

# Types of Myocardial Infarction Among Human Immunodeficiency Virus–Infected Individuals in the United States

Heidi M. Crane, MD, MPH; Pathmaja Paramsothy, MD; Daniel R. Drozd, MD; Robin M. Nance, MS; J. A. Chris Delaney, PhD; Susan R. Heckbert, MD, PhD; Matthew J. Budoff, MD; Greer A. Burkholder, MD; James H. Willig, MD; Michael J. Mugavero, MD; William C. Mathews, MD; Paul K. Crane, MD, MPH; Richard D. Moore, MD, MHA; Joseph J. Eron, MD; Sonia Napravnik, PhD; Peter W. Hunt, MD; Elvin Geng, MD; Priscilla Hsue, MD; Carla Rodriguez, PhD; Inga Peter, MD; Greg S. Barnes, MS; Justin McReynolds, MS; William B. Lober, MD; Kristina Crothers, MD; Matthew J. Feinstein, MD; Carl Grunfeld, MD; Michael S. Saag, MD; Mari M. Kitahata, MD, MPH; for the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort

 Supplemental content

**IMPORTANCE** The Second Universal Definition of Myocardial Infarction (MI) divides MIs into different types. Type 1 MIs result spontaneously from instability of atherosclerotic plaque, whereas type 2 MIs occur in the setting of a mismatch between oxygen demand and supply, as with severe hypotension. Type 2 MIs are uncommon in the general population, but their frequency in human immunodeficiency virus (HIV)–infected individuals is unknown.

**OBJECTIVES** To characterize MIs, including type; identify causes of type 2 MIs; and compare demographic and clinical characteristics among HIV-infected individuals with type 1 vs type 2 MIs.

**DESIGN, SETTING, AND PARTICIPANTS** This longitudinal study identified potential MIs among patients with HIV receiving clinical care at 6 US sites from January 1, 1996, to March 1, 2014, using diagnoses and cardiac biomarkers recorded in the centralized data repository. Sites assembled deidentified packets, including physician notes and electrocardiograms, procedures, and clinical laboratory tests. Two physician experts adjudicated each event, categorizing each definite or probable MI as type 1 or type 2 and identifying the causes of type 2 MI.

**MAIN OUTCOMES AND MEASURES** The number and proportion of type 1 vs type 2 MIs, demographic and clinical characteristics among those with type 1 vs type 2 MIs, and the causes of type 2 MIs.

**RESULTS** Among 571 patients (median age, 49 years [interquartile range, 43–55 years]; 430 men and 141 women) with definite or probable MIs, 288 MIs (50.4%) were type 2 and 283 (49.6%) were type 1. In analyses of type 1 MIs, 79 patients who underwent cardiac interventions, such as coronary artery bypass graft surgery, were also included, totaling 362 patients. Sepsis or bacteremia (100 [34.7%]) and recent use of cocaine or other illicit drugs (39 [13.5%]) were the most common causes of type 2 MIs. A higher proportion of patients with type 2 MIs were younger than 40 years (47 of 288 [16.3%] vs 32 of 362 [8.8%]) and had lower current CD4 cell counts (median, 230 vs 383 cells/ $\mu$ L), lipid levels (mean [SD] total cholesterol level, 167 [63] vs 190 [54] mg/dL, and mean (SD) Framingham risk scores (8% [7%] vs 10% [8%]) than those with type 1 MIs or who underwent cardiac interventions.

**CONCLUSIONS AND RELEVANCE** Approximately half of all MIs among HIV-infected individuals were type 2 MIs caused by heterogeneous clinical conditions, including sepsis or bacteremia and recent use of cocaine or other illicit drugs. Demographic characteristics and cardiovascular risk factors among those with type 1 and type 2 MIs differed, suggesting the need to specifically consider type among HIV-infected individuals to further understand MI outcomes and to guide prevention and treatment.

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort members are listed at the end of this article.

**Corresponding Author:** Heidi M. Crane, MD, MPH, Department of Medicine, University of Washington, 325 Ninth Ave, PO Box 359931, Seattle, WA 98106 (hcrane@uw.edu).

