HHS Public Access

Author manuscript

JAMA Cardiol. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

JAMA Cardiol. 2017 March 01; 2(3): 260–267. doi:10.1001/jamacardio.2016.5139.

Types of myocardial infarction among HIV-infected individuals in the United States

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Abstract

Importance—The Universal Definition of Myocardial Infarction divides myocardial infarctions into different types. Type 1 myocardial infarctions result spontaneously from atherosclerotic plaque instability, whereas Type 2 myocardial infarctions occur in the setting of oxygen demand/supply mismatch such as with severe hypotension. Type 2 myocardial infarctions are uncommon in the general population but the frequency of Type 2 myocardial infarctions in HIV-infected individuals is unknown.

Objective—To characterize myocardial infarctions including type; identify causes for Type 2 myocardial infarctions, and compare demographic and clinical characteristics among HIV-infected individuals with Type 1 vs. Type 2 myocardial infarctions.

Setting/Design—Longitudinal HIV clinical care cohort at 6 U.S. sites.

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The following have no conflicts of interest to report: H Crane, P Crane, Kitahata, Rodriguez, Drozd, Mathews, Napravnik, Moore, Nance, Peter, Crothers, Feinstein, Delaney, McReynolds, Heckbert, Peter, Paramsothy, Geng, Barnes, Grunfeld, and Lober. The following have received grant support or served as consultants: Dr Hunt with Merck and Gilead, Dr. Greer with DefiniCare, Dr. Willig with DefiniCare, BMS, Gilead, Pfizer, and Tibotect, Dr. Saag with BMS, BI, Abbvie, Gilead, Merck, and ViiV, Dr. Mugavero with BMS, Gilead, Merck, Pizer, DefiniCare, Dr. Eron with Merck, Glaxo Smith Kline, ViiV, BMS, Abbvie, Gilead, Tibotec/Janssen, Dr. Hsue with Gilead and Pfizer, and Dr. Budoff has consulted for General Electric.

This work was presented in part at the 19th Conference on Retroviruses and Opportunistic Infections.

Events—Potential myocardial infarctions from 1996–2014 were identified in the centralized data repository using diagnoses and cardiac biomarkers. Sites assembled de-identified packets including physician notes, ECGs, procedure and clinical laboratory results. Two physician experts adjudicated each event, categorizing each definite/probable myocardial infarction as a Type 1 or Type 2 myocardial infarction, and identifying Type 2 myocardial infarction causes.

Results—Among 571 definite/probable myocardial infarctions, 288 (50%) were Type 2; sepsis and recent cocaine/crack use were the most common causes (35% and 14% of Type 2 myocardial infarctions, respectively). Individuals with Type 2 myocardial infarctions were younger on average and had lower CD4 cell counts, lipid levels, and Framingham risk scores than those with Type 1 myocardial infarctions.

Limitations—Missing events or ascertainment bias is always a concern although we used both diagnoses and biomarkers to minimize this as much as possible. In addition, although we used a standardized approach with multiple expert adjudicators, distinguishing MI type with certainty can be difficult and there may be some misclassification of type.

Conclusions/Relevance—Approximately half of myocardial infarctions among HIV-infected individuals were Type 2. Type 2 myocardial infarctions were caused by heterogeneous clinical conditions including sepsis and cocaine/crack use. Demographic characteristics and cardiovascular risk factors among those with Type 1 and Type 2 myocardial infarctions differed, suggesting the need to specifically consider type among HIV-infected individuals to further understand myocardial infarction outcomes and to guide prevention and treatment.

Introduction

There are many unanswered questions regarding the risk of cardiovascular disease (CVD) including myocardial infarction (MI) in HIV-infected individuals. Studies have suggested that MI rates may be higher in HIV-infected vs. uninfected individuals[1–4]. HIV may impact lipid levels and endothelial function, leading to increased CVD risk[5–7]. Antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality[8–11] but some, particularly older ART agents, may increase CVD risk[12–15]. Many previous studies have used unadjudicated MI outcomes and have not differentiated MI types. These limitations may have contributed to conflicting findings regarding CVD risk in HIV-infected populations[1,16,17].

