HIV-Associated Thrombotic Microangiopathy in the Era of Highly Active Antiretroviral Therapy: An Observational Study

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The prevalence and predisposing factors of thrombotic microangiopathy (TMA) in the era of highly active antiretroviral therapy (HAART) were evaluated among patients in the Collaborations in Human Immunodeficiency Virus (HIV) Outcomes Research/US cohort. Of 6022 patients, 17 (0.3%) had TMA, with unadjusted incidences per 100 person-years of 0.079 for TMA, 0.009 for thrombotic thrombocytopenic purpura, and 0.069 for hemolytic-uremic syndrome. Compared with patients without TMA, patients with TMA had lower mean $CD4^+$ cell counts (197 vs. 439 cells/mm^3; $P = .0009$) and higher mean $\log_{10}$ HIV-1 RNA levels (4.6 vs. 3.3 copies/mL; $P = .0001$) at last follow-up and a significantly greater incidence of acquired immune deficiency syndrome (82.4% vs. 55.3%; $P = .025$), *Mycobacterium avium* complex infection (17.6% vs. 3.3%; $P = .018$), hepatitis C (29.4% vs. 11.3%; $P = .001$), and death (41.2% vs. 7.4%; $P < .0001$). The prevalence of herpes and use of antiherpetics were slightly higher for patients with TMA, but unadjusted distributions were not statistically significant. TMA in a cohort surveyed after the introduction of HAART was rare and was associated with advanced HIV disease.

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by intravascular platelet clumping, leading to the clinical pentad of microangiopathic hemolytic anemia, thrombocytopenia, fever, and neurological and renal abnormalities [1, 2]. Hemolytic-uremic syndrome (HUS) is a closely related condition with predominantly renal manifestations and is characterized by a constellation of symptoms, including microangiopathic hemolytic anemia, thrombocytopenia, fever, and renal failure [1, 3]. Idiopathic TTP primarily occurs in adults, whereas HUS also develops in ~15% of children infected with *Escherichia coli* strain O157:H7 [4, 5]. TTP and adult HUS are considered part of a spectrum of diseases collectively known as "thrombotic microangiopathies" (TMA) because they have similar clinical and histological characteristics and result in endothelial cell damage [6, 7]. TMA is a rare condition in healthy, immunocompetent persons (incidence, ~1/90,000), with a mortality rate in excess of 95% if left untreated [8, 9]. However, dramatic improvements in prognosis and survival rates have been demonstrated in adult patients with TMA treated with plasma exchange therapy [10–12].

Although the precise etiology of TMA is unknown, it has been associated with bacterial toxins [13], immune complexes and autoimmune disorders [14, 15], cancer and antineoplastic therapy [16, 17], bone marrow and organ transplantation [18, 19], and drugs such as IFN-α, ticlopidine, quinine, simvastatin, and rifampicin [20–24]. Recent research into the molecular basis of TMA suggests that the deficiency of a specific von Willebrand factor–cleaving protease could promote the formation of intra-arterial platelet aggregation and is therefore a strong risk factor for the development of TMA [25, 26].

An association between TMA and HIV was first rec-

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ognized in 1984 [27] and since then, both TTP and HUS have been reported in HIV-infected patients [28–31]. TMA in persons with HIV infection does not differ clinically from that in persons not infected with HIV and occurs regardless of the route of transmission of HIV [29], with advanced immunosuppression, opportunistic infections, and various drugs commonly used in advanced disease all considered to be potential risk factors [30–33]. Complete deficiency of the von Willebrand factor–cleaving protease has also been reported in HIV-associated TTP [34]. Demonstration of p24 antigen in the endothelial cell suggests either a direct cytopathic effect of the virus or functional impairment of the endothelium [35].

