The Journal of Infectious Diseases

MAJOR ARTICLE

Is the Risk of Myocardial Infarction in People With Human Immunodeficiency Virus (HIV) Associated With Atazanavir or Darunavir? A Nested Case-Control Study Within the French Hospital Database on HIV

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(See the Editorial commentary by Triant and Siedner, on pages 498–3.)

Background. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study has reported an increased risk of cardiovascular diseases in people with human immunodeficiency virus who were exposed to darunavir (DRV) but not to atazanavir (ATV). Our objective was to evaluate associations between ATV or DRV exposures and the risk of myocardial infarction (MI) in a nested case-control study within ANRS-CO4 French Hospital Database on HIV (FHDH).

Methods. Cases were individuals who had a first validated MI between 2006 and 2012. Up to 5 controls were selected at random with replacement among individuals with no history of MI, followed at the time of MI diagnosis, and matched for age and sex. Conditional logistic regression models were used to adjust for potential confounders (MI risk factors and HIV-related parameters) and for cumulative exposure to each antiretroviral drug (ARV).

Results. Overall, 408 MI cases and 1250 controls were included: 109 (27%) cases and 288 (23%) controls had been exposed to ATV, and 41 (10%) cases and 107 (9%) controls had been exposed to DRV. There was no significant association between exposure to ATV (adjusted odds ratio [OR] = 1.54; 95% confidence interval [CI], .87–2.73) or DRV (adjusted OR = 0.51; 95% CI, .11–2.32) and the risk of MI.

Conclusions. In FHDH, exposures to ATV or to DRV were not significantly associated with the risk of MI, adjusting for complete ARV history, contrary to the analysis in DAD.

Keywords. antiretroviral drugs; atazanavir; darunavir, HIV; myocardial infarction.

People with human immunodeficiency virus (PWH) have a higher incidence of myocardial infarction (MI) compared with the general population [1–4]. The use of first-generation protease inhibitors (PIs)—indinavir, lopinavir, and amprenavir/fosamprenavir—has been associated with an increased risk of MI [5, 6], but today these PIs are no longer recommended, at least in high-income countries [7]. More recent PIs, atazanavir and darunavir, are potent antiretroviral drugs (ARVs) with more favorable lipid profiles than lopinavir [8, 9]. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, an international PWH multicohort study, has reported an association between exposure to darunavir and the risk of cardiovascular disease (CVD) in PWH, whereas no association was evident with atazanavir [10]. This analysis accounted for exposure to only 3 drugs: lopinavir, indinavir, and abacavir. Earlier analyses in DAD have found these drugs to be associated with an increased risk of CVD [5]. In contrast, a study based on pooled data from 19 Janssen-sponsored clinical trials, postmarketing, and epidemiological data did not suggest an important risk of CVD for users of darunavir [11]. Finally, a cohort study found a reduced risk of CVD with atazanavir versus other PIs including

Received 20 April 2019; editorial decision 3 August 2019; accepted 20 September 2019; published online December 11, 2019.

Presented in part: 22nd International AIDS Conference, July 23–27, 2018, Amsterdam, the Netherlands.

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The Journal of Infectious Diseases® 2020;221:516–22

DOI: 10.1093/infdis/jiz481

darunavir among treatment-naive PWH [12]. In this context of discordant results, and thanks to the large French Hospital Database on HIV (FHDH ANRS CO4), we aimed to evaluate associations between exposure to atazanavir or darunavir and the risk of MI in a nested case-control study within FHDH.

METHODS

The French Hospital Database on HIV

The FHDH is a hospital-based, open multicenter cohort, and inclusion have been ongoing since 1989 [13]. Individuals are eligible if they have documented human immunodeficiency virus (HIV)-1 or HIV-2 infection and give written informed consent to participate. Data are collected prospectively on standardized forms, which include demographic characteristics, the date and type of clinical events recorded according to the *International Disease Classification* (ICD), antiretroviral therapy (ART), and biological markers. The FHDH project has been approved by the French data protection authority (Commission National de l'Informatique et des Libertés on November 27, 1991, Journal Officiel, January 17, 1992).

