1.09)	0.91 (0.82-1.01)
Lamivudine, cumulative exposure	1043	269	1.06 (1.00-1.13)	0.96 (0.85-1.07)
Stavudine, cumulative exposure	718	199	1.09 (1.02-1.16)	1.11 (0.99-1.24)
Tenofovir, cumulative exposure	238	65	1.19 (0.99-1.44)	1.00 (0.77-1.28)
Zalcitabine, cumulative exposure	314	92	1.08 (0.94-1.24)	0.98 (0.81-1.20)
Zidovudine, cumulative exposure	998	256	1.03 (0.98-1.08)	1.09 (1.00-1.19)
NNRTIs				
Efavirenz, cumulative exposure	404	109	1.00 (0.90-1.10)	1.01 (0.87-1.17)
Nevirapine, cumulative exposure	380	111	1.00 (0.90-1.10)	1.00 (0.87-1.14)
PIs				
Amprenavir/fosamprenavir ± ritonavir–, cumulative exposure	117	46	1.41 (1.17-1.69)	1.53 (1.21-1.94)
Indinavir ± ritonavir–, cumulative exposure	497	146	1.10 (1.01-1.19)	1.07 (0.94-1.20)
Lopinavir + ritonavir, cumulative exposure	290	94	1.35 (1.17-1.55)	1.33 (1.09-1.61)
Nelfinavir, cumulative exposure	453	131	1.08 (0.98-1.19)	1.10 (0.97-1.26)
Saquinavir ± ritonavir–, cumulative exposure	324	92	1.02 (0.91-1.13)	0.93 (0.80-1.09)

Abbreviations: CI, confidence interval; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; OR, odds ratio; PIs, protease inhibitors; –, without a booster.

[a] Adjusted for hypertension, smoking, family history of premature coronary artery disease, cocaine or intravenous drug use, plasma human immunodeficiency virus type 1 RNA level, CD4 to CD8 cell ratio, and exposure to the antiretroviral drugs listed in the table and to emtricitabine, atazanavir with or without ritonavir, ritonavir alone, and tipranavir with ritonavir.

sure. Saquinavir is known to offer a better triglyceride profile than the other PIs, in particular lopinavir with ritonavir.[26] This might perhaps explain the difference that we observed in the risk of MI for this PI compared with others. The 2 studies also gave similar results for NNRTIs. No effect of exposure to efavirenz or nevirapine was found in either study, although efavirenz has a more negative effect than does nevirapine on the lipid profile.[27]

Available studies[24,28-30] have given divergent results for NRTIs, most likely because prescription of this drug class has been associated with multiple confounding factors that were handled differently in the different studies. This might, for example, explain why an association between didanosine exposure and MI was found in the D:A:D study[5] but not in the Strategies for Management of Anti-Retroviral Therapy (SMART) study[6] or in the present study. The D:A:D study showed no increase in the risk of MI after exposure to thymidine analogues, although this was its main hypothesis.[5] In contrast, we found that exposure to stavudine or zidovudine increased the risk of MI. This latter result is unlikely to be explained by confounding factors because the OR was 1.06 in the univariate model and 1.09 in the multivariate model. Further independent studies are needed to settle this issue because these drugs are still widely used in developing countries.[31] The fat redistribution induced by these drugs might explain the observed effects.[32] Without knowledge of the D:A:D study analysis of 2008,[5] we would have examined only cumulative exposure to abacavir and would therefore have found no association with MI. Only because we were asked to confirm or refute the D:A:D study results did we explore current and past use of abacavir in addition to cumulative exposure. Although we found that recent abacavir treatment initiation was associated with an increased risk of MI in the full data set (OR, 2.01; 95% CI, 1.11-3.64), the association disappeared when we restricted the analysis to nonusers of cocaine and intravenous drugs (1.27; 0.64-2.49). Because this latter result was obtained in an analysis including 81% of the full sample, it is unlikely that the difference between the 2 analyses is explained mainly by a power issue. The estimated OR in the restricted analysis (1.27) was much smaller than that obtained in the full sample. Note that the D:A:D and SMART studies were not adjusted for exposure to cocaine or intravenous drugs but rather for transmission groups. In addition, most patients enrolled in these 2 studies had already received ART previously (73% in the D:A:D study[33] and 95% in the SMART study[34]). This could induce a larger selection bias than the present study, in which only 24% of patients had received ART before enrollment. Moreover, recurrent MI was not excluded from the D:A:D and SMART studies. All these differences could explain why different results were obtained for NRTIs in the D:A:D, the SMART, and the present studies. In addition, the SMART study[6] included only a few cases of MI (n=19), and other studies[7,12,29,30] with low numbers of events could not exclude a small increase in the risk of MI associated with abacavir. In a recently published cohort study[31] involving 67 cases of MI, an association between exposure to abac-