Reports of the prevalence of TMA in HIV-infected persons varies from 1.4% in the pre-HAART era to none during the HAART era in a cohort study [36] and 7% in patients hospitalized with advanced HIV disease [37]. Because the magnitude of HIV-associated TMA in the HAART era remains an area of uncertainty, the incidence of TMA in HIV-infected persons, along with potentially predisposing clinical factors, were determined in the Collaborations in HIV Outcomes Research/US (CHORUS) cohort.

METHODS

Study population. The study population consisted of HIV-positive adults enrolled in the CHORUS database, an observational prospective cohort comprising patients from 4 outpatient clinics in the United States—Comprehensive Care Center, Nashville; Liberty Medical Group, New York; Pacific Horizon Medical Group, San Francisco; and Pacific Oaks Medical Group, Los Angeles. After informed consent was obtained, comprehensive data on sociodemographic and clinical variables were collected via an electronic medical-record system at every clinic visit. In addition, detailed information on AIDS-defining events and HIV care before enrollment was also collected. Results from laboratory tests conducted during the course of routine clinical care were entered into the database via an electronic interface. Details about the CHORUS database have been published elsewhere [38].

Case identification. Case patients were persons who had diagnoses of TMA, HUS, or TTP during follow-up. In addition, a comprehensive search was conducted for potentially undiagnosed cases of HUS or TTP in the database. Diagnoses, laboratory results, and data regarding vital signs were evaluated to identify patients with a constellation of diagnoses and symptoms consistent with each disease. For HUS, these symptoms included anemia (a diagnosis or hemoglobin level of <12 g/dL for males and 11 g/dL for females), renal dysfunction (characterized by anuria, oliguria, hematuria, proteinuria, serum creatinine greater than twice the upper limit of normal, blood urea nitrogen greater than twice the upper limit of normal, lactate dehydrogenase level greater than twice the upper limit of normal, or an abnormal result for urine dipstick assay), thrombocytopenia (platelet count of <60,000/mm^3), and a fever of >37.7°C. A pentad of symptoms was used for the identification of patients with TTP. These included all of the 4 conditions for HUS as well as the occurrence of neurological symptoms, such as stupor, coma, cognitive dysfunction, confusion, disorientation, epilepsy, and seizure or dementia (excluding HIV dementia). Each search was repeated with the requirement for fever excluded, because there were concerns regarding the underreporting of fever. On the basis of reported cases in clinical practice [39], a triad of laboratory findings—namely, the presence of peripheral schistocytes (fragmented erythrocytes), thrombocytopenia, and elevated lactate dehydrogenase level—was used to define a case in patients with a confirmed finding of schistocytosis.

To ensure accurate identification of cases, 2 clinicians blinded to all other patient information independently evaluated the data regarding diagnoses and symptoms and confirmed whether they represented cases of TMA (HUS or TTP). Concordance between the clinicians was used to evaluate variability in case identification.

Statistical methods. Statistical models could not be fit to the data because of small numbers of patients with TMA, HUS, or TTP in CHORUS. Descriptive statistics were generated for patients who had TMA (HUS or TTP) versus those who remained free of the disease until the end of follow-up. Patients with TMA were compared with matched subjects without TMA with respect to sociodemographic and clinical variables such as age, race, sex, route and duration of HIV infection, AIDS status, specific AIDS-defining diseases, antiretroviral therapy, and CD4$^+$ cell and HIV-1 RNA levels at event for case patients and at last follow-up for non–case patients. *P* values were generated for χ^2 test and Fisher's exact test for categorical variables, and Wilcoxon rank sum test and Student's *t* test for continuous measures.

Case descriptions were generated for all incident cases of TMA (HUS and TTP). In addition to sociodemographic and HIV- and AIDS-related information, data on other potentially predisposing factors were also evaluated. These included preexisting cancer at the time of TMA incidence and the use of specific drugs known to be associated with TMA: ticlopidine, clopidogrel, mitomycin, cyclosporine, tacrolimus, quinine, ciprofloxacin, clofazimine, didanosine, ethambutol, fluconazole, ethinyl estradiol, trimethoprim-sulfamethoxazole, and zidovudine. In addition, coinfection with herpes simplex virus and hepatitis B and C viruses was also assessed.