Study Design

We conducted a case-control study nested in the FHDH and restricted to HIV-1 infected individuals. We chose this approach because of the time-varying nature of ARV use, the large size of the cohort, and the long duration of follow-up. Moreover, compared with a full cohort approach using a survival analysis with time-dependent variables, a nested case-control analysis provides estimates of odds ratios (ORs) from conditional logistic regression models that are unbiased estimates of relative risk [14]. We focused on the 2006–2012 period because atazanavir was available in France beginning in 2002 and darunavir was available beginning in 2006, initially through expanded access programs. During this period, there were 81 294 PWH with at least 1 follow-up visit in the FHDH.

Case Definition

Cases comprised individuals enrolled in the FHDH who had a first prospectively reported MI between January 2006 and December 2012. The diagnosis of MI (ICD I21) was confirmed by a cardiologist (F.B.) who was provided with cardiac signs and symptoms, troponin and/or creatinine kinase levels, and electrocardiographic findings, as recorded in the medical records. We used the American College of Cardiology/European Society of Cardiology definition [15]. Only definite and probable cases of MI and possible death from MI were included. The index date was the date of MI diagnosis.

Selection of Controls

Up to 5 controls enrolled in the FHDH were randomly selected using the incidence density sampling method [16], among individuals with no history of MI, who were under follow-up at the time of MI diagnosis in the corresponding case (±6 months) in the same clinical center, and matched for sex and age (±3 years).

Potential Confounders

It was important to consider pre-existing risk factors for MI that might have influenced the choice of ARV during the study period. Therefore, we explored traditional risk factors unlikely to be on the causal pathway between PI exposure and the risk of MI: body mass index (BMI) (<21/21 ≤ BMI < 24/24 ≤ BMI < 27/≥27), smoker status (no/yes), family history of premature coronary artery disease (CAD), hypertension or antihypertensive treatment (no/yes), current cocaine and/or intravenous drug use (no/yes). We also studied the potential effect of (1) geographic origin (sub-Saharan Africa/other) and (2) the following HIV-related variables on the risk of MI: prior acquired immune deficiency syndrome (AIDS) status, CD4 T-cell nadir, CD4 T-cell count, CD8 T-cell count, CD4 to CD8 T-cell ratio, and viral load (VL). Hypercholesterolemia or hypertriglyceridemia or lipid-lowering treatment and diabetes or antidiabetic treatment, which could be on the causal pathway between ARV exposure and the risk of MI, were collected to be used in sensitivity analyses if a significant association was found between exposure to any ARV and the risk of MI.

Data Collection

The date of MI diagnosis (for cases), sex, age, geographic origin, HIV parameters, and a detailed history of prescribed ARV up to the index date were extracted from the FHDH and validated in the medical records by trained medical assistants using a predefined case report form for both cases and controls. We also collected smoking status, family history of premature CAD, hypertension, antihypertensive medication, diabetes, antidiabetic treatment, hypercholesterolemia (including lipid-lowering treatment), and hypertriglyceridemia from the medical records. All biological parameters were measured within 3 months before the date index.

Statistical Analysis

Characteristics of cases and controls were compared by using univariable conditional logistic regression. Exposure to each ARV was considered as the cumulative duration of exposure per 5 years up to the index date. Conditional logistic regression models were used to quantify the relation between exposure to atazanavir or darunavir and the risk of MI. In a first multivariable model, the exposures of all ARVs were included. In a second multivariable model, we included exposure to all drugs plus the potential confounders. These confounders were classic MI risk factors, geographic origin, and HIV-related variables that differentiated cases and controls. In a sensitivity analysis, diabetes or antidiabetic treatment, hypercholesterolemia (including use of lipid-lowering drugs), and hypertriglyceridemia were added in the multivariable model. To replicate an analysis that is close to that conducted by the DAD study, we performed a sensitivity analysis accounting only for exposures to lopinavir, indinavir, and abacavir. Because parameters with missing data

can influence the results, all values missing for fewer than 50% of individuals were replaced by using a multiple imputation method, and missing values were randomly sampled from their predicted distributions [17]. Ten sets of imputations were used to create 10 complete datasets. All 10 datasets were analyzed and combined with Rubin's rules. SAS software (version 9.4; SAS Institute Inc., Cary, NC) was used for all statistical analyses.

