

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

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(See the editorial commentary by Aberg and Ribaldo, on pages 315–17.)

Background. The risk of myocardial infarction (MI) in patients with human immunodeficiency virus (HIV) infection has been assessed in 13 anti-HIV drugs in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.

Methods. Poisson regression models were adjusted for cardiovascular risk factors, cohort, calendar year, and use of other antiretroviral drugs and assessed the association between MI risk and cumulative (per year) or recent (current or in the past 6 months) use of antiretroviral drugs, with >30,000 person-years of exposure.

Results. Over 178,835 person-years, 580 patients developed MI. There were no associations between use of tenofovir, zalcitabine, zidovudine, stavudine, or lamivudine and MI risk. Recent exposure to abacavir or didanosine was associated with an increased risk of MI. No association was found between MI risk and cumulative exposure to nevirapine, efavirenz, nelfinavir, or saquinavir. Cumulative exposure to indinavir and lopinavir-ritonavir was associated with an increased risk of MI (relative rate [RR] per year, 1.12 and 1.13, respectively). These increased risks were attenuated slightly (RR per year, 1.08 [95% confidence interval {CI}, 1.02–1.14] and 1.09 [95% CI, 1.01–1.17], respectively) after adjustment for lipids but were not altered further after adjustment for other metabolic parameters.

Conclusions. Of the drugs considered, only indinavir, lopinavir-ritonavir, didanosine, and abacavir were associated with a significantly increased risk of MI. As with any observational study, our findings must be interpreted with caution (given the potential for confounding) and in the context of the benefits that these drugs provide.

The prevalence of traditional cardiovascular disease (CVD) risk factors, such as smoking and dyslipidemia,

is generally higher in the human immunodeficiency virus (HIV)-infected population, compared with the

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general population [1], although the situation has improved somewhat over the past few years [2, 3]. We have previously demonstrated an increased risk of myocardial infarction (MI) among patients exposed to combination antiretroviral therapy (CART) for longer periods [4], particularly those exposed to protease inhibitors (PIs) [5] and those recently exposed to the nucleoside reverse-transcriptase inhibitors (NRTIs) abacavir and didanosine [6]. In contrast, no association was found between the risk of MI and exposure to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) [5] or any of the other NRTIs studied [6].

Several drugs from the PI class have been reported to cause dyslipidemia, hyperglycemia, and overt diabetes mellitus [7–12], and clinicians deciding which particular PI to prescribe often take this into account. Because individual drugs within the PI class differ in their propensity to cause metabolic disturbances, it is important to identify the contribution of each PI to the risk of MI. Drugs from the NNRTI class have also been associated with the development of dyslipidemia [13, 14]. The extent to which either of the 2 commonly used NNRTIs, efavirenz and nevirapine, is associated with the risk of MI remains to be determined. We now have sufficient follow-up time among individuals exposed to several specific PIs and NNRTIs to robustly describe the associations between these drugs and the risk of MI. Furthermore, since the publication of our findings linking recent use of abacavir and didanosine to an increased risk of MI [6], we have also accrued sufficient follow-up time on a more recently approved NRTI, tenofovir, to permit an analysis of the association between this drug and the risk of MI.

METHODS

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is an international collaboration of 11 cohorts that follows 33,308 HIV type 1–infected patients at 212 clinics in Europe, the United States, and Australia. For the purpose of our analyses, an individual was defined as having hypertension if the individual had a systolic blood pressure of >140 mm Hg, had a diastolic blood pressure of >90 mm Hg, or was receiving antihypertensive medication or angiotensin-converting enzyme inhibitors. Dyslipidemia was considered present if the individual had a total cholesterol level of ≥ 6.2 mmol/L, had a high-density lipoprotein (HDL) cholesterol level of ≤ 0.9 mmol/L, had a triglyceride level of ≥ 2.3 mmol/L, or was receiving lipid-lowering drugs. Ten-year predicted risk of coronary heart disease was determined using the Framingham equation [15].

Outcomes. All incident cases of MI during follow-up were reported to the study coordinating office for validation and coding. Reported MIs were classified as definite, possible, or unclassifiable, according to criteria applied in the World Health

Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study [16] and independently of knowledge of a patient's antiretroviral treatment history. Other validated outcomes included strokes (definitive or possible), invasive cardiovascular procedures (coronary artery angioplasty or bypass, or carotid endarterectomy), diabetes mellitus, and death.