On the basis of the observed rate of TMA in 2 hospital-based cohorts [36, 37], the expected χ^2 frequencies of TMA were calculated for CHORUS. The observed frequencies for all 3 studies were compared by means of χ^2 statistics.

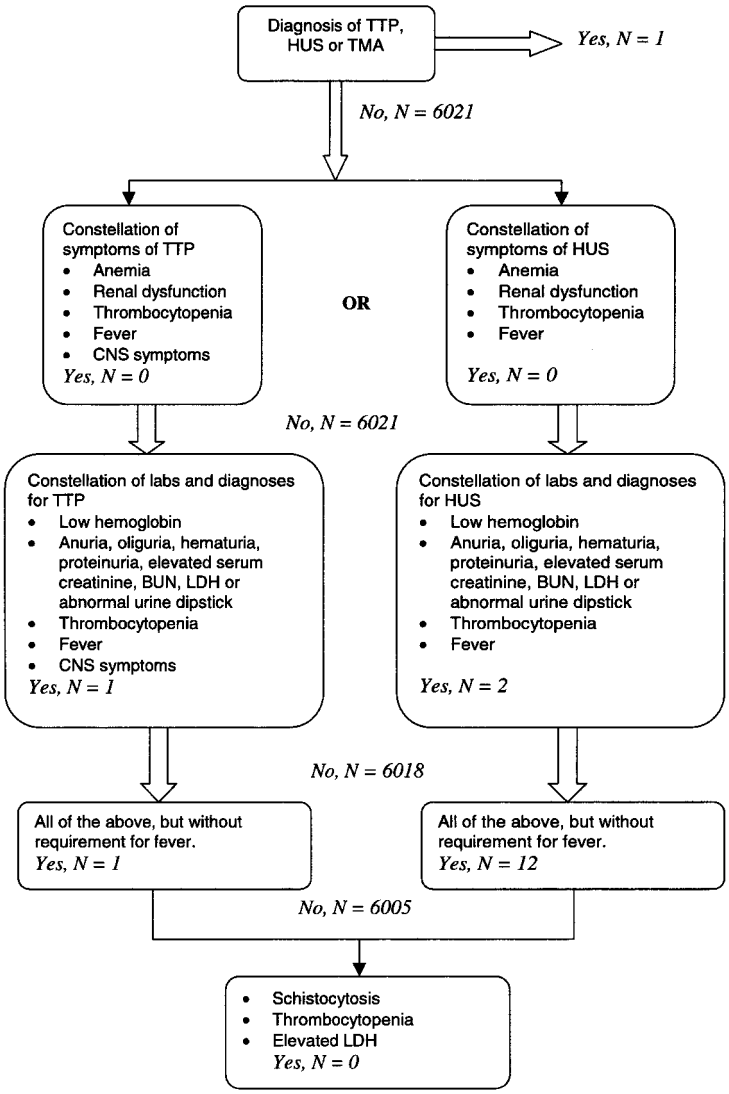

Figure 1. Identification of thrombotic microangiopathy (TMA) cases in the Collaborations in HIV Outcomes Research/US cohort. BUN, blood urea nitrogen; CNS, central nervous system; HUS, hemolytic-uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

RESULTS

Analysis population. A total of 6022 HIV-positive patients who consented to participate in the CHORUS study between 1 June 1997 and 21 May 2003 were included in the analysis population. There were 21,446.8 person-years of follow-up in this cohort, with a median duration of 4.1 years (range, 0–5.9 years) of follow-up. The vast majority of these patients had received antiretroviral therapy before entering the cohort (80%), with 66% having received HAART before enrollment. About 21% of CHORUS patients initiated HAART at or after enrollment. The rate of loss to follow-up was 12.5%, and the death rate for the cohort was just under 8%.