The Universal Definition of MI classifies MI into 5 types according to the underlying mechanism of myocardial ischemia[18]. Type 1 MI events (T1MI) result spontaneously from atherosclerotic plaque instability. Type 2 MI events (T2MI) are secondary to causes other than atherosclerotic plaque rupture, including hypotension, hypoxia, and stimulant induced spasm resulting in increased oxygen demand or decreased supply. Type 3 MIs are deaths occurring with symptoms suggestive of MI and cardiac biomarkers were not measured. Type 4 and 5 MIs occur in the setting of coronary revascularization procedures. Different MI types may portend a different prognosis and optimal medical management approach[19].

Studies are needed to understand the impact of HIV and its treatment on the frequency of MI and MI types. Understanding MI types will require clearly defined clinical endpoints with accurate event identification and categorization. We developed an MI adjudication protocol

in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort[20]. We conducted this study to characterize MIs by type in a large and diverse cohort of HIV-infected individuals. We were interested in whether demographic and clinical characteristics including CVD risk factors would be similar for HIV-infected individuals with T1MI and T2MI. While estimates of T2MI incidence vary in the general population, T2MIs account for a minority of MIs[21–28]. We hypothesized that T2MIs in HIV may be common and would have distinct demographic and clinical characteristics including CVD risk factors compared with those with T1MI. If confirmed, these hypotheses would lend support to the idea that T1MI and T2MI are distinct clinical entities that represent different biological phenomena and should be treated as such among those with HIV.

Methods

Study cohort

The CNICS cohort includes HIV-infected individuals receiving care at 8 clinical sites across the United States[29]. Individuals who had an incident MI between 1/1/1996, and 3/1/2014 from 6 sites (Johns Hopkins University; University of Alabama at Birmingham; University of California at San Diego; University of California at San Francisco; University of North Carolina at Chapel Hill; and University of Washington) were included in analyses. Sites received institutional review board approval for CNICS and written informed consent was obtained from participants.

Data Source

The CNICS data repository integrates comprehensive clinical data from all outpatient and inpatient encounters[29]. These data include laboratory test results such as cardiac biomarkers and lipid values; medications such as those used for diabetes, dyslipidemia, and hypertension; blood pressure values; and diagnoses[29].

MI events

Potential MIs were identified retrospectively in the CNICS data repository by the presence of a clinical MI diagnosis or coronary intervention such as coronary artery bypass graft (CABG) or elevated troponin or CK-MB values[20]. For each potential MI, the site assembled de-identified packets that included available physician notes, ECGs, results from imaging studies, and laboratory results. These packets enabled adjudicators to review primary clinical data, eliminating errors that could potentially arise from local completion of case report forms. The names of antiretroviral medications were redacted to eliminate the possibility that knowledge of specific medications would influence evaluations of the potential MI. Two expert physician adjudicators independently reviewed each packet, followed by a 3rd reviewer if needed to resolve discrepancies. Reviewers considered ECGs, cardiac biomarker values, documented chest pain without another suggested cause, and wall motion abnormalities if imaging such as ventriculogram results were available. ECG criteria included the presence of evolving Q-waves, ST-elevations, and new left bundle branch block (LBBB) with different algorithms in the setting or absence of chest pain and cardiac biomarker elevations to determine Definite, Probable, or No MI. For example, a new LBBB would be classified as a Definite vs. Probable MI based on abnormal vs. equivocal cardiac

biomarkers. Reviewers entered standardized data into a web application regarding all MI criteria met including type of ECG abnormalities. Reviewers entered additional risk factor information including family history of CVD that was not already in the CNICS data repository.

Reviewers identified events that were likely falsely positive rather than true MIs. They identified specific potential reasons for false positive results such as isolated cardiac biomarker elevations without other evidence for MI in the setting of renal failure or pericarditis.

Reviewers categorized events as T1MI or T2MI, and identified potential causes for T2MI based on the clinical scenario such as an MI occurring while septic[20]. Patients with type 3 MI were not included because by definition, cardiac biomarkers are unavailable. There were only 3 MIs that occurred in the setting of cardiac procedures, so Type 4 and 5 MIs are not further described. Reviewers also identified patients who did not meet criteria for an MI but had a coronary intervention including CABG surgery, percutaneous transluminal coronary angioplasty (PTCA), or stent placement. If an individual had both an MI and a coronary intervention as part of their incident event, the event was categorized by MI type. Only an individual's first MI was included.