Statistical analysis. Seven NRTIs (zidovudine, stavudine, didanosine, zalcitabine, lamivudine, abacavir, and tenofovir), 4 PIs (indinavir, nelfinavir, lopinavir-ritonavir, and saquinavir), and 2 NNRTIs (efavirenz and nevirapine) reached the prespecified follow-up requirements: an exposure time of at least 30,000 person-years of follow-up (PYFU) with a median individual postexposure follow-up of >1 year. In order to meet these thresholds, we combined the follow-up of patients exposed to indinavir with that of patients without concomitant ritonavir use; similarly, we combined the follow-up from patients exposed to saquinavir with that of patients without ritonavir. Thus, our main analyses describe associations between any exposure to these 2 drugs (saquinavir and indinavir) and the development of MI, regardless of concomitant ritonavir use. However, as a sensitivity analysis, we also explored the separate associations of each drug with MI risk when used with or without ritonavir; of note, these analyses were based on $<30,000$ PYFU and therefore should be interpreted with caution.

Determination of the risk of MI. Full details of the analytical approach have been described elsewhere [4, 17]. Individuals were followed up prospectively from enrolment in D:A:D to the date of the first occurrence of MI during prospective follow-up, the date of death, 6 months after a patient's last clinic visit, or 1 February 2008, whichever occurred first. As in previous analyses, each person's follow-up was divided into a series of consecutive 1-month periods, and a patient's cumulative and current exposure to each antiretroviral drug at the start of each period was determined (including exposure to treatment before enrollment in D:A:D). Each person's covariate data were also updated at the start of each month, permitting a time-varying analysis. Any follow-up and events that occurred in that patient-month were then attributed to the characteristics of the patient at the start of that month.

Relationships between exposure to each drug and MI. Poisson regression models (GENMOD procedure in SAS software, version 9.1; SAS) were used to quantify the relationship between exposure to each drug and the risk of MI. All *P* values quoted are 2-sided, and results for which $P < .05$ were considered statistically significant. All regression models were also adjusted for patient demographic characteristics (age, sex, HIV transmission group, and ethnicity), calendar year, clinical cohort, cardiovascular risk factors that are unlikely to be associated with use of CART (smoking status, family history of CVD, previous cardiovascular event [including previous MIs],

and body mass index), and exposure to each of the other antiretroviral drugs that was in use over the study period (the 13 drugs listed above, as well as ritonavir when used as a single PI, amprenavir, and atazanavir, which were all also used in smaller numbers of patients). Where numbers were sufficiently large, specific categories were generated for missing data to ensure that all individuals and observed events were included in the analyses. An approximate test of heterogeneity, based on the difference between the log-likelihoods from this main model (which included separate covariates representing exposure to each of the PIs) and a model that included only a covariate for exposure to PIs as a class, was performed to assess whether there was evidence that at least 1 PI drug had an association with MI that was different from the others.

The models described above did not adjust for factors that could lie on the causal pathway between receipt of each drug and the development of MI (eg, lipids and elevated blood pressure). Thus, we explored whether any effects could be mediated through changes in the levels of other risk factors for MI that may be modified by CART, including lipids (total cholesterol, HDL cholesterol, and triglyceride levels [$\log_2$ -transformed]), systolic and diastolic blood pressure, glucose level, the presence of diabetes mellitus, physician-defined lipodystrophy, and the use of lipid-lowering therapy or antihypertensive medication. This was achieved by the incorporation of the latest measurements of these variables as time-updated covariates. All lipid measurements were included, regardless of fasting status. We also considered whether any effects could be explained by different responses of HIV RNA level or CD4⁺ cell count to CART in patients receiving the different drugs by incorporating the latest value for these variables as time-updated continuous covariates.

In our analyses, we assume that the risk of MI associated with exposure to each PI is persistent and does not diminish after discontinuation of that drug. Thus, when a patient discontinues a PI, any follow-up and events continue to be attributed to the level of exposure to the PI at the time of discontinuation. However, if patients at risk of CVD who are receiving drugs thought to be associated with an increased CVD risk are selectively switched away from these drugs, our approach may underestimate the associations of interest. We investigated this possibility by reclassifying any follow-up and events that occurred >6 months after discontinuation of each PI in such a way that they were no longer attributed to the previous drug.