Among eligible study subjects, 17 (0.3%) of 6022 patients were identified as having cases of TMA, and the other 6005 did not have a diagnosis or exhibit any of the qualifying symptoms of TMA within a 90-day window. The sequential process by which disease criteria were applied and cases were identified is illustrated in figure 1.

Univariate analysis. An unadjusted comparison of demographic and clinical characteristics by case status is presented in table 1. The distributions for age, race/ethnicity, and sex were comparable across case patients and non–case patients. A significantly higher proportion of case-patients were likely to have AIDS (82.4% vs. 55.3%; $P = .025$) and, more specifically, disseminated *Mycobacterium avium* complex infection (17.6% vs. 3.3%; $P = .018$). Compared with patients without TMA, patients with TMA had lower mean $CD4^+$ cell counts (197 vs. 439 cells/mm^3; $P = .0009$) and higher mean $\log_{10}$ HIV-1 RNA levels (4.6 vs. 3.3 copies/mL; $P = .0001$) and were more likely to have hepatitis C virus coinfection (29.4% vs. 11.3%; $P =$

Table 1. Unadjusted comparison of sociodemographic and clinical variables across thrombotic microangiopathy (TMA) status in the Collaborations in HIV Outcomes Research/US cohort.

Characteristic	TMA case patients (n = 17)	Non–case patients (n = 6005)	P
Site			
1	1 (5.9)	2016 (33.6)	.005[a]
2	2 (11.8)	1265 (21.1)	
3	8 (47.1)	1992 (33.2)	
4	6 (35.3)	732 (12.2)	
Age at baseline, years			
Mean (SD)	39.9 (5.2)	43.1 (8.6)	.129[b]
Median (range)	41 (31–50)	43 (20–82)	.119[c]
Sex			
Male	15 (88.2)	5456 (90.9)	.665[a]
Female	2 (11.8)	549 (9.1)	
Race/ethnicity			
White	10 (58.8)	4485 (74.7)	.130[a]
African American	3 (17.6)	892 (14.9)	
Hispanic	4 (23.5)	438 (7.3)	
Other	0	190 (3.2)	
HIV acquired by homosexual or bisexual contact	10 (58.8)	4512 (75.1)	.109[d]
Duration of HIV infection, months[e]			
Mean (SD)	97.5 (50.8)	115.4 (58.9)	.211[b]
Median (range)	70.0 (26–208)	115.0 (0–243)	.183[c]
AIDS[f]	14 (82.4)	3318 (55.3)	.025[d]
Cytomegalovirus infection	1 (5.9)	234 (3.9)	.492[a]
Mycobacterium avium complex infection	3 (17.6)	201 (3.3)	.018[a]
Pneumocystis carinii pneumonia	3 (17.6)	582 (9.7)	.225[a]
Kaposi's sarcoma	1 (5.9)	344 (5.7)	1.000[a]
Cryptococcosis	0	0	…
Died during follow-up	7 (41.2)	444 (7.4)	<.0001[a]
Hepatitis B virus coinfection[f]	7 (41.2)	2213 (36.9)	.384[d]
Hepatitis C virus coinfection[f]	5 (29.4)	679 (11.3)	.001[d]
Escherichia coli infection[f]	0	0	…
Herpes simplex virus diagnosis[f]	7 (41.2)	1947 (32.4)	.441[d]
Use of medications[f]			
Antiherpetics	8 (47.1)	1688 (28.1)	.083[d]
TMA-associated drug	3 (17.7)	2294 (38.2)	.131[a]
Cancer chemotherapy	1 (5.9)	125 (2.1)	.302[a]
$CD4^+$ cell count at last follow-up, cells/mm^3			
Mean (SD)	197 (162)	439 (273)	.0009[b]
Median (range)	150 (48–597)	407 (1–1665)	.0003[c]
Log_{10} HIV-1 RNA level at last follow-up, copies/mL			
Mean (SD)	4.6 (1.2)	3.3 (1.2)	.0001[b]
Median (range)	4.9 (2.0–5.9)	3.1 (1.0–6.7)	.0003[c]

NOTE. If not specified otherwise, data are no. (%) with characteristic.