There are many unanswered questions regarding the risk of cardiovascular disease (CVD), including myocardial infarction (MI), in human immunodeficiency virus (HIV)-infected individuals. Studies have suggested that rates of MIs may be higher in HIV-infected individuals vs those without HIV.<sup>1-4</sup> Human immunodeficiency virus may affect lipid levels and endothelial function, leading to increased risk of CVD.<sup>5-7</sup> Antiretroviral therapy (ART) has reduced HIV-associated morbidity and mortality,<sup>8-11</sup> but some ART agents, particularly older ones, may increase the risk of CVD.<sup>12-15</sup> Previous studies have used unadjudicated MI outcomes and have not differentiated the types of MI.<sup>1,16,17</sup> These limitations may have contributed to conflicting findings regarding CVD risk in HIV-infected populations.

The Second Universal Definition of Myocardial Infarction<sup>18</sup> classifies MI into 5 types according to the underlying mechanism of myocardial ischemia. Type 1 MI events (T1MI) result spontaneously from instability of atherosclerotic plaque. 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 without measurement of cardiac biomarkers. Type 4 and 5 MIs occur in the setting of coronary revascularization procedures. Different MI types may portend a different prognosis and optimal approach to medical management.<sup>19</sup>

Studies are needed to understand the effect of HIV and its treatment on the frequency and types of MI. Understanding the types of MI will require clearly defined clinical end points 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.<sup>20</sup> 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 those with T2MI. Although estimates of the incidence of T2MI vary in the general population, T2MIs account for a minority of MIs.<sup>21-28</sup> We hypothesized that T2MIs in HIV-infected individuals may be common and patients who experience them would have distinct demographic and clinical characteristics, including CVD risk factors, compared with HIV-infected individuals who experience 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.<sup>29</sup> Individuals from 6 of the 8 sites (The Johns Hopkins University, University of Alabama at Birmingham, University of California-San Diego, University of California-San Francisco, The Uni-

### Key Points

**Question** How common are type 1 vs type 2 myocardial infarctions (MIs) among human immunodeficiency virus (HIV)-infected patients, and do patient characteristics differ by MI type?

**Findings** Among patients with HIV, type 2 MIs occur almost as often as type 1 MIs; sepsis and vasospasm induced by use of cocaine or other illicit drugs are the most common causes of type 2 MIs. Patients with HIV who experience type 2 MIs are younger, with less traditional cardiovascular disease risk factors, than those who experience type 1 MIs.

**Meaning** Type 2 MIs are common among HIV-infected individuals and are caused by heterogeneous clinical conditions; differences in demographic and clinical characteristics among those who experience type 1 and type 2 MIs suggest the need to specifically consider type among HIV-infected individuals to further understand MIs and guide prevention and treatment.

versity of North Carolina at Chapel Hill, and University of Washington) who had an incident MI between January 1, 1996, and March 1, 2014, were included in the analyses. Each site provided 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.<sup>29</sup> These data include laboratory test results, such as cardiac biomarkers and lipid values; medications, such as those used for type 1 or type 2 diabetes, dyslipidemia, and hypertension; blood pressure values; and diagnoses.<sup>29</sup>

### MI Events

Potential MIs were identified retrospectively in the CNICS data repository by the presence of a clinical diagnosis of MI or documentation of a coronary intervention, such as coronary artery bypass graft or elevated troponin or creatine kinase MB values.<sup>20</sup> For each potential MI, the site assembled deidentified packets that included available physician notes, electrocardiograms (ECGs), imaging studies, and laboratory tests. 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 (most often P.P., S.R.H., or M.J.B.) independently reviewed each packet, followed by a third reviewer if needed to resolve discrepancies. Reviewers considered ECGs, cardiac biomarker values, documented chest pain without another suggested cause, and wall motion abnormalities if results of imaging, such as ventriculogram, were available. Electrocardiographic criteria included the presence of evolving Q-waves, ST-segment elevations, and new left bundle branch block; reviewers used different algorithms in the setting or absence of chest pain and elevations of cardiac biomarkers to determine definite, probable, or no MI. For example, a new left bundle