RESULTS

Characteristics of patients with MI. The 33,308 patients contributed a total of 178,835 PYFU to the analysis (median per

person, 5.8 PYFU [interquartile range {IQR}, 3.9–7.5 PYFU]), over which time 580 patients experienced an MI (event rate, 3.2 events per 1000 PYFU [95% confidence interval {CI}, 3.0–3.5 events per 1000 PYFU]). Those experiencing an MI were mostly men (90.7%), white (59.5%), and infected with HIV through sex with men (57.4%) and had a median age at the time of MI of 49 years; cardiovascular risk profiles of the men experiencing an MI, as well as those of all other patients, are shown in Table 1. Of those who experienced an MI, 573 (98.8%) had been exposed to antiretroviral therapy, 114 of whom were not receiving therapy at the time of their MI. The median latest CD4⁺ cell count before the diagnosis of MI and the nadir CD4⁺ cell count were 440 cells/ μ L (IQR, 292–628 cells/ μ L) and 128 cells/ μ L (IQR, 50–240 cells/ μ L), respectively. For over half (302 [52.1%]) of the 580 patients who developed MI, the latest HIV RNA level was <50 copies/mL before the MI. Among all patients experiencing an MI, the 10-year predicted risk of coronary heart disease was known to be high (ie, >20%) in 18.1% and moderate (ie, 10%–20%) in 30.3%; in contrast, only 4.2% and 14.5% of those not experiencing an MI fell into the high- and moderate-risk categories, respectively.

The cardiovascular risk profiles of patients who had ever been exposed to any of the drugs are shown in Table 2 for each drug. Although some differences were apparent in the characteristics of patients exposed to each of the drugs, these differences were not large. Of note, the characteristics of patients exposed to abacavir and tenofovir were similar.

Risk of MI according to exposure to individual drugs. Incidence rates of MI according to cumulative exposure are shown in Figure 1 for the 4 PIs and 2 NNRTIs and in Figure 2 for the 7 NRTIs. Among the PIs, after adjustments (Table 3), there was a significantly increased risk of MI in patients with longer exposure to indinavir (relative rate [RR] per additional year, 1.12 [95% CI, 1.07–1.18]) or lopinavir-ritonavir (RR, 1.13 [95% CI, 1.05–1.21]), but there were no significant associations between MI risk and longer exposure to either nelfinavir (RR, 1.04 [95% CI, 0.98–1.11]) or saquinavir (RR, 1.04 [95% CI, 0.98–1.11]) ($P = .03$ for approximate test of heterogeneity between drugs from the PI class). In the sensitivity analyses, we also considered whether recent exposure to each PI was a stronger predictor of MI risk than was cumulative exposure—this was not the case. There were no significant associations between the development of MI and cumulative exposure to either efavirenz (RR, 1.02 [95% CI, 0.96–1.08]) or nevirapine (RR, 0.97 [95% CI, 0.92–1.03]). Of the NRTIs, the only significant association between MI risk and cumulative exposure was with abacavir (RR, 1.07 [95% CI, 1.00–1.14]); recent exposure to abacavir (RR, 1.70 [95% CI, 1.17–2.47]) or didanosine (RR, 1.41 [95% CI, 1.09–1.82]) were both associated with an increased risk of MI. There were no significant associations be-

Table 1. Cardiovascular Risk Profiles

Characteristic	No. (%) of patients	
	With MI (n = 580)	Without MI (n = 32,728)
Male sex	526 (90.7)	24,143 (73.8)
Age, median years (IQR)	49 (43–65)	44 (38–50)
BMI >26	109 (18.8)	5675 (17.3)
Current smoker	260 (44.8)	9386 (28.7)
Ex-smoker	173 (29.8)	9850 (30.1)
Cardiovascular disease		
In own history	116 (20.0)	823 (2.5)
In family history	79 (13.6)	2707 (8.3)
Diabetes mellitus	96 (16.6)	1730 (5.3)
Hypertension		
Using antihypertensive medication	198 (34.1)	3602 (11.0)
Any hypertension	252 (43.5)	6290 (19.2)
Latest lipid levels		
Total cholesterol level, median mmol/L (IQR)	5.7 (4.7–6.6)	4.8 (4.1–5.6)
HDL cholesterol level, median mmol/L (IQR)	1.1 (0.9–1.3)	1.2 (1.0–1.5)
Triglyceride level, median mmol/L (IQR)	2.2 (1.5–3.9)	1.6 (1.0–2.4)
Using lipid-lowering medication	209 (36.0)	4084 (12.5)
Any dyslipidemia	434 (74.8)	14,506 (44.3)
Lipodystrophy	243 (41.9)	8566 (26.2)
Predicted 10-year CHD risk ^a		
Low (<10%)	152 (26.2)	17,509 (53.5)
Moderate (10%–20%)	176 (30.3)	4740 (14.5)
High (>20%)	105 (18.1)	1371 (4.2)
Not known	147 (25.3)	9108 (27.8)
Categorization of MI ^b		
Definitive	371 (64.0)	NA
Possible	132 (22.8)	NA
Unclassifiable	77 (13.3)	NA
Fatal MI event	148 (25.5)	NA

NOTE. Data are no. (%) of patients, unless otherwise indicated. Risk profiles for patients experiencing a myocardial infarction (MI) were calculated at the time of the first MI experienced during follow-up; those for patients not experiencing an MI were calculated at the time of the last D:A:D follow-up visit. BMI, body mass index (calculated as mass in kilograms divided by the square of height in meters); CHD, coronary heart disease; HDL, high-density lipoprotein; IQR, interquartile range; NA, not applicable.