RESULTS

Baseline Characteristics of Participants

Overall, 408 MI cases were validated and matched to at least 1 control (1250 controls, mean of 3 controls per case). Characteristics of cases and controls are shown in Table 1. The median year of MI diagnosis was 2008 (interquartile range [IQR], 2007–2009). At enrollment in FHDH, 81% of participants were ARV naive. In the case population, median age was 49 years and 88% of individuals were men. At the index date, the cases were different from the controls on a majority of HIV-related factors including a lower CD4 nadir, a higher CD8 level, a higher proportion of cases with VL >50 copies/mL, and with a history of AIDS-defining event, and those less likely to be from sub-Saharan origin. The classic MI risk factors were more frequent among the cases, except for obesity. The individuals with BMI <21 kg/m^2 were more frequent among the cases.

At time of MI diagnosis, 27% (n = 109) of cases had been exposed to atazanavir with a mean duration of 2.1 years, a median duration of 1.9 years (10th–90th percentile: 0.1–4.7) and 10% (n = 41) to darunavir with a mean duration of 1.2 years, a median duration of 1.0 year (10th–90th percentile: 0.2–2.5). The corresponding figures for controls were 23% (288) with a mean duration of exposure of 2.0 years, a median duration of 1.7 years (10th–90th percentile: 0.2–4.6) for atazanavir and 9% (n = 107) with a mean duration of exposure of 1.4 years, a median duration of 1.2 years (10th–90th percentile: 0.1–2.7) for darunavir. Ten cases and 34 controls had been exposed to unboosted atazanavir, and 1 case and 4 controls had been exposed to unboosted darunavir. With a total of 408 cases and 1250 controls, the OR that could be detected with 80% power and a 5% type-one error was above 1.65 or below 0.61 for DRV exposure and above 1.45 or below 0.69 for ATV exposure. The potential confounders accounted for in multivariable models were sub-Saharan origin, family history of premature CAD, hypertension, smoker status, current cocaine and/or intravenous drugs use, BMI, VL, CD4 nadir, and CD4/CD8 ratio.

Impact of Atazanavir or Darunavir Exposure on the Risk of Myocardial Infarction

As shown in figure 1, no association was found between atazanavir exposure or darunavir exposure and the risk of MI in all the models including the sensitivity analyses. For atazanavir, the univariable OR was 1.32, the OR adjusted for exposure to other ARVs was 1.39, and the OR in the fully adjusted model was 1.54. The corresponding figures in analyses accounting only for exposure to abacavir, indinavir, and lopinavir were 1.27 and 1.29. For darunavir, the univariable OR was 1.14, whereas the OR adjusted for exposure to other ARVs was 0.61, and the OR in the fully adjusted model was 0.51. The corresponding figures in analyses accounting only for exposure to abacavir, indinavir, and lopinavir were 0.86 and 0.79. It is interesting to note that the OR for darunavir was smaller in the analysis accounting for complete treatment history than in the analysis similar to DAD, ie, accounting only for exposure to lopinavir, indinavir, and abacavir, whereas the reverse was observed for atazanavir. In the models including diabetes, hypercholesterolemia, and hypertriglyceridemia, the ORs were 1.22 (95% confidence interval [CI], .68–1.82) for atazanavir exposure and 0.44 (95% CI, .09–2.05) for darunavir exposure.

DISCUSSION

We found no significant association between the risk of MI in HIV-infected individuals and exposure to atazanavir or darunavir. We used several approaches to minimize biases including the choice of a case-control design nested within the FHDH cohort [14], use of controls matched for age and sex, which are 2 important risk factors for MI [18], as well as adjustment for both HIV-related parameters and classic MI risk factors. These classic risk factors were associated with the risk of MI in our study, supporting the reliability of our data. We did not include recurrent MI to avoid a possible selection bias, because the treatment choice could be influenced by a previous MI. Of note, however, durations of atazanavir and darunavir exposure in those exposed were relatively short with mean duration of 2.1 years and 1.2 years, respectively, with somewhat larger CIs for darunavir. Therefore, we cannot exclude that longer duration of exposure would lead to different results.