[a] Fisher's exact test.
[b] Student's t test.
[c] Wilcoxon rank sum test.
[d] χ^2 test.
[e] Months between diagnosis of HIV infection and end of follow-up.
[f] At or before event for case-patients and at last follow-up for non–case-patients.

Table 2. Demographic and clinical characteristics of thrombotic microangiopathy (TMA) case patients in the Collaborations in HIV Outcomes Research/US cohort.

Case patient no.	Sex	Age (years)	Race/ethnicity	TMA symptoms	Herpes[a]	Hepatitis B[a]	Hepatitis C[a]	Antiherpetic use[a]	Cancer drug[a] use	Other medications[a,b]
1	M	35	Hispanic	HUS: anemia, elevated LDH level, low platelet count	No	No	No	No	No	No
2	M	43	White	HUS: anemia, low platelet count, fever, abnormal urinalysis results	No	No	No	Acyclovir	No	Zidovudine
3	M	40	White	TTP: anemia, CNS symptoms, low platelet count, abnormal urinalysis results	Yes	Yes	No	Acyclovir	No	No
4	M	44	African American	HUS: anemia, low platelet count, abnormal urinalysis results	No	No	Yes	No	No	No
5	M	31	African American	HUS	No	No	No	No	No	No
6	M	42	White	HUS: anemia, low platelet count, fever, abnormal urinalysis results	Yes	No	No	Acyclovir	No	Zidovudine
7	F	33	White	HUS: anemia, elevated BUN level, elevated platelet count	Yes	Yes	No	Acyclovir	No	No
8	M	39	White	TTP: anemia, low platelet count, abnormal urinalysis results, fever, CNS symptoms	No	Yes	No	No	No	No
9	M	32	White	HUS: anemia, low platelet count, high LDH level	Yes	No	No	No	No	No
10	M	44	African American	HUS: anemia, elevated creatinine level, low platelet count	Yes	No	Yes	Acyclovir	No	Zidovudine
11	M	45	White	HUS: anemia, low platelet count, hematuria	Yes	No	No	No	No	No
12	M	50	White	HUS: anemia, elevated creatinine level, low platelet count	No	No	No	Acyclovir	No	No
13	M	42	Hispanic	HUS: anemia, low platelet count, high creatinine level	No	Yes	No	Acyclovir	IFN-α2A	No
14	M	35	White	HUS: anemia, low platelet count, abnormal urinalysis results	No	Yes	Yes	No	No	No
15	M	43	Hispanic	HUS: anemia, high creatinine level, low platelet count	Yes	Yes	Yes	Acyclovir	No	No
16	M	40	White	HUS: anemia, low platelet count, abnormal urinalysis results	No	No	No	No	No	No
17	F	41	Hispanic	HUS: anemia, high creatinine level, low platelet count	No	Yes	Yes	No	No	No

NOTE. No case patient was infected with *Escherichia coli*. BUN, blood urea nitrogen; CNS, central nervous system; F, female; HUS, hemolytic-uremic syndrome; LDH, lactate dehydrogenase; M, male; TTP, thrombotic thrombocytopenic purpura.

[a] At or before event.

[b] Drugs that have been known to be associated with TMA (ticlopidine, clopidogrel, mitomycin, cyclosporine, tacrolimus, quinine, ciprofloxacin, clofazimine, didanosine, ethambutol, fluconazole, ethinyl estradiol, trimethoprim-sulfamethoxazole, and zidovudine).

.001) and to die during follow-up (41.2% vs. 7.4%; $P < .0001$). The unadjusted incidences for TTP, HUS, and all TMA in this cohort were 0.009, 0.069, and 0.079 per 100 person-years of follow-up.