Statistical Analysis

We used Chi-squared and t-tests for categorical and continuous variables to assess differences in demographic and clinical characteristics among individuals with T1MI or cardiac intervention versus T2MI. We considered age, sex, self-reported race/ethnicity and risk factor for HIV transmission, body mass index (BMI) closest to the MI, CD4 cell count and HIV-1 viral load (VL) closest to the MI, and CD4 nadir and peak HIV VL. We considered the most recent lipid values prior to the MI including total cholesterol (TC), high density lipoprotein cholesterol (HDL), non-high density lipoprotein cholesterol (non-HDL), low density lipoprotein cholesterol (LDL), and triglycerides. We also considered statin and anti-hypertensive medication use. As in prior studies[30], we defined diabetes based on any of the following criteria prior to the MI: a) hemoglobin A1c ≥6.5 OR b) use of a diabetes-specific medication such as insulin OR c) use of a diabetes-related medication frequently but not exclusively used to treat diabetes (e.g. biguanides) in the setting of also having a diabetes diagnosis[30]. A diabetes diagnosis alone did not meet the definition. We computed and compared 10-year coronary heart disease (CHD) risk scores from the Framingham Risk Assessment Tool[31] using mean and categorical scores (≤10 low risk, 10–20 intermediate risk, and ≥20 high risk). We examined smoking status.

We also conducted a sensitivity analysis comparing those with T1MI with individuals who had a coronary intervention without an MI.

Results

Of 26,909 HIV-infected patients evaluated during the ascertainment period, 1689 met ascertainment criteria for a potential MI at least once. Among these, 571 (28% of 2037) events were adjudicated as an MI, of which 65% (370/571) were classified as Definite MI,

and 35% (201/571) as Probable MI. Among the definite/probable MIs, 50% were T1MI and 50% T2MI. An additional 79 (4%) events did not meet MI criteria, but patients had severe enough atherosclerotic disease that they underwent a coronary intervention such as a CABG. Among those with an adjudicated MI, 77% were men, and the median age was 49 (interquartile range IQR 43–55), and the current median CD4 cell count was 326 cells/mm^3 (IQR 136–571). The current CD4 count was drawn a median of 47 days before the MI (IQR 15–108 days).

A higher proportion with a T2MI were under 40 years of age, female, African-American, not on ART, and their HIV transmission risk factor was intravenous drug use compared with those with a TIMI (Table 1).

A higher proportion of those with a T2MI also had a low CD4 count and high HIV VL compared with those with a T1MI (Table 1) with a median current CD4 cell count of 230 cells/mm^3 vs. 383 cells/mm^3 for those with a T1MI.

Diabetes and hypertension were equally prevalent among those with T1MI vs. T2MI (Table 2). However, a higher proportion of individuals with a T1MI were receiving a statin prior to the event and had higher mean TC, non-HDL, and LDL levels compared with those who had a T2MI. Individuals with a T1MI were also more likely to be current smokers. Those with a T1MI had a higher mean 10-year Framingham CHD risk score than those with a T2MI (Table 2). Intermediate Framingham risk scores were present in 21% of those with T1MI vs. 16% with T2MI, and high-risk scores were present in 12% of T1MI vs. 8% of T2MI (p value=0.047).

Sepsis (35%), cocaine or other drug-induced vasospasm (14%) and hypertensive emergency (10%) were the most frequently identified likely causes of T2MI (Table 3). A diverse array of clinical conditions were identified for the remaining T2MIs.

Compared with patients with a T1MI, those with a coronary intervention without meeting MI criteria were more likely to be male, had a lower VL, and a higher 10-year Framingham CHD risk score but did not differ on other HIV-specific or CVD risk factors from those with a T1MI (eTables 1–2).

Discussion

We examined MI types in a large, nationally distributed HIV cohort. T2MIs were common, comprising half of MIs. We identified characteristics that differed between individuals with T1MI and T2MI. On average, individuals who had a T2MI were younger, had a lower CD4 count and higher VL, and fewer traditional CVD risk factors including less dyslipidemia, lower current smoking rates, and lower CHD risk scores. Individuals with a T2MI were significantly different from those with T1MI with regard to demographic and clinical characteristics, particularly CVD risk factors. Our results suggest that in HIV-infected individuals, T1MI and T2MI may represent distinct clinical entities that require different approaches to prevention and treatment, as noted in the general population[19]. This study is the first to report a high proportion of T2MI occurring among HIV-infected individuals.