In the univariable analysis of the DAD study over the period 2009 to 2016, the univariable incidence rate ratio (IRR) of CVD event per 5 years of darunavir exposure was 1.93 (95% CI, 1.63–2.28) [10], whereas in our study over 2006 to 2011, the univariable OR of MI was 1.14 (95% CI, 0.36–3.59) per 5 years of darunavir exposure. Given our study design (a case-control study nested in a cohort study with incidence density sampling for the selection of controls), the OR provides an estimate of the IRR that is estimated in the DAD study, and one can directly compare the 2 parameters [19]. In both studies, the multivariable analyses accounting for potential confounders allowed us to reduce the IRR of CVD or MI associated with darunavir exposure; however, in the DAD study, cumulative use of darunavir remained associated with an increased risk of CVD. The discrepancy between the 2 studies could be explained by differences in the definitions of the event and/or in the way of accounting for potential confounders and/or by a problem of under notification of CVD diagnosis in DAD. The DAD study assessed the risk of all cardiovascular events including MI, strokes, sudden cardiac deaths, and invasive cardiovascular

Table 1. Characteristics of Participants

Characteristics	Controls (n = 1250)		Cases (n = 408)		*P**
	n, Median	%, [IQR]	n, Median	%, [IQR]	
Age	49	[44–57]	49	[44–57]	
Gender					
Men	1108	88.6	361	88.5	
Women	142	11.4	47	11.5	
Sub-Saharan Origin					
Yes	131	10.5	18	4.4	.0002
No	1119	89.5	390	95.6	
HIV-Related Factors					
HIV-1 Diagnosis Period					
<1997	653	52.2	279	68.4	<.0001
≥1997	597	47.8	129	31.6	
Period of First ARV Initiation					
≤1996	397	34.3	177	45.3	<.0001
>1996	762	65.7	214	54.7	
Not relevant (naive participant)	91		17		
Naive or No Treatment at Index Date					
No	1118	89.4	368	90.2	.6381
Yes	132	10.6	40	9.8	
Naive at Inclusion in the Cohort					
No	222	17.8	99	24.3	.0040
Yes	1028	82.2	309	75.7	
Nadir CD4 (cells/mm^3)[a]	185	[79–299]	161	[60–276]	.0387**
CD4 (cells/mm^3) at index date[a]	495	[357–692]	498	[313–698]	.3664**
CD8 (/mm^3) at index date[a]	837	[594–1130]	914	[620–1328]	<.0001**
CD4/CD8 at index date[a]	0.61	[0.40–0.90]	0.51	[0.33–0.78]	.0003**
Viral load (copies/mL) at index date[a]: >50 copies/mL	304	24.3	127	31.1	.0070**
Prior AIDS Event					
No	902	72.1	268	65.6	.0091**
Yes	348	27.9	140	34.4	
Classical Risk Factors for MI					
BMI[a]					
<21	274	21.9	130	31.8	<.0001**
21 ≤ BMI < 24	405	32.4	152	37.3	
24 ≤ BMI < 27	335	26.8	79	19.4	
≥27	236	18.9	47	11.5	
Smoking Status[a]					
No	617	49.4	78	19.2	<.0001**
Yes	633	50.6	330	80.8	
Family History of Premature Coronary Artery Disease[a]					
No	1137	91.0	329	80.6	<.0001**
Yes	113	9.0	79	19.4	
Hypertension or Antihypertensive Treatment[a]					
No	1032	82.6	304	74.4	.0001**
Yes	218	17.4	104	25.6	
Current Cocaine and/or Intravenous Drug Use[a]					
No	1205	96.4	377	92.3	.0003**
Yes	45	3.6	31	7.7	
Diabetes or Antidiadiabetic Treatment					
No	1162	93.0	370	90.7	.0998
Yes	88	7.0	38	9.3	
Hypercholesterolemia or Treatment[a]					
No	889	71.2	220	53.9	<.0001**
Yes	361	28.8	188	46.1	
Hypertriglyceridemia[a]					

Table 1. Continued

Characteristics	Controls (n = 1250)		Cases (n = 408)		*P**
	n, Median	%, [IQR]	n, Median	%, [IQR]	
No	899	71.9	240	58.7	<.0001**
Yes	351	28.1	168	41.3	
Number of Cardiovascular Risk Factors					
0	207	16.5	3	0.8	
1 or 2	756	60.5	239	58.5	.0003
≥3	287	23.0	166	40.7	

Abbreviations: AIDS, acquired immune deficiency syndrome; ARV, antiretroviral drug; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; MI, myocardial infarction.