branch block would be classified as a definite vs probable MI on the basis of abnormal vs equivocal cardiac biomarkers. Reviewers entered standardized data into a web application regarding all MI criteria that were met, including the type of abnormalities seen on ECG results. Reviewers entered additional information on risk factors, 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 elevations of cardiac biomarkers 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 the patient had sepsis.<sup>20</sup> 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 coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or placement of a stent. 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  $\chi^2$  and *t* tests for categorical and continuous variables, respectively, to assess differences in demographic and clinical characteristics among individuals with T1MI or cardiac intervention vs those with T2MI. We considered age; sex; self-reported race/ethnicity and risk factors for HIV transmission; body mass index, CD4 cell count, and HIV-1 viral load measured on the closest date to the MI; and CD4 nadir and peak HIV viral load. We considered the most recent lipid values measured prior to the MI, including total cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. We also considered use of statins and antihypertensive medications. As in prior studies,<sup>30</sup> we defined diabetes (either type 1 or type 2) based on any of the following criteria prior to the MI: hemoglobin A<sub>1c</sub> level of 6.5 or more; use of a diabetes-specific medication, such as insulin; or use of a diabetes-associated medication frequently but not exclusively used to treat diabetes (eg, biguanides) in the setting of also having a diagnosis of diabetes.<sup>30</sup> A diagnosis of diabetes alone did not meet the definition. We computed and compared 10-year coronary heart disease (CHD) risk scores from the Framingham Risk Assessment Tool<sup>31</sup> using mean and categorical scores ( $\leq 10$ , low risk; 11-20, intermediate risk; and  $> 20$ , high risk). We also examined smoking status. We conducted a sensitivity analysis comparing patients with T1MI with individuals who had a coronary intervention performed without an MI.

## Results

Of 26 909 HIV-infected patients evaluated during the ascertainment period, 1689 met the criteria for a potential MI at least once

for a total of 2037 potential events. Among these patients, 571 of 2037 (28.0%) events were adjudicated as an MI, of which 370 (64.8%) were classified as definite MI and 201 (35.2%) as probable MI. Among the definite and probable MIs, 283 (49.6%) were T1MI and 288 (50.4%) were T2MI. An additional 79 of 2037 events (3.9%) did not meet criteria to be classified as an MI, but the patients had atherosclerotic disease that was severe enough to require a coronary intervention, such as a coronary artery bypass graft, totaling 362 patients with a T1MI or coronary intervention. Among those with an adjudicated MI or coronary intervention, 500 of 650 were men (76.9%), the median age was 49 years (interquartile range, 43-55 years), and the current median CD4 cell count was 326 cells/ $\mu$ L (interquartile range, 136-571). The current CD4 count was measured a median of 47 days before the MI (interquartile range, 15-108).

A higher proportion of patients with a T2MI than those with a T1MI or coronary intervention were younger than 40 years (47 of 288 [16.3%] vs 32 of 362 [8.8%]), female (81 of 288 [28.1%] vs 69 of 362 [19.1%]), African American (202 of 288 [70.1%] vs 156 of 362 [43.1%]), and not receiving ART (134 of 288 [46.5%] vs 91 of 362 [25.1%]), with an HIV transmission risk factor of injection drug use (107 of 288 [37.2%] vs 78 of 362 [21.5%]) (Table 1). A higher proportion of those with a T2MI also had a low median CD4 cell count (230 vs 383 cells/ $\mu$ L) and high HIV viral load (1808 vs 116 cells/mL) compared with patients with a T1MI.