^a Predicted 10-year CHD risk based on the Framingham equation (patients with a previous cardiovascular event were assumed to have high [>20%] risk).

^b MIs categorized according to the Dundee classification.

tween MI risk and recent exposure to any of the other NRTIs; in particular, there was no association between the risk of MI and either cumulative (RR per year, 1.04 [95% CI, 0.91–1.18]) or recent (RR, 1.14 [95% CI, 0.85–1.53]) exposure to tenofovir.

Table 3 shows the associations between MI risk and recent use of abacavir and didanosine, as well as those between MI risk and cumulative exposure to abacavir, lopinavir-ritonavir, and indinavir after adjustment. Adjustment for these measurements had only minimal effect on the estimates. Further adjustment for latest CD4⁺ cell count and HIV RNA level also did not substantially modify any of the estimates.

Sensitivity analysis. The RR per year of exposure to indinavir when received with ritonavir (22,186 PYFU among individuals exposed to this combination) was 1.18 (95% CI, 1.07–1.30); that for individuals exposed to indinavir without concomitant exposure to ritonavir (57,961 PYFU) was 1.11 (95% CI, 1.05–1.18). Similarly, the RR per year of exposure to saquinavir was 1.06 (95% CI, 0.97–1.14; 24,727 PYFU) when received concomitantly with ritonavir, but it was 1.07 (95% CI, 0.97–1.20; 26,145 PYFU) when received without ritonavir.

When we reran the analyses in such a way that patient follow-up and events occurring >6 months after discontinuation of

Table 2. Cardiovascular Risk Profiles of Patients Exposed to Each of the Drugs under Study

Characteristic	NRTIs						PIs					NNRTIs	
	AZT	ddl	ddC	d4T	3TC	ABC	TDF	IDV	NFV	LPV	SQV	NVP	EFV
No. of patients exposed	25,754	13,851	4951	16,840	28,835	12,511	13,100	11,985	10,370	9995	8070	12,194	13,522
Total follow-up, years ^a	138,108	74,407	29,676	95,320	152,009	53,300	39,157	68,469	56,529	37,136	44,657	61,855	58,946
Male sex	74.4	75.4	77.0	75.1	74.6	75.7	75.1	77.5	71.5	77.0	78.1	74.0	75.7
Age (>45 years for men or >55 years for women)	34.6	35.6	39.0	35.5	34.1	38.2	39.0	38.2	32.7	37.7	39.2	35.7	35.7
BMI >26	18.6	16.0	14.1	16.3	18.9	17.9	18.4	16.7	17.9	17.7	16.1	18.8	18.6
Current smoker	35.4	38.2	38.9	37.0	34.6	33.3	31.4	37.2	36.8	33.1	35.2	30.4	33.4
Ex-smoker	25.9	24.7	25.4	24.9	25.7	26.8	30.7	25.5	23.7	28.0	27.9	29.4	25.2
Family history of MI	8.5	8.7	7.8	8.6	8.4	9.3	9.0	8.8	8.8	8.5	9.0	8.4	9.0
Personal history of CVD	2.2	2.4	3.0	2.4	2.2	2.8	2.5	2.8	2.4	2.4	2.5	2.5	2.4
Diabetes mellitus	5.2	6.0	7.3	6.0	5.1	6.3	6.0	6.3	5.4	5.5	6.1	5.3	6.1
Hypertension	16.0	16.5	16.5	16.6	15.9	17.6	19.1	17.8	16.1	17.1	17.5	16.4	16.9
Dyslipidemia	49.8	54.7	59.0	55.0	49.2	53.4	50.1	55.8	51.8	58.0	58.6	49.4	51.5
Predicted 10-year CHD risk													
10%–20%	13.0	14.6	15.5	14.2	12.7	14.8	15.1	15.3	13.2	15.1	14.9	11.9	14.1
>20% (highest risk)	6.2	6.7	7.6	6.8	6.0	7.0	6.2	7.8	6.4	6.9	6.9	6.0	6.5

NOTE. Data are percentage of follow-up time contributed by patients with each of the characteristics, unless otherwise indicated. 3TC, lamivudine; AZT, zidovudine; BMI, body mass index (calculated as mass in kilograms divided by the square of height in meters); CHD, coronary heart disease; CVD, cardiovascular disease; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; EFV, efavirenz; IDV, indinavir; LPV, lopinavir-ritonavir; MI, myocardial infarction; NFV, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; SQV, saquinavir; TDF, tenofovir.