Table 5. Baseline Characteristics of the 31 Cases With Short-term/Recent Exposure to Abacavir

Characteristic	Cases With Recent Abacavir Exposure (n=31)	Other Cases (n=258)	*P* Value
General characteristics			
Male sex, No. (%)	28 (90)	229 (89)	>.99[a]
Age, median (IQR), y	44 (40-52)	47 (41-54)	.19
BMI ≥30	0	10 (4)	.67[a]
Current smoker, No. (%)[b]	23 (74)	163 (63)	.14[a,c]
Smoking cessation ≤3 y, No. (%)	4 (13)	20 (8)	
Cardiovascular disease			
Family history of premature CAD[b]	7 (32)	46 (18)	.81[c]
Hypertension or hypertension treatment[b]	4 (13)	55 (21)	.27[a,c]
Current cocaine or intravenous drug use	9 (29)	29 (11)	.01[a]
Diabetes or diabetes treatment[b]	3 (10)	42 (16)	.44[a,c]
Glucose, median (IQR), mg/dL	90 (83-112)	95 (88-108)	.38
Latest lipid measurements, use of lipid-lowering medication			
Hypercholesterolemia or hypercholesterolemia treatment, No. (%)[b]	13 (42)	137 (53)	.28[a,c]
Hypertriglyceridemia, No. (%)[b]	15 (48)	149 (58)	.50[a,c]
Cholesterol, median (IQR), mg/dL			
Total	201 (170-232)	212 (174-259)	.15
LDL	120 (100-151)	131 (93-166)	.31
HDL	39 (31-39)	35 (39-50)	.35
Triglycerides, median (IQR), mg/dL	159 (106-283)	168 (115-292)	.41
No. of cardiovascular risk factors, No. (%)[d]			
0	1 (3)	4 (2)	
1 or 2	19 (61)	152 (59)	.57[a]
≥3	11 (36)	102 (40)	
Characteristics linked to HIV infection			
Plasma HIV type 1 RNA, median (IQR), copies/mL	56 (50-5844)	138 (50-3900)	.65
Plasma HIV type 1 RNA ≤50 copies/mL, No. (%)	15 (48)	110 (43)	.54
CD4 cell nadir, median (IQR), cells/mm^3	158 (30-254)	132 (44-236)	.78
CD4 cell count, median (IQR), cells/mm^3	345 (216-545)	435 (268-647)	.10
CD4 to CD8 cell ratio ≥1, No. (%)[c]	1 (3)	18 (7)	.89[a,c]
CD8 cell count, median (IQR), cells/mm^3	984 (708-1189)	1052 (713-1406)	.39
Delay between HIV diagnosis and index date, median (IQR), y	9.9 (7.0-13.3)	10.1 (6.3-14.8)	.81
AIDS before index date, No. (%)	31 (100)	108 (42)	.04
No treatment before index date, No. (%)	0	11 (4)	<.001
No treatment at index date, No. (%)	0	15 (6)	<.001
Time receiving ART, median (IQR), y	5.2 (2.8-7.5)	6.8 (4.0-9.3)	.005
No. of different therapeutic lines, No. (%)	4 (2-6)	5 (2-8)	.22
No. of different antiretroviral drugs, median (IQR)	8 (5-9)	7 (4-10)	.91
Patients receiving abacavir when MI occurs, No. (%)	28 (90)	51 (20)	.01
Exposure to thymidine analogue, No. (%)	30 (97)	246 (95)	>.99[a]
Exposure to any PI except saquinavir, No. (%)	27 (87)	212 (82)	.62[a]

Abbreviations: ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; PI, protease inhibitor.

SI conversion factors: To convert cholesterol (total, LDL, and HDL) to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] Fisher exact test.

[b] Information on smoking was available for 30 cases and 246 other cases; family history of premature CAD, 22 cases and 177 other cases; hypertension, 30 cases and 255 other cases; diabetes, all cases; hypercholesterolemia, 30 cases and 254 other cases; hypertriglyceridemia, 30 cases and 250 other cases; and CD4 to CD8 cell ratio, 30 cases and 248 other cases.

[c] *P* value is calculated including missing data.