Diabetes and hypertension were equally prevalent among those with a T1MI or coronary intervention (76 of 362 [21.0%] and a T2MI (67 of 288 [23.3%]) (Table 2). However, a higher proportion of individuals with a T1MI or coronary intervention were receiving a statin prior to the event (118 of 362 [32.6%] vs 56 of 288 [19.4%]) and had higher mean (SD) total cholesterol (190 [54] vs 167 [63] mg/dL), non-high-density lipoprotein cholesterol (149 [52] vs 125 [60] mg/dL), and low-density lipoprotein cholesterol levels (108 [43] vs 87 [40] mg/dL) (to convert cholesterol to millimoles per liter, multiply by 0.0259) compared with those who had a T2MI. Individuals with a T1MI were also more likely to be current smokers than those with a T2MI (181 of 362 [50.0%] vs 116 of 288 [40.3%]). Those with a T1MI had a higher mean (SD) 10-year Framingham CHD risk score than those with a T2MI (10% [8%] vs 8% [7%]) (Table 2). Intermediate Framingham risk scores were present in 76 (21.0%) of those with a T1MI or cardiac interventions vs 47 (16.3%) with a T2MI, and high-risk scores were present in 45 (12.4%) patients with a T1MI or cardiac intervention vs 24 (8.3%) of those with a T2MI ( $P = .046$ ).

Sepsis or bacteremia (100 [34.7%]), vasospasm induced by use of cocaine or other illicit drugs (39 [13.5%]), and hypertensive emergency (28 [9.7%]) were the most frequently identified likely causes of T2MI (Table 3). A diverse array of clinical conditions, including respiratory failure, noncoronary cardiac conditions, and hypotension, were identified as causes of the remaining T2MIs.

Patients who underwent a coronary intervention without meeting criteria for an MI were more likely than those with a T1MI to be male and have a lower viral load and higher 10-year Framingham CHD risk score but did not differ on other HIV-specific or CVD risk factors (eTables 1 and 2 in the Supplement).

Table 1. Clinical and Demographic Characteristics of HIV-Infected Individuals With T1MI vs T2MI

Characteristic	No. (%) <sup>a</sup>		P Value
	T1MI (n = 362) <sup>b</sup>	T2MI (n = 288)	
<b>Sex</b>			
Male	293 (80.9)	207 (71.9)	.006
Female	69 (19.1)	81 (28.1)	
<b>Age, y</b>			
<40	32 (8.8)	47 (16.3)	.01
40-49	152 (42.0)	106 (36.8)	
50-59	125 (34.5)	99 (34.4)	
60-69	43 (11.9)	22 (7.6)	
≥70	10 (2.8)	14 (4.9)	
<b>Race/ethnicity</b>			
White	171 (47.2)	65 (22.6)	<.001
African American	156 (43.1)	202 (70.1)	
Hispanic	19 (5.3)	14 (4.9)	
Other or unknown	16 (4.4)	7 (2.4)	
<b>HIV transmission risk factor</b>			
Heterosexual	101 (27.9)	93 (32.3)	<.001
Men who have sex with men	166 (45.9)	75 (26.0)	
Injection drug use	78 (21.5)	107 (37.2)	
Other or unknown	17 (4.7)	13 (4.5)	
<b>Antiretroviral therapy</b>			
Yes	271 (74.9)	154 (53.5)	<.001
No	91 (25.1)	134 (46.5)	
<b>CD4 count measured on the closest date to the event, cells/μL</b>			
0-200	94 (26.0)	128 (44.4)	<.001
201-350	72 (19.9)	57 (19.8)	
>350	195 (53.9)	103 (35.8)	
<b>CD4 cell count nadir, cells/μL</b>			
0-200	212 (58.6)	199 (69.1)	.02
201-350	79 (21.8)	48 (16.7)	
>350	70 (19.3)	41 (14.2)	
<b>HIV-1 RNA measured on the closest date to the event, copies/μL</b>			
<400	217 (59.9)	127 (44.1)	<.001
400-9999	47 (13.0)	49 (17.0)	
10 000-99 999	63 (17.4)	59 (20.5)	
≥100 000	34 (9.4)	53 (18.4)	
<b>HIV-1 RNA, peak, copies/μL</b>			
<400	43 (11.9)	20 (6.9)	.02
400-9999	35 (9.7)	31 (10.8)	
10 000-99 999	112 (30.9)	70 (24.3)	
≥100 000	171 (47.2)	167 (58.0)	

Abbreviations: HIV, human immunodeficiency virus; T1MI, type 1 myocardial infarction events; T2MI, type 2 myocardial infarction events.