^a Total follow-up among patients ever exposed to each drug.

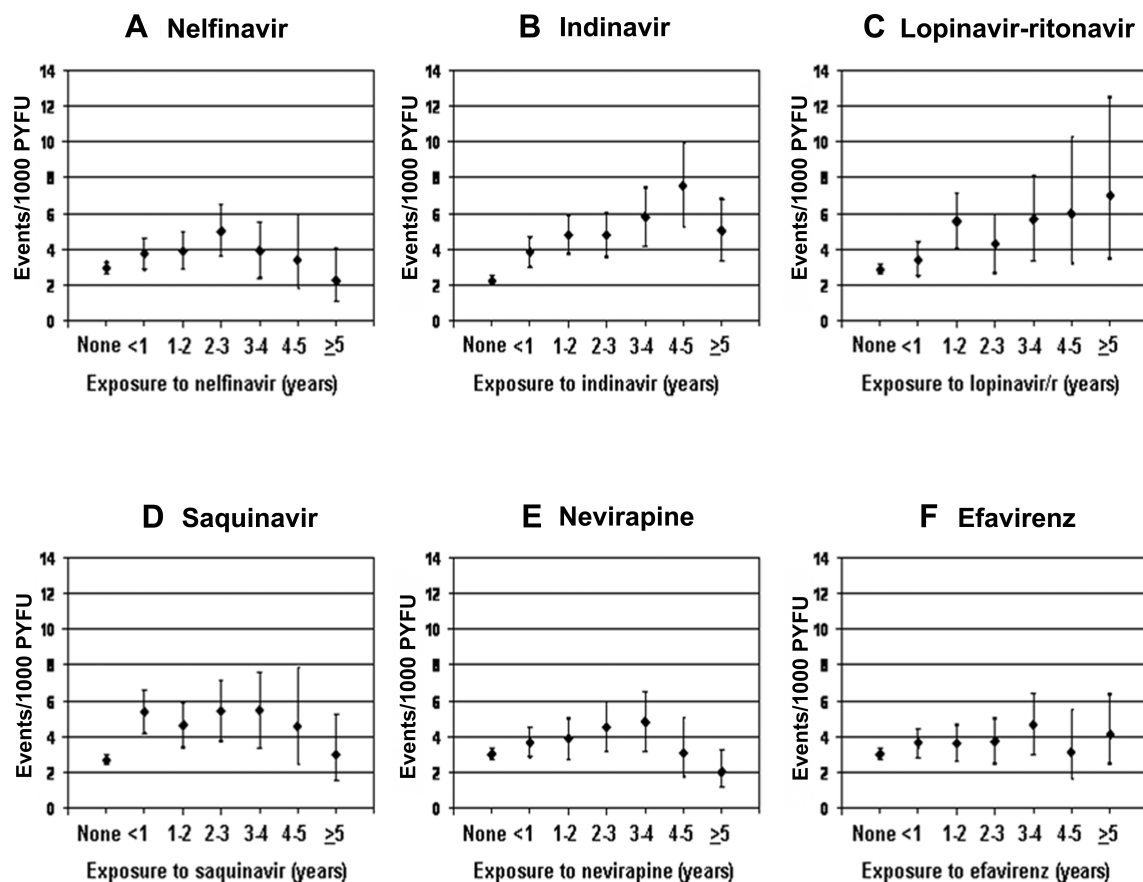


Figure 1. Incidence rates of myocardial infarction according to cumulative exposure to the 4 protease inhibitors (A–D) and 2 nonnucleoside reverse-transcriptase inhibitors (E, F) in this study. The error bars indicate the 95% confidence interval. PYFU, person-years of follow-up.

each PI no longer contributed to the risk associated with those drugs, the estimates from the model were modified only slightly (eg, the RR associated with each year of exposure to lopinavir-ritonavir decreased from 1.13 to 1.12, whereas that for exposure to indinavir increased from 1.12 to 1.14).

DISCUSSION

We examined the association between exposure to 13 antiretroviral drugs from the 3 main drug classes and the risk of MI. Of the drugs examined, cumulative exposure to indinavir (with or without ritonavir boosting), lopinavir-ritonavir, and abacavir, as well as recent exposure to abacavir and, to a lesser extent, didanosine, were each associated with an increased risk of MI. No increased risk of MI was noted with use of other NRTIs, including tenofovir, or with use of efavirenz or nevirapine. As in previous analyses, the associations between MI risk and either lopinavir-ritonavir or indinavir did not appear to be fully explained by an increased risk of dyslipidemia in patients with longer exposure to these drugs.