[d] Cardiovascular risk factors are older than 50 years for men or 60 years for women, current smoker or smoking cessation in the previous 3 years, family history of premature CAD, hypertension, hypercholesterolemia, diabetes, and cocaine or intravenous drug use.

avir treated as a time-dependant covariate (yes or no) and an increased risk of MI was found. However, the analysis was not adjusted for tobacco exposure or family history, the lipid profile was not available, and only hospitalization for MI was accounted for, not death due to MI. This result is slightly different from that of the D:A:D study or the SMART study, and, again, the differences could be explained by differences in definitions of the event or in the way of accounting for potential confounders.

Most PIs studied to date have been found to increase the risk of MI, and this increase is not solely mediated by an effect on lipid metabolism. The 10-year OR of the risk of MI was estimated to be 4 for exposure to all the PIs except saquinavir. To translate this result into practical terms, one can calculate the number of patients to treat for 10 years with a PI to observe an additional MI (number needed to harm). For a patient whose risk of MI is the risk observed in the French HIV-infected pa-

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tients in this study, that is, 1.2 per 100 after 10 years, the number needed to harm is estimated to be 29, meaning that for 29 patients treated with a PI for 10 years with this level of risk of MI, there will be an additional MI. If one considers a patient whose 10-year risk is 20%, the number needed to harm is estimated to be 3, meaning that for 3 patients treated with a PI for 10 years there will be an additional MI. This means that long-term exposure to this drug class should be avoided if virologically possible in patients with multiple cardiovascular risk factors. There are currently no data sets, including our own, in which exposure to atazanavir with or without ritonavir or darunavir with or without ritonavir is sufficient to conclude on these 2 newer PIs.

We found no association between NNRTI exposure and risk of MI, and this result also seems to be robust.

The results for NRTIs are more complex and are more likely to be affected by residual confounding. Although cumulative exposure to thymidine analogues seemed to increase the risk of MI, the observed association with short-term/recent exposure to abacavir disappeared when restricting the analysis to nonusers of cocaine or intravenous drugs. Together, these elements suggest that the relationship between exposure to abacavir and risk of MI cannot be considered causal.

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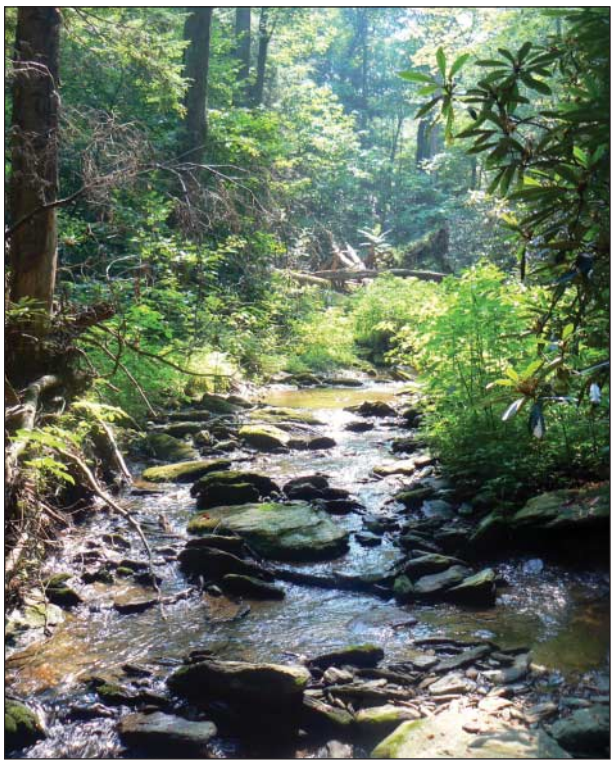
REFERENCES