<sup>a</sup> One patient was missing data on CD4 cell count and HIV-1 RNA data prior to myocardial infarction and was excluded from those rows.

<sup>b</sup> Type 1 myocardial infarction also includes patients with cardiac interventions, such as coronary artery bypass graft surgery.

## Discussion

We examined MI types in a large, nationally distributed cohort of individuals with HIV. Type 2 myocardial infarctions were common, comprising half of all MIs. We identified characteristics that differed between individuals with T1MI and T2MI. On average, individuals who had a T2MI were younger and had a lower CD4 cell count, higher viral

load, and fewer traditional CVD risk factors, including less dyslipidemia, lower current rates of smoking, and lower CHD risk scores. Individuals with a T2MI were significantly different from those with a 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.<sup>19</sup> To our knowl-

Table 2. Cardiovascular Disease Risk Factors Among HIV-Infected Individuals With T1MI vs T2MI

Characteristic	Value <sup>a</sup>		P Value
	T1MI (n = 362) <sup>b</sup>	T2MI (n = 288)	
Diabetes			
No	286 (79.0)	221 (76.7)	.49
Yes	76 (21.0)	67 (23.3)	
Systolic blood pressure, mean (SD), mm Hg	132 (23)	130 (24)	.33
Antihypertensive medication			
No	164 (45.3)	124 (43.1)	.57
Yes	198 (54.7)	164 (56.9)	
Lipid levels, mean (SD), mg/dL			
HDL cholesterol	40 (15)	42 (19)	.18
LDL cholesterol	108 (43)	87 (40)	<.001
Non-HDL cholesterol	149 (52)	125 (60)	<.001
Total cholesterol	190 (54)	167 (63)	<.001
Triglycerides	227 (182)	208 (272)	.38
Statin use			
No	244 (67.4)	232 (80.6)	<.001
Yes	118 (32.6)	56 (19.4)	
Smoking			
No	125 (34.5)	136 (47.2)	.005
Former	56 (15.5)	36 (12.5)	
Current	181 (50.0)	116 (40.3)	
BMI, mean (SD)	26 (5)	24 (6)	.001
Framingham CHD risk score, mean (SD), % 10-y event risk	10 (8)	8 (7)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; HDL, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL, low-density lipoprotein cholesterol; T1MI, type 1 myocardial infarction events; T2MI, type 2 myocardial infarction events.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup> Type 1 myocardial infarction also includes patients with cardiac interventions such as coronary artery bypass graft surgery.

edge, 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 Myocardial Infarction<sup>18</sup> and endorsed by major cardiology societies<sup>32</sup>; however, differentiating between the 2 types can be challenging.<sup>19</sup> Categorization of MI by type has increased over time, but the *International Classification of Diseases* coding system lacks distinct categories for T2MI,<sup>32</sup> which likely limits capture of this diagnosis in clinical settings. However, nonspecific codes for other acute and subacute forms of ischemic heart disease (*International Classification of Diseases, Ninth Revision* code 411.89 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code I24.8) have been used for this purpose.<sup>33</sup> Lack of data on MI type has been attributed to the relatively recent introduction of the Universal Definition of Myocardial Infarction, presumed underreporting of T2MI, and lack of consistency in T2MI criteria.<sup>32</sup>

Despite these limitations, studies have found that T2MIs are much less common than T1MIs in most populations, comprising less than 2% to 26% of all MIs, depending on adjudication methods and population,<sup>22-28</sup> but usually less than 10% of all MIs.<sup>23-28</sup> In a Danish study of hospitalized patients, there were 541 MIs, of which 26% were T2MI.<sup>22</sup> In contrast, the proportion of T2MI in our population of HIV-infected individuals was almost twice as high as in the Danish study. This difference may be owing to an increased likelihood of bacteremia and infections, re-