*, *P* values by conditional logistic regression.

**, *P* values after imputing missing values.

[a]Number of missing values for CD4 nadir: n = 44; CD4: n = 4; CD8: n = 47; CD4/CD8: n = 47; VL: n = 6; prior AIDS event: n = 3; BMI: n = 33; smoking status: n = 147; family history of premature coronary artery disease: n = 417; hypertension or antihypertensive treatment: n = 1; current cocaine and/or intravenous drug use: n = 2; hypercholesterolemia or treatment: n = 4; hypertriglyceridemia: n = 131.

procedures. However, in DAD, when the analysis was restricted to MI only, the association with darunavir exposure remained significant (multivariable IRR = 1.51; 95% CI, 1.13–2.02). In terms of confounders, the DAD investigators chose to account for exposure to only 3 ARVs (abacavir, lopinavir, and indinavir). This is a potential important bias, because exposure to any antiretroviral may influence more recent exposure and therefore confound the association. It is a strength of our study to have accounted for the complete antiretroviral history. It would be interesting to see whether, similar to our analysis, accounting for complete treatment history in DAD would reduce the risk for darunavir. In the DAD study, the events are reported electronically on specific forms and are centrally validated. However, because centers reporting MI are those caring for HIV infection, some MI case may not have been reported. There is potential for selection bias if physicians tend to more systematically report MI cases exposed to darunavir because of its known impact on lipid profile. In our study, a similar issue may arise, but we checked that control are truly control with no MI prior to the index date and found that 4 of those selected to be control had had an MI and were therefore not elligible to be a control (no MI reported in the database) and eventually found to have had MI, and these were considered as cases in the analysis. The relatively small number of MI in DAD over 2009–2016 (n = 432 with no prior CVD over a median follow-up of 7.0 years in 35 711 participants) compared

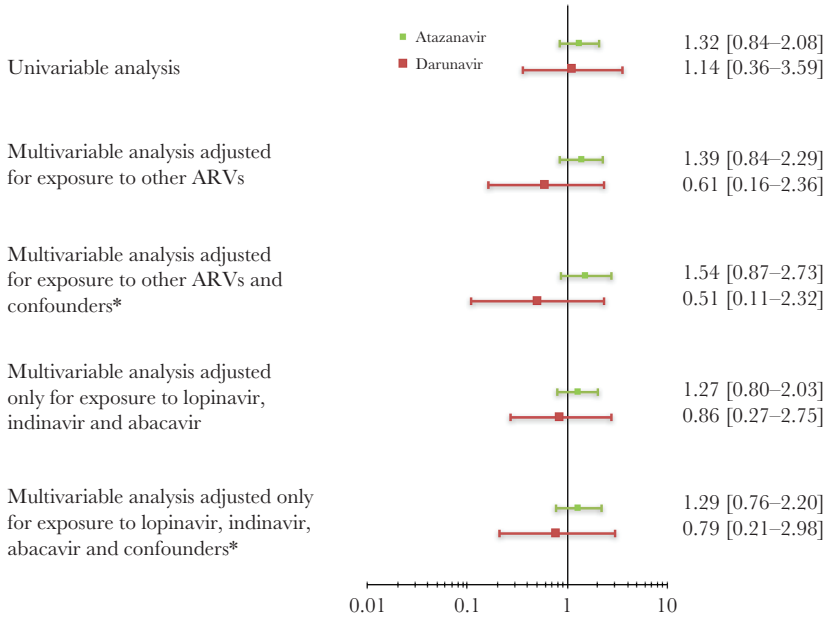

Figure 1. Odds ratios and 95% confidence intervals of the risk of myocardial infarction according to exposure to atazanavir or darunavir. ARV, antiretroviral drug.

with our study over 2006–2011—whereas DAD is conducted in countries that tend to have a higher incidence of MI compared with France—is an indication that this phenomenon of underreporting might be present. Our study design has the advantage to permit the prospective collection of MI cases from all FHDH participating centers, as well as to validate the cases as cases, but also to validate that the controls did not had an MI, which would be very costly in a cohort approach. Finally, one should note that although the direction of the association is different between the 2 studies, the CI for darunavir exposure in the DAD study is completely enclosed in the CI of the present study, and it is possible that the 2 studies are not discrepant.