Of interest, the associations reported for the 2 PIs (12% per

year for indinavir and 13% per year for lopinavir-ritonavir) are both slightly lower than that previously reported from the D:A:D study for the PI drug class as a whole (16% per additional year) [5]. Our previously reported findings were not, however, adjusted for exposure to NRTIs, either as a class or as individual drugs. There are differences between the individual drugs from the PI class in their propensity to cause metabolic disturbances [8–15]. In particular, lopinavir-ritonavir can cause elevated triglyceride levels [9, 18, 19], whereas indinavir (particularly when used with concomitant ritonavir) and saquinavir are both associated with the development of other lipid perturbations [20, 21]. Two recent trials showed that ritonavir-boosted saquinavir was associated with a better lipid profile than was lopinavir-ritonavir [22, 23], although the significant difference between the 2 drugs in the ratio between fasting total cholesterol level and HDL level was not detected at 48 weeks after randomization [23]. The associations that we found between MI risk and exposure to saquinavir were similarly not affected by concomitant exposure to ritonavir. Furthermore, although the reported associations between MI risk and exposure to indinavir and lopinavir-ritonavir were reduced slightly after adjustment for

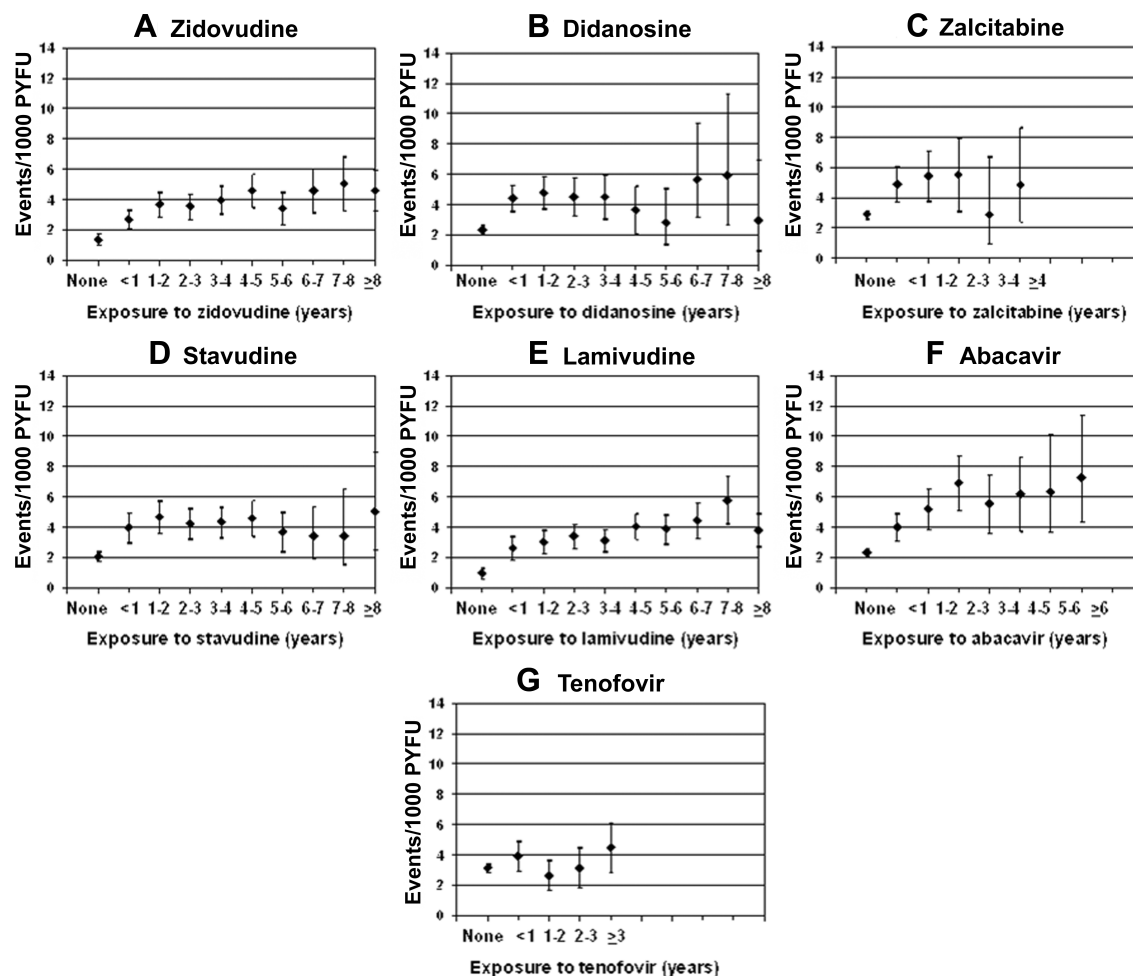


Figure 2. Incidence rates of myocardial infarction according to cumulative exposure to the 7 nucleoside reverse-transcriptase inhibitors in this study. The error bars indicate the 95% confidence interval. PYFU, person-years of follow-up.