1. Gallet B, Pulik M, Genet P, Chedin P, Hiltgen M. Vascular complications associated with use of HIV protease inhibitors. *Lancet*. 1998;351(9120):1958-1959.
2. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors [letter]. *Lancet*. 1998;351(9112):1328.
3. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D; Clinical Epidemiology Group from the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003;17(17):2479-2486.
4. Friis-Møller N, Reiss P, Sabin CA, et al; DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
5. Sabin CA, Worm SW, Weber R, et al; 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*. 2008; 371(9622):1417-1426.
6. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22(14):F17-F24.
7. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr*. 2009;51(1):20-28.
8. Department of Health and Human Services. Archived guidelines. AIDSinfo Web site. http://www.aidsinfo.nih.gov/Guidelines/ArchivedGuidelines.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=18&ClassID=6. Accessed December 2, 2009.
9. European AIDS Clinical Society (EACS) guidelines. http://www.europeanaidsclinicalsociety.org/guidelines.asp. Accessed December 2, 2009.
10. Hsue PY, Hunt PW, Wu Y, et al. Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS*. 2009;23 (15):2021-2027.
11. Kristoffersen US, Kofoed K, Kronborg G, Benfield T, Kjaer A, Lebech AM. Changes in biomarkers of cardiovascular risk after a switch to abacavir in HIV-1-infected individuals receiving combination antiretroviral therapy. *HIV Med*. 2009;10 (10):627-633.
12. Smith KY, Patel P, Fine D, et al; HEAT Study Team. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment (HEAT study). *AIDS*. 2009;23(12):1547-1556.
13. Satchell C, O'Connor E, Peace A, et al. Platelet hyper-reactivity in HIV-1-infected patients on abacavir-containing ART. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 11, 2009; Montreal, Quebec, Canada. Abstract 151LB.
14. Organisation Mondiale de la santé. *Classification Statistique Internationale des Maladies et des Problèmes de santé Connexes, 10th Revision*. Geneva, Switzerland: Organisation Mondiale de la Santé; 1993.
15. Yeni P. *Rapport 2008: Prise en charge médicale des patients infectés par le VIH*. Paris, France: Medecine-Sciences, Flammarion; 2008.
16. Luepker RV, Apple FS, Christenson RH, et al; AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. *Circulation*. 2003;108 (20):2543-2549.

17. Guiguet M, Mary-Krause M, Ename B, Costagliola D, Grabar S. Influence of control selection in nested case-control studies: the example of exposure to antiretroviral treatment (ART) and the risk of myocardial infarction (MI) in the French Hospital Database on HIV (FHDH-ANRS CO4). *Pharmacoepidemiol Drug Saf*. 2008; 17(5):468-474.
18. AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé). Argumentaire pour la prise en charge des patients dyslipidémiques. 2005. http://www.afssaps.fr/Recommandations-de-bonne-pratique/Prise-en-charge-du-patient-dyslipidemique-recommandations-de bonne-pratiques/%28language%29/fre-FR. Accessed December 2, 2009.
19. McCord J, Jneid H, Hollander JE, et al; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. *Circulation*. 2008;117(14):1897-1907.
20. Anand SS, Islam S, Rosengren A, et al; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29(7):932-940.
21. Ancelle-Park R. Expanded European AIDS case definition. *Lancet*. 1993;341(8842): 441.
22. Bedimo R, Westfall A, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular disease in the HAART era. Paper presented at: 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 20, 2009; Cape Town, South Africa. Abstract MoAb202.
23. Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence-based Medicine: How to Practice and Teach EBM*. 3rd ed. Edinburgh, Scotland: Churchill Livingstone; 2005.
24. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study. *J Infect Dis*. 2010;201(3):318-330.
25. Lefèvre C, Boccara F, Auclair M, Capeau J, Caron M. Some protease inhibitors induce human endothelial cell dysfunction and prelamin A accumulation. Scientific poster presented at: 10th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; November 6-8, 2008; London, England.
26. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. 2009;50(4):367-374.
27. van Leth F, Phanuphak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. *PLoS Med*. 2004;1(1):e19. Accessed May 1, 2010.
28. Benson CA, Ribaudo H, Zheng E, et al. No association of abacavir use with risk of myocardial infarction or severe cardiovascular disease events (ACTG A5001/ALLRT study). Scientific poster presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 8-11, 2009; Montreal, Quebec, Canada. Abstract 721.
29. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis*. 2009;49(10):1591-1601.
30. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med*. 2010;11(2):130-136.
31. Mercier S, Gueye NF, Cournil A, et al. Lipodystrophy and metabolic disorders in HIV-1-infected adults on 4- to 9-year antiretroviral therapy in Senegal: a case-control study. *J Acquir Immune Defic Syndr*. 2009;51(2):224-230.
32. Calmy A, Hirschel B, Cooper D, Carr A. A new era of antiretroviral drug toxicity. *Antivir Ther*. 2009;14(2):165-179.
33. Smith C. D:A:D Study Group. Association between modifiable and non-modifiable risk factors and specific causes of death in the HAART era: the Data Collection on Adverse Events of Anti-HIV Drugs Study. Paper presented at: 16th Conference on Retroviruses and Opportunistic Infections; February 11, 2009; Montreal, Quebec, Canada. Abstract 145.
34. El-Sadr WM, Lundgren JD, Neaton JD, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count: guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.

Images From Our Readers



Kelly's Run Trail, Lancaster County, Pennsylvania.

Courtesy of: Scott Lauter, MD, Internal Medicine Hospital Specialists, Lancaster General Hospital, Lancaster, Pennsylvania.