Case descriptions. Demographic, clinical, and HIV- and AIDS-related characteristics of TMA case patients are presented in tables 2 and 3. As indicated in table 2, only one patient had a frank diagnosis of HUS (case 5), one patient exhibited a tetrad and another exhibited a pentad of symptoms consistent with TTP (cases 3 and 8, respectively), and 14 patients had a triad of symptoms for HUS, consisting of anemia, low platelet counts, and either an abnormal urinalysis result or an elevated lactate dehydrogenase level. A majority of the patients (81.3%) were identified as having cases after the requirement for fever was excluded as a qualifying symptom of TMA. With the exception of 2 women, all cases occurred in men, and most of them had acquired HIV infection through homosexual or bisexual contact. Among patients who had a $CD4^+$ cell measure at diagnosis of TMA, 64% had <200 cells/mm^3 and nearly 86% had <350 cells/mm^3, indicating a more progressed population. Among patients who had AIDS before diagnosis of TMA, the most common AIDS-defining diseases were HIV wasting, *Pneumocystis carinii* pneumonia, *M. avium* complex infection, candidiasis, and cryptococcosis. The vast majority of TMA case patients had received antiretroviral therapy (88%) or HAART (88%). Three case patients had taken at least one medication thought to be associated with TMA, and 8 patients had taken an antiherpetic medication (acyclovir) before diagnosis of TMA. Nearly half of the case patients had hepatitis B virus coinfection ($n = 7$), whereas about one-third ($n = 5$) were coinfected with hepatitis C virus.

In the clinical assessment of potential cases, 2 blinded physicians concurred on the identification of 15 of 17 cases, a concurrence rate of 88.2%.

DISCUSSION

The incidence of TMA was found to be 0.3% in a prospective analysis of 6022 HIV-positive patients enrolled in the CHORUS cohort during the period 1 June 1997 through 21 May 2003. Patients with TMA were found to have more advanced disease, as indicated by lower $CD4^+$ cell counts and higher HIV-1 RNA levels. A significantly greater proportion of these patients had a previous diagnosis of AIDS and AIDS-defining illnesses and had a higher incidence of death during follow-up than did patients without TMA.

The frequency of TMA has been reported to be higher in HIV-infected patients than in the normal population, and even greater in those with advanced disease [28–31]. Published reports of the incidence of TMA evaluated during the pre-

Table 3. Clinical characteristics related to HIV/AIDS for thrombotic microangiopathy (TMA) case patients in the Collaborations in HIV Outcomes Research/US cohort.

Case patient no.	Route of HIV acquisition	Duration of HIV infection (months)[a]	AIDS[b] manifestation(s)	$CD4^+$ cell count at diagnosis of TMA	Log_{10} HIV-1 RNA level at diagnosis of TMA	Antiretroviral therapy (months)	HAART (months)	Protease inhibitor therapy (months)
1	Homosexual/bisexual contact	67	HSV, HIV wasting, PCP, candidiasis	59.0	5.2	31	23	23
2	Homosexual/bisexual contact	208	No	164.0	4.7	162	67	91
3	Homosexual/bisexual contact	154	No	597.0	2.0	27	1	2
4	Injection drug use	69	HIV wasting, MAC infection, PCP	136	5.2	67	27	19
5	Homosexual/bisexual contact	70	Nonspecific	88.0	4.6	35	28	28
6	Homosexual/bisexual contact	47	PCP	149.0	2.6	48	31	31
7	Heterosexual contact	162	Cryptococcosis	48.0	NA	22	13	13
8	Homosexual/bisexual contact	142	HIV wasting	51.0	5.9	100	35	35
9	Homosexual/bisexual contact	62	HIV wasting, MAC infection, CMV retinitis	60.0	5.7	30	21	29
10	Heterosexual contact	55	HIV wasting, cryptococcosis	NA	NA	2	2	2
11	Injection drug use	70	Nonspecific	NA	5.9	0	0	0
12	Homosexual/bisexual contact	161	AIDS dementia, HIV wasting, candidiasis	440.0	NA	127	15	11
13	Homosexual/bisexual contact	94	Kaposi sarcoma, HIV wasting	303.0	2.9	80	35	36
14	Injection drug use	87	Nonspecific	296	5.1	0	0	0
15	Injection drug use	26	HSV infection	150.0	4.5	22	4	0
16	Homosexual/bisexual contact	64	Nonspecific	214.0	5.2	7	3	7
17	Heterosexual contact	120	Nonspecific	NA	4.5	22	22	22