changes in lipids, these reductions were small (from 1.12 to 1.08 for indinavir and from 1.13 to 1.09 for lopinavir-ritonavir). Taken together, our results would suggest that the increased risk of MI found in patients receiving these PIs may not solely be a consequence of the dyslipidemia caused by these drugs.

Other possible explanations for the increased risk of MI associated with exposure to some of the PIs may include increased inflammation and coagulation. A recent article reported that the PI drug class was associated with increased levels of fibrinogen [24]. Of interest, in that study the levels of fibrinogen were higher in patients receiving PIs (particularly lopinavir-ritonavir) compared with those receiving NNRTIs.

Although the risk associated with each additional year of exposure to indinavir and lopinavir-ritonavir appears to be modest, the extent of exposure to each drug must be taken into account when assessing individual risk. Our preliminary analyses (Figure 1) demonstrated that the risk of MI increases with longer exposure to each drug, unlike the MI risk associated with NRTIs; because patients are seldom treated with PIs for

only a single year, our estimates will translate into a clinically relevant risk when considered over a longer period of time. For example, our estimates would suggest that 5 years of exposure to lopinavir-ritonavir would be associated with an increased risk of MI of 84%, an excess risk that is roughly equivalent to that associated with aging by 10 years (which is associated with an 80% increased risk of MI in the same analysis).

Newer drugs within the PI class, in particular atazanavir, have been reported to cause fewer lipid perturbations [25, 26] than does lopinavir-ritonavir and has been reported to cause dyslipidemia to an extent similar to that caused by ritonavir-boosted saquinavir [26, 27]. Additional follow-up will allow us to explore the risk of MI associated with atazanavir use, as well as with use of more recently introduced PIs, such as darunavir.

Individual drugs from the NRTIs. As previously reported, we found that recent exposure to abacavir and, to a lesser extent, didanosine were associated with an increased risk of MI. The increased risk associated with recent exposure to abacavir was, however, diminished [6], while at the same time, a slight in-

Table 3. Adjusted Relative Rate (RR) and 95% Confidence Interval (CI) of Myocardial Infarction

Characteristic	RR of myocardial infarction (95% CI)				
	Abacavir, recent exposure	Abacavir, cumulative exposure (per year)	Didanosine, recent exposure	Indinavir, cumulative exposure (per year)	Lopinavir-ritonavir, cumulative exposure (per year)
Estimates from main model	1.70 (1.17–2.47)	1.07 (1.00–1.14)	1.41 (1.09–1.82)	1.12 (1.07–1.18)	1.13 (1.05–1.21)
Further adjustment					
Latest total cholesterol, HDL cholesterol, and triglyceride levels	1.73 (1.33–2.24)	1.07 (1.00–1.14)	1.30 (0.97–1.74)	1.08 (1.02–1.14)	1.09 (1.01–1.17)
Latest glucose level	1.69 (1.34–2.14)	1.07 (1.00–1.14)	1.41 (1.09–1.81)	1.12 (1.06–1.18)	1.13 (1.05–1.21)
Presence of lipohypertrophy and/or lipoatrophy	1.70 (1.35–2.15)	1.07 (1.00–1.14)	1.41 (1.09–1.82)	1.12 (1.07–1.18)	1.13 (1.05–1.21)
Latest systolic and/or diastolic blood pressure	1.71 (1.32–2.22)	1.07 (1.00–1.14)	1.30 (0.98–1.73)	1.10 (1.04–1.16)	1.13 (1.05–1.21)
Presence of diabetes mellitus	1.69 (1.34–2.14)	1.07 (1.00–1.14)	1.39 (1.08–1.80)	1.12 (1.06–1.18)	1.13 (1.05–1.21)

NOTE. Adjusted RR and 95% CI of myocardial infarction associated with cumulative exposure to abacavir, indinavir, and lopinavir-ritonavir and that associated with recent exposure to abacavir and didanosine, before and after adjustment for the latest measurements of various metabolic parameters potentially lying on the pathway between drug exposure and development of myocardial infarction. All estimates also adjusted for age, sex, human immunodeficiency virus (HIV) infection risk group, ethnicity, calendar year, clinical cohort, family history of cardiovascular disease, prior cardiovascular disease, smoking status, and body mass index.