sulting in sepsis, and increased prevalence of the use of cocaine or other illicit drugs in those with HIV. In addition, the Danish study did not exclude individuals with prior MI: 27% of participants in the Danish study with T2MI had a history of MI, 17% prior percutaneous coronary intervention, and 10% prior coronary artery bypass graft.<sup>22</sup> In contrast, we focused on initial events. Although 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.<sup>19</sup> Prevention and treatment of atherosclerotic CVD, including statin use, antiplatelet agents, and coronary procedures, have been studied and disseminated in T1MI guidelines<sup>34,35</sup>; 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 bacteremia or vasospasm induced by cocaine or other illicit drugs. 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.<sup>36</sup> Factors that lead to T2MI have not been well characterized in the general population. The most common presumed causes of T2MI in the Danish study were anemia, arrhythmias, and respiratory failure.<sup>22</sup> A New York study found that surgery, anemia, and sepsis were common presumed causes of T2MI.<sup>33</sup> Arrhythmias were also a common presumed cause of T2MI in several studies of the general population.<sup>21,28,37</sup> In contrast, we found that sepsis or

bacteremia and use of cocaine or other illicit drugs were common with T2MI. These results suggest that HIV-infected individuals have a different set of presumed T2MI causes than the general population.<sup>21,28,37</sup>

### T1MI vs T2MI

We found substantial differences in demographic and clinical characteristics among HIV-infected individuals who experienced a T1MI vs those who experienced a T2MI. Higher proportions of those with a T2MI were younger, female, and had poorer control of their HIV infection as measured by current CD4 cell count and viral load. This finding contrasts with population studies of individuals not infected with HIV in which patients with T2MI were older than those with T1MI.<sup>21,28</sup> In the general population, people with T2MI tend to be seriously ill. We similarly found that those with a T2MI tended to be sicker than those with a T1MI in terms of HIV status.

### Adjudication

Central adjudication is preferable to local adjudication with or without secondary central review.<sup>20</sup> Clinical definitions of MI have changed over time.<sup>38</sup> 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. Although diagnoses alone, such as from billing data, are commonly used for ascertainment, possibly with concomitant verification using other data elements,<sup>1,4,16,39-41</sup> the sensitivity of this approach is not optimal.<sup>42</sup> A previous study has demonstrated that using clinical diagnoses alone results in missing substantial numbers of patients with T2MI.<sup>20</sup> This finding is not surprising since there is no relevant *International Classification of Diseases* code to document myocardial injury owing to severe extracardiac causes, such as sepsis.<sup>32,43</sup> Experts have advocated the development of distinct diagnostic codes for T2MI.<sup>19</sup> Studies with cardiac biomarkers in their ascertainment criteria therefore likely more accurately capture T2MIs vs studies that rely on diagnoses alone. The Universal Definition of Myocardial Infarction has not established what constitutes a significant level of hypertension, hypotension, and other risk factors; therefore, identifying T2MI must rely on clinical judgment.<sup>21</sup>

### Strengths and Limitations

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

Our study has some 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 results of ECGs to identify silent events; however, this approach has been shown to have a low probability of detecting MIs.<sup>44</sup> Ascertainment may be incomplete for events that occur outside CNICS sites, although we requested medical records. We

**Table 3. Most Likely Causes of T2MI Among HIV-Infected Individuals**

Cause	No. (%)
Sepsis or bacteremia	100 (34.7)
Use of cocaine or other illicit drug	39 (13.5)
Hypertensive urgency or emergency	28 (9.7)
Respiratory failure	26 (9.0)
Noncoronary cardiac <sup>a</sup>	23 (8.0)
Other or unknown	16 (5.6)
Hypotension <sup>b</sup>	15 (5.2)
Procedure associated <sup>c</sup>	12 (4.2)
Gastrointestinal bleeding	11 (3.8)
Neurologic	6 (2.1)
Overdose	5 (1.7)
Anemia	4 (1.4)
Rhabdomyolysis	3 (1.0)

Abbreviations: HIV, human immunodeficiency virus; T2MI, type 2 myocardial infarction events.

<sup>a</sup> Noncoronary cardiac causes include nonatherosclerotic causes, such as those associated with congestive heart failure and cardiac tumor.