T1MI vs. T2MI in HIV-infected vs. other populations

Distinguishing T1MI from T2MI has been recommended since 2007 by the second Universal Definition of MI[18] and endorsed by major cardiology societies[32] but can be challenging[19]. Categorization of MI by type has increased over time, but the International Classification of Diseases (ICD) coding system lacks distinct categories for T2MI[32] likely limiting capture in clinical settings. However, non-specific ICD-9 411.89 and ICD-10 I24.8 codes “other acute and subacute forms of ischemic heart disease” have been used for this purpose[33]. Lack of data on MI type has been attributed to the relatively recent introduction of the Universal Definition of MI, presumed under-reporting of T2MI, and lack of consistency in T2MI criteria[32].

Despite these limitations, studies have found that T2MI are much less common than T1MI in most populations consisting of <2–26% of MIs, depending on adjudication methodology and population[22–28], usually <10% of all MIs[23–28]. In a Danish study of hospitalized patients, there were 541 MIs of which 26% were T2MI[22]. In contrast, the proportion of T2MI in our HIV population was almost twice as high as the Danish study. This may be due to an increased likelihood of bacteremia and infections resulting in sepsis and increased prevalence of cocaine use in those with HIV. In addition, the Danish study did not exclude individuals with prior MI: 27% in the Danish study with T2MI had a history of a prior MI, 17% prior PCI, and 10% prior CABG. In contrast, we focused on initial events. While more data are needed, our findings suggest that the proportion of T2MI among HIV-infected individuals is higher than in many other populations. These differences have important clinical implications[19]. Prevention and treatment of atherosclerotic CVD, including statin use, anti-platelet agents, and coronary procedures have been studied and disseminated in T1MI guidelines however optimal management and prevention of T2MIs is unclear.

Causes of T2MI

We found that almost half of T2MIs were in the setting of sepsis or illicit drug-induced vasospasm, most often cocaine. Cocaine increases myocardial oxygen demand by increasing blood pressure, heart rate, and myocardial contractility and can also decrease myocardial blood supply by inducing coronary vasoconstriction[34]. Factors that lead to T2MI have not been well characterized in the general population. The most common presumed T2MI causes in the Danish study were anemia, arrhythmias, and respiratory failure[22]. A New York study found surgery, anemia, and sepsis were common[33]. Arrhythmias were also a common presumed T2MI cause in several general population studies[21,28,35]. In contrast, we found sepsis and cocaine use were common with T2MI. These results suggest that HIV-infected individuals have a very different set of presumed T2MI causes than the general population[21,28,35].

T1MI vs. T2MI

We found substantial differences in demographic and clinical characteristics among HIV-infected individuals who experienced a T1MI vs. T2MI. Higher proportions with a T2MI were younger, female, and had poorer control of their HIV infection as measured by current CD4 and VL. This contrasts with HIV-uninfected population studies in which patients with T2MI were older than those with T1MI[21,28]. In the general population, people with T2MI

tend to be seriously ill. We similarly found that those with a T2MI tended to be sicker in terms of HIV status than those with a T1MI.

Adjudication

Central adjudication is preferable to local adjudication with or without secondary central review[20]. Clinical MI definitions have changed over time[36]. In particular, events that used to be characterized as unstable angina would now be considered an MI. We therefore ascertained potential MIs using cardiac biomarkers in addition to diagnoses. While diagnoses alone such as from billing data are commonly used for ascertainment, possibly with concomitant verification using other data elements[4,16,37–40], the sensitivity of this approach is not optimal[41]. We have previously demonstrated that using clinical diagnoses alone results in missing substantial numbers of T2MI in particular[20]. This is not surprising since there is no relevant ICD code to document myocardial injury due to severe extra-cardiac causes such as sepsis[32,42]. Experts have advocated the development of distinct T2MI diagnostic codes[19]. Studies with cardiac biomarkers in their ascertainment criteria therefore likely do a better job capturing T2MIs vs. those that rely on diagnoses alone. It is worth noting that the Universal MI Definition has not established what is a significant level of hypertension, hypotension, etc. therefore T2MI must rely on clinical judgment[21].

Strengths

CNICS is large and geographically and ethnically diverse with comprehensive clinical data. We ascertained for potential events using both abnormal cardiac biomarkers and clinical diagnoses in order to increase the sensitivity of ascertainment and more fully capture the MI burden in HIV. However, this may make comparing rates of T2MI to other cohorts with a less sensitive approach challenging. Adjudication facilitates capturing MI type and potential causes of T2MI.