NOTE. CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HSV, herpes simplex virus; PCP, *Pneumocystis carinii* pneumonia; MAC, *Mycobacterium avium* complex infection; NA, not available.

[a] Time between HIV diagnosis and diagnosis of TMA.

[b] At or before event.

HAART era vary considerably, depending on the type of study performed, diagnostic criteria used to evaluate patients, and stage of HIV disease. A multicenter, randomized, comparative clinical trial of valacyclovir versus acyclovir for prophylaxis against cytomegalovirus performed between December 1992 and October 1994 (AIDS Clinical Trials Group [ACTG] protocol 204) reported the incidence of TMA to be 1.5% (18/1227) among patients with advanced HIV disease [40]. A review of 214 hospitalized patients who died of AIDS between 1987 and 1994 at several medical centers in Louisiana revealed evidence of TMA in 15 patients (7%) at the time of death [41]. Another prospective study of 1423 HIV-infected patients hospitalized at the Cochin Hospital in Paris between November 1991 and December 1993 reported TTP or HUS in 9 patients (0.6%) [29].

A more recent study evaluated the incidence of TMA in HIV-infected persons during both the pre-HAART (January 1985–December 1996) and the HAART (January 1997–December 2000) periods at the Institute of Infectious Diseases and Tropical Medicine in Milan. TMA was reported in 17 (1.4%) of 1223 patients in a retrospective cohort of HIV-infected persons during the pre-HAART era, whereas a prospective evaluation of 347 patients in the HAART era revealed no cases of TMA [36].

In another prospective evaluation of 350 HIV-infected patients admitted consecutively during May 1996 through February 1997 to the Johns Hopkins Hospital in Baltimore, TMA was reported in 25 patients, with an incidence of 7% [37]. Along with the symptoms typically diagnostic of TMA, grade 2 schistocytosis was detected in 24% of these patients by peripheral blood smear examination. The relatively high incidence of TMA reported in this study could be attributed to the greater prevalence of advanced HIV disease in this population. Patients had median $CD4^+$cell counts of 36 cells/mm^3 (range, 0–1141 cells/mm^3) and median HIV-1 RNA levels of 94,000 copies/mL (range, from undetectable to 10^6 copies/mL), and 72% of patients presented with Centers for Disease Control and Prevention stage C HIV disease.

The 0.3% (17/6022) incidence of TMA in CHORUS, which demonstrates the lower incidence during the HAART era, is generally consistent with the findings in the prospective HAART-era Italian cohort [36]. Given the rates of TMA observed in the retrospective pre-HAART Italian cohort [36] and at the Johns Hopkins hospital [37], the CHORUS cohort would expect to see 28 and 40 cases, respectively. The distribution of cases observed in the CHORUS cohort was significantly lower than that observed in these 2 studies ($P < .001$). This result was not unexpected, because TMA is associated with advanced HIV disease, and the CHORUS cohort, formed in the era following the introduction of HAART, represents a somewhat stable population, in which the leading cause of death is not AIDS but comorbidities such as hepatitis [42].