<sup>b</sup> Hypotension not owing to sepsis, gastrointestinal bleeding, drug overdose, or other listed causes.

<sup>c</sup> Events that occur in the setting of noncardiac procedures, such as abdominal surgery and lower extremity amputation.

used troponin assays; however, they have become more sensitive over time and are not biologically equivalent owing to biochemical differences in assays and the reference populations used to determine upper reference limits.<sup>45</sup> Although 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,<sup>32</sup> and correctly classifying falsely positive events vs T2MI can be difficult. However, events were reviewed independently by 2 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 performed for patients with T1MI and rarely done for those with T2MI. It is therefore unknown whether most patients with T2MI had obstructive disease. Finally, because our study is the first to describe MI types in patients with HIV, the findings have not been replicated, although the pattern of T1MI and T2MI in approximately half the patients was seen across the 6 CNICS sites.

### Future Studies

Type 2 myocardial infarctions are increasingly recognized in the general population, and additional research is needed to better define and manage these events.<sup>46</sup> The importance of applying ECG classifications, such as ST-segment elevation MI vs non-ST-segment elevation MI, to categorizing T2MI is unclear, as these classifications are intended to help guide decisions regarding clinical reperfusion therapy in patients with T1MI.<sup>32</sup>

Research is needed to better understand the complex association between traditional and HIV-specific CVD risk factors, the genetic predisposition to develop MI and potential interactions with ART, and the role of behavioral factors. Further evaluation is needed to understand the role of sepsis and risk for T2MI. Such information can guide interventions to alter

these associations 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 the use of anticoagulation therapy, will differ by type. It is unclear if T1MI or T2MI will decrease in the current era now that ART is initiated 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 United States demonstrates that approximately half of

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

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**Author Affiliations:** Department of Medicine, University of Washington, Seattle (H. M. Crane, Paramsothy, Drozd, Nance, Delaney, P. K. Crane, Rodriguez, Barnes, McReynolds, Lober, Crothers, Kitahata); Department of Epidemiology, University of Washington, Seattle (Delaney, Heckbert); Department of Medicine, University of California-Los Angeles (Budoff); Department of Medicine, University of Alabama at Birmingham (Burkholder, Willig, Mugavero, Saag); Department of Medicine, University of California-San Diego (Mathews); Department of Medicine, The Johns Hopkins University, Baltimore, Maryland (Moore); Department of Medicine, The University of North Carolina at Chapel Hill (Eron, Napravnik); Department of Medicine, University of California-San Francisco (Hunt, Geng, Hsue, Grunfeld); Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York (Peter); Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle (Barnes, McReynolds, Lober); Department of Medicine, Northwestern University, Chicago, Illinois (Feinstein).

**Author Contributions:** Dr H.M. Crane had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** H.M. Crane, Drozd, Moore, Hsue, Lober, Grunfeld, Saag, Kitahata.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** H.M. Crane, Nance, Kitahata.

**Critical revision of the manuscript for important intellectual content:** Paramsothy, Drozd, Nance, Delaney, Heckbert, Budoff, Burkholder, Willig, Mugavero, Mathews, P.K. Crane, Moore, Eron, Napravnik, Hunt, Geng, Hsue, Rodriguez, Peter, McReynolds, Lober, Crothers, Feinstein, Grunfeld, Saag, Kitahata.

**Statistical analysis:** H.M. Crane, Nance, Delaney, Rodriguez.

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**Study supervision:** H.M. Crane.

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**Group Information:** The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort site Principal Investigators include Michael S. Saag, MD, and Michael J. Mugavero, MD (University of Alabama at Birmingham); Mari M. Kitahata, MD, MPH (University of Washington, Seattle); Benigno Rodriguez, MD (Case Western Reserve University, Cleveland, Ohio); Elvin Geng, MD (University of California-San Francisco); Steven Boswell, MD (Fenway Health, Boston,

Massachusetts); Christopher Mathews, MD, MSPH (University of California-San Diego); Richard D. Moore, MD, MHA (Johns Hopkins University, Baltimore, Maryland); and Joseph J. Eron, MD (The University of North Carolina at Chapel Hill).

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