Limitations

Our study has limitations. Silent T1MI can be missed and T2MI may be missed in critically ill people in whom cardiac biomarkers are not assessed. We did not systematically examine ECGs to identify silent events, however this approach has been shown to have a low detection probability[43]. Ascertainment may be incomplete for events that occur outside CNICS sites although we request medical records. We used troponin assays, however they have become more sensitive over time and are not biologically equivalent due to biochemical differences in assays and reference populations used to determine upper reference limits[44]. While we categorized MI by type using carefully reviewed clinical data, there is debate regarding what criteria should be used to categorize an event as T2MI[32] and correctly classifying falsely positive events vs. T2MI can be difficult. However, events were reviewed independently by two physicians, and resolved by a third reviewer in case of disagreement, ensuring consistency in our approach to diagnosis and classification. Cardiac catheterization to verify obstructive coronary disease was frequently not done for T1MI and rarely done for T2MI. It is therefore unknown whether most of those with T2MI had obstructive disease. Lastly, because our study is the first to describe MI types in HIV, the findings have not been replicated although the pattern of ~ half T1MI vs. T2MI was seen across the 6 CNICS sites.

Future studies

T2MI are increasingly recognized in the general population and additional research is needed to better define and manage these events[45]. The importance of applying ECG classifications such as ST segment elevation MI (STEMI) vs. non-ST segment elevation MI (NSTEMI) to categorizing T2MI is unclear as these classifications are intended to help guide clinical reperfusion therapy decisions in T1MI[32].

Research is needed to better understand the complex relationship between traditional and HIV-specific CVD risk factors, the genetic predisposition to develop MI and the potential interactions with ART, and the role of behavioral factors. Further evaluation to understand the role of sepsis and risk for T2MI is needed. Such information can guide interventions to alter these relationships and improve prognosis, as well as improve risk prediction and risk-reduction strategies. Differentiating MI type is important clinically as it is likely that optimal interventions, such as use of anticoagulation therapy, will differ by type. It is unclear if T1MI or T2MI will decrease in the current era now that ART initiation is earlier and with potentially less metabolically active regimens. Classification of MI type will result in a better understanding of these important outcomes among those with HIV.

Conclusions

Our large cohort study of HIV-infected individuals across the US demonstrates that approximately half of MIs are T2MI. Individuals with T2MI were younger and sicker in terms of their HIV but with lower Framingham CHD risk scores than those with T1MI suggesting these events may be due to different mechanisms among different populations. These findings have important implications for studying MIs, understanding the higher MI rates and extent MI burden can be reduced by CVD risk factor modification among HIV-infected individuals, particularly given the unknown role, if any, of atherosclerosis in T2MI. Understanding MI types may help clarify unanswered questions regarding risk factors, risk scoring, and prognosis. Most importantly, these findings are important clinically, as T1MI and T2MI may require different approaches for prevention and treatment in HIV-infected individuals.

Acknowledgments

This work was supported by grants from the National Institutes of Health including R01HL126538, R561HL126538, R01HL125027, the CNICS grant (R24 AI067039), the UW Center for AIDS Research CFAR Grant (AI27757), UNC CFAR grant (AI50410), UAB CFAR grant (AI027767), Johns Hopkins CFAR grant (AI094189), and the American Heart Association Grant-in-Aid Grant (09050129G). The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr. Heidi Crane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms. Nance and Dr. Delaney conducted the analyses.

Funding sources: This work was supported by grants from the National Institutes of Health including R01HL126538, R561HL126538, R01HL125027, the CNICS grant (R24 AI067039), the UW Center for AIDS Research CFAR Grant (AI27757), UNC CFAR grant (AI50410), UAB CFAR grant (AI027767), JHU CFAR grant (AI094189), and the American Heart Association Grant-in-Aid Grant (09050129G). The funding agreements ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

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Table 1

Clinical and demographic characteristics of HIV-infected individuals with T1MI vs. T2MI