The study conducted by Janssen, which contains analyses of 19 Janssen-sponsored clinical trials, analyses of postmarketing pharmacovigilance database, and analyses of administrative claim database, does not suggest that a CVD should be considered an important risk for users of darunavir [11]. Regarding the analysis in the study of the US Veterans [12], the authors compared the risk of cardiovascular outcomes in naive PWH initiating ART with a regimen including either atazanavir (n = 1529) or other PIs (n = 2053), in the majority PIs known to be associated with an increased risk of CVD (lopinavir [n = 1087], indinavir [n = 98], and fosamprenavir [n = 169] or amprenavir [n = 11]; for a total of 1365 [66.5%]), and only a limited number of darunavir users (n = 424, 20.7%). Given that, it is difficult to conclude on the risk associated with darunavir exposure from this study.

CONCLUSIONS

In conclusion, in this large, case-control study nested within FHDH, we found no evidence of excess risk of MI after exposure to darunavir or atazanavir, which is reassuring because PIs remain widely used in real-life management of PWH.

Notes

Acknowledgments. We are grateful to all French Hospital Database on HIV (FHDH) participants and research assistants, without whom this work would not have been possible. Members of FHDH-ANRS CO4 are listed at http://www.ccde.fr/main.php?main_file=fl-1171464013-677.html.

Authors' contributions. D. C., S. L., M. M.-K., S. G., and F. B. designed the study. N. d. C., L. C., X. D., C. D., M. P., S. R.-B., A. S., P. T., L. W., D. Z., C. K., and F. R. included patients. S. L. supervised data monitoring. V. P. analyzed the data. V. P. and D. C. drafted the manuscript. All authors interpreted the data, provided critical revision of the manuscript, and approved the final version.

Financial support. FHDH is funded by France Recherche Nord&Sud Sida-hiv Hépatites (ANRS), Institut National de la Santé et de la Recherche Médicale (INSERM), and the French Ministry of Health. This work was funded by ANRS.

Potential conflict of interests. D. C. received fees for lectures from Janssen-Cilag, MSD, and Gilead and fees as a consultant for Merck Switzerland. Her team received grants for conducting postmarketing studies for Janssen-Cilag and MSD. S. L. received travel grants from Boehringer Ingelheim. N. d. C. received research grants from Gilead. L. C. received fees for registration to conferences and travel expenses from Abbvie, BMS, Gilead Sciences, Janssen-Cilag, and MSD. X. D. received fees for consultancy from Sanofi-Pasteur and research grants from Pfizer. C. D. received travel grants, honoraria, or study grants from various pharmaceutical companies, including Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. S. R.-B. received fees as a member of the French Janssen board. A. S. received fees as a member of the French Gilead HIV board and for lectures from Gilead and ViiV Healthcare. P. T. sporadically works as a consultant for Gilead and MSD. L. W. received a research grant from Pfizer for participating in a cohort study (2016–2018) and fees from MSD for lectures and participation in a scientific board for an immunological symposium (2001–2019). C. K. received the following: fees for consultancy or boards from Janssen, MSD, and ViiV Healthcare; fees for lectures from MSD and Viiv Healthcare; and research grants from Janssen, MSD, and ViiV Healthcare. F. R. received research funding or honoraria from or consulted for Gilead Sciences, Janssen, Merck, MSD, Theratechnologies, and ViiV Healthcare. F. B. reports research grants from Amgen (2017) and lecture fees from Janssen (2017, 2018), Gilead (2015–2018), ViiV Healthcare (2018), Amgen (2015–2018), Sanofi (2016–2018), MSD (2017, 2018), and Servier (2018). All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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