An accurate diagnosis of TMA in patients with HIV can be complicated by the fact that the clinical spectrum of TMA is highly varied, and symptoms can be similar to those seen in several other HIV-associated diseases and comorbidities. Therefore, TMA cases in members of the CHORUS cohort were identified by means of a series of sequential steps involving evaluation of clinical symptoms and laboratory findings, followed by independent confirmation of identified cases by 2 physicians. On the basis of these evaluations, 15 of the 17 cases in the CHORUS cohort were diagnosed by the presence of HUS-related symptoms and 2 by symptoms consistent with TTP. This distribution was found to be consistent with the Italian study, which reported 14 cases of HUS and 3 cases of TTP [36], and with the Johns Hopkins study [37], in which renal dysfunction was more common (6%) than neurological dysfunction and fever (2%) in patients with a diagnosis of TMA.

The current study confirms an increased risk of the manifestations associated with TMA in patients with more advanced HIV disease. In CHORUS, patients with TMA had significantly lower $CD4^+$cell counts and higher HIV-1 RNA levels than those who did not manifest TMA. In another retrospective case-control study [33], the mean $CD4^+$ cell count for 16 HIV-infected patients given a diagnosis of TMA between December 1992 and December 1994 was significantly lower than the mean for 64 controls without TMA (29 vs. 107 cells/mm^3; $P = .009$). Cytomegalovirus disease was the only opportunistic infection associated with TMA in this study. The risk of developing TMA was significantly higher among patients with cryptosporidiosis and those with AIDS-related cancers in the retrospective Italian cohort [36]. Patients with TMA in the CHORUS database had a significantly increased diagnosis of AIDS as well as disease due to *M. avium* complex. In an analysis of potential risk factors associated with TMA among patients in the clinical trial of valacyclovir prophylaxis (ACTG protocol 204) [31], the relative risk of developing *M. avium* complex infection was greater in patients with TMA (2.9; 95% CI, 1.1–7.2).

The prognosis for HIV-infected patients with TMA has been reported to be very poor, with high mortality rates, especially among those with severe disease. Despite treatment of patients, mortality rates were 100% for TMA and 71% for HUS in the Italian study [36]. In the French study [29], 8 of 9 patients with TMA died within 3 months of the diagnosis. In the Johns Hopkins study [37], TMA was independently associated with death (relative odds, 4.46; 95% CI, 1.54–12.46; $P < .01$) after adjustment for $CD4^+$ cell levels and Centers for Disease Control and Prevention disease stage were adjusted for. Consistent with these reports, a significantly higher fatality rate was seen among CHORUS patients with TMA than among those without the syndrome. However, because several AIDS-related infections and neoplasms have been shown to be associated with TMA,

it is possible that TMA may be a part of the terminal illness rather than an independent cause of death.

Several drugs commonly prescribed for patients with advanced HIV disease have been reported to be associated with an increased risk of TMA. In the ACTG 204 clinical trial [31], the relative risk of developing TMA was increased in patients who had received various concurrent medications, such as valacyclovir, fluconazole, clofazimine, ethambutol, and trimethoprim-sulfamethoxazole. Fluconazole was also considered to be associated with TMA in a retrospective case-control study [33] but was not found to be associated with TMA in the prospective Johns Hopkins study [37]. In the latter study, no patients received valacyclovir, and acylovir use was not found to be associated with TMA. A few patients in the CHORUS cohort were exposed to drugs reported to be associated with TMA. However, because many of these drugs are used for specific manifestations of advanced HIV disease, it is not clear whether the opportunistic diseases, the drugs commonly used to treat them, or both are causally related to the development of TMA.

In summary, the incidence of a TMA-like syndrome among patients in the CHORUS database was similar to the rate reported among similar populations in previous studies. Clinical manifestations consistent with TMA were associated with evidence of more advanced HIV disease. Results of this study also show that HAART has resulted in a dramatic decline in the incidence of TMA. Because TMA is relatively rare, the use of a longitudinal cohort such as CHORUS and other similar cohorts, may be useful in expanding our understanding of TMA in HIV-infected patients.

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