creased risk associated with cumulative exposure to abacavir was found. These changes may simply reflect chance findings, because exposure to this drug has increased (both estimates remain within the CIs previously reported). However, it may be that increased exposure to the drug has allowed us to more accurately capture the risk associated with cumulative exposure to the drug, which was previously undetectable, or that rapid changes in patient management have meant that some of those at highest risk of an MI have already switched away from abacavir to other drugs. Since the publication of our earlier findings on this drug, several studies have presented data to support an association between abacavir use and MI risk [28–30], whereas others have presented data that does not support this association [31, 32]. An explanation for the different findings of these studies remains to be elucidated, although study design (observational vs experimental), patient inclusion criteria, concomitant use of PIs, and duration of follow-up may all play a role.

There have been reports of associations between tenofovir and several renal toxicities [33–35]. However, the drug is thought to cause fewer lipid perturbations than do other NRTIs [36, 37]. In the present analysis, neither cumulative nor recent exposure to the drug was associated with an excess risk of MI, although CIs remain wide, reflecting the relatively recent introduction of this drug into routine use and hence the limited total exposure time. There have been concerns that our findings regarding abacavir exposure may simply reflect channeling bias, whereby individuals at the highest risk of MI (as determined through traditional CVD risk factors) may have been preferentially treated with this drug. Although we have previously provided arguments against this hypothesis [6], our experience suggests that tenofovir has also tended to be used preferentially in individuals with known higher CVD risk (and our present analysis would suggest that the cardiovascular risk factors of those exposed to tenofovir are not markedly different from the risk factors of those exposed to abacavir). Thus, if for some reason our analyses are unable to remove any bias that results from channeling, then we would expect to see an (artifactual) association between MI risk and tenofovir exposure similar to the association found with abacavir exposure. Of note, recent suggestions that the association between MI risk and abacavir may be a consequence of channeling patients at risk of chronic kidney disease (a risk factor for CVD) away from antiretroviral drugs with known adverse effects (particularly tenofovir and indinavir) do not appear to be supported in our study [38].

Individual drugs from the NNRTIs. We did not observe any associations between the development of MI and recent or cumulative exposure to either nevirapine or efavirenz, consistent with previous findings on this drug class [5]. Although efavirenz has been reported to cause elevated triglyceride levels [13, 14, 39], these increases do not appear to translate into an

increased risk of clinical CVD. Recent studies have reported that nevirapine is associated with increases in HDL [40, 41], suggesting that the drug may have beneficial effects on cardiovascular risk. Of note, whereas the relative risk associated with cumulative exposure to nevirapine was <1 , suggesting a possible cardioprotective role, this association was not strong and was not statistically significant ($P = .34$).

Limitations. We did not formally adjust P values to take account of the multiple tests performed. This is in line with many other analyses of cohort studies in which the value of such adjustments is debated [42, 43]. We have focused our attention only on associations that are robust in sensitivity analyses and highly significant, which suggests that they are unlikely to be chance findings. As with any observational study, our findings cannot be assumed to reflect causal associations and must be interpreted cautiously because of the potential for unmeasured confounding. Although an optimal study design would require the use of a randomized trial, the large sample size and follow-up required for such a trial renders it unlikely to be feasible. HIV treatment patterns are complex [44], and any analysis of treatment exposure in an observational study will always reflect a simplification of a more complex reality. Finally, our findings suggest that, within the PI drug class, some PIs (ie, indinavir and lopinavir-ritonavir) are associated with a stronger MI risk than are others. Although an approximate test of heterogeneity suggested some evidence that the different drugs within the PI class do have different propensity to cause MI, the P value from this test was only marginally significant ($P = .02$), and the CIs for the individual estimates do overlap. Thus, additional follow-up will allow us to more fully explore possible differences between drugs within the PI class.

In summary, we examined the risk of MI associated with exposure to individual antiretroviral drugs from 3 major drug classes in this large prospective cohort study. Of the individual drugs examined, indinavir, lopinavir-ritonavir, abacavir, and didanosine were all associated with an increased risk of MI. This risk appeared to increase with cumulative exposure to the 2 PIs and could partly be explained by the dyslipidemia caused by these drugs. In contrast, associations between MI risk and abacavir and didanosine exposure were largely confined to those patients with recent exposure to the drugs and did not appear to be driven by dyslipidemia. The overall rate of MI remains relatively low in this study, and any toxicities of antiretroviral drugs must always be interpreted in the context of the benefits that these drugs provide, but our findings do highlight the need for studies to continue to examine the complications associated with specific antiretroviral drugs.

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