Characteristic	T1MI* N=362 N (%)	T2MI N=288 N (%)	P-value
Sex			0.006
Male	293 (81)	207 (72)	
Female	69 (19)	81 (28)	
Age, years			0.01
<40	32 (9)	47 (16)	
40–49	152 (42)	106 (37)	
50–59	125 (35)	99 (34)	
60–69	43 (12)	22 (8)	
≥70	10 (3)	14 (5)	
Race/Ethnicity			<0.001
White	171 (47)	65 (23)	
African-American	156 (43)	202 (70)	
Hispanic	19 (5)	14 (5)	
Other/unknown	16 (4)	7 (2)	
HIV Transmission Risk Factor			<0.001
Heterosexual	101 (28)	93 (32)	
Men who have sex with men	166 (46)	75 (26)	
Injection drug use	78 (22)	107 (37)	
Other/unknown	17 (5)	13 (5)	
Antiretroviral therapy			<0.001
Yes	271 (75)	154 (53)	
No	91 (25)	134 (47)	
CD4 count closest to event (cells/μl)			<0.001
0–200	94 (26)	128 (44)	
201–350	72 (20)	57 (20)	
>350	195 (54)	103 (36)	
CD4 cell count nadir (cells/μl)			0.02
0–200	212 (59)	199 (69)	
201–350	79 (22)	48 (17)	
>350	70 (19)	41 (14)	

Characteristic	T1MI* N=362 N (%)	T2MI N=288 N (%)	P-value
HIV-1 RNA closest to event			<0.001
<400	217 (60)	127 (44)	
400–10,000	47 (13)	49 (17)	
10,000–100,000	63 (17)	59 (20)	
>100,000	34 (9)	53 (18)	
HIV-1 RNA, peak			0.02
<400	43 (12)	20 (7)	
400–10,000	35 (10)	31 (11)	
10,000–100,000	112 (31)	70 (24)	
>100,000	171 (47)	167 (58)	

* T1MI also includes patients with coronary interventions

One patient was missing CD4 and VL data prior to the MI and was excluded from those rows

Table 2

Cardiovascular disease risk factors among HIV-infected individuals with MI by MI type (T1MI vs. T2MI)

Characteristic	T1MI* N=362 N (%)	T2MI N=288 N (%)	P-value
Diabetes (N, %)			0.5
No	286 (79)	221 (77)	
Yes	76 (21)	67 (23)	
Blood pressure mean (mean, SD)			0.3
Systolic (mmHg)	132 (23)	130 (24)	
Anti-hypertensive medication (N, %)			0.6
No	164 (45)	124 (43)	
Yes	198 (55)	164 (57)	
Lipid Levels mean (mean, SD)			
HDL (mg/dL)	40 (15)	42 (19)	0.2
LDL (mg/dL)	108 (43)	87 (40)	<0.001
Non-HDL (mg/dL)	149 (52)	125 (60)	<0.001
Total Cholesterol (mg/dL)	190 (54)	167 (63)	<0.001
Triglycerides (mg/dL)	227 (182)	208 (272)	0.4
Statin use (N, %)			<0.001
No	244 (67)	232 (81)	
Yes	118 (33)	56 (19)	
Smoking (N, %)			0.005
No	125 (35)	136 (47)	
Former	56 (15)	36 (13)	
Current	181 (50)	116 (40)	
Body mass index (mean, SD)			
BMI (kg/m^2)	26 (5)	24 (6)	0.001
Risk Score (mean, SD)			<0.001
Framingham CHD (% 10 year event risk)	10 (8)	8 (7)	

*T1MI also include cardiac interventions such as coronary artery bypass graft (CABG) surgery

HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; non-HDL; non-high density lipoprotein cholesterol

Table 3

Most likely causes for Type 2 MI among HIV-infected individuals

Cause	Number, %
Sepsis/bacteremia	100, 35
Cocaine or other illicit drug induced	39, 14
Hypertensive urgency/emergency	28, 10
Respiratory failure	26, 9
Non-coronary cardiac *	23, 8
Other/unknown	16, 6
Hypotension **	15, 5
Procedure related ***	12, 4
GI bleed	11, 4
Neurologic	6, 2
Overdose	5, 2
Anemia	4, 1
Rhabdomyolysis	3, 1

* Non-coronary cardiac causes include non-atherosclerotic causes such as related to a congestive heart failure and cardiac tumor

** Hypotension not due to sepsis, GI bleed, overdose or other listed causes

*** These are not cardiac procedures (which typically get classified as a Type 4 MI), instead these are events that occur in the setting of surgeries such as abdominal surgery and lower extremity amputation