Intravenous Thrombolysis for Stroke and Presumed Stroke in Human Immunodeficiency Virus–Infected Adults

A Retrospective, Multicenter US Study

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Background and Purpose—Human immunodeficiency virus (HIV) infection has been shown to increase both ischemic and hemorrhagic stroke risks, but there are limited data on the safety and outcomes of intravenous thrombolysis with tPA (tissue-type plasminogen activator) for acute ischemic stroke in HIV-infected patients.

Methods—A retrospective chart review of intravenous tPA-treated HIV patients who presented with acute stroke symptoms was performed in 7 large inner-city US academic centers (various search years between 2000 and 2017). We collected data on HIV, National Institutes of Health Stroke Scale score, ischemic stroke risk factors, opportunistic infections, intravenous drug abuse, neuroimaging findings, and modified Rankin Scale score at last follow-up.

Results—We identified 33 HIV-infected patients treated with intravenous tPA (mean age, 51 years; 24 men), 10 of whom were stroke mimics. Sixteen of 33 (48%) patients had an HIV viral load less than the limit of detection while 10 of 33 (30%) had a CD4 count <200/mm^3. The median National Institutes of Health Stroke Scale score at presentation was 9, and mean time from symptom onset to tPA was 144 minutes (median, 159). The median modified Rankin Scale score for the 33-patient cohort was 1 and for the 23-patient actual stroke cohort was 2, measured at a median of 90 days poststroke symptom onset. Two patients had nonfatal hemorrhagic transformation (6%; 95% confidence interval, 1%–20%), both in the actual stroke group. Two patients had varicella zoster virus vasculitis of the central nervous system, 1 had meningovascular syphilis, and 7 other patients were actively using intravenous drugs (3 cocaine, 1 heroin, and 3 unspecified), none of whom had hemorrhagic transformation.

Conclusions—Most HIV-infected patients treated with intravenous tPA for presumed and actual acute ischemic stroke had no complications, and we observed no fatalities. Stroke mimics were common, and thrombolysis seems safe in this group. We found no data to suggest an increased risk of intravenous tPA-related complications because of concomitant opportunistic infections or intravenous drug abuse. **(*Stroke*. 2018;49:228-231. DOI: 10.1161/STROKEAHA.117.019570.)**

Key Words: CD4 lymphocyte count ■ CVA (cerebrovascular accident) ■ HIV infections ■ intracranial hemorrhages ■ stroke ■ tissue-type plasminogen activator

Human immunodeficiency virus (HIV), which affects ≈37 million people globally,[1] is an independent risk factor for stroke.[2] Several mechanisms have been proposed in acute ischemic stroke (AIS): vessel disease either from HIV itself or from antiretroviral therapy, dyslipidemia and impaired glucose tolerance from specific classes of antiretroviral therapy, central nervous system opportunistic infections (CNS OIs), HIV-induced antiphospholipid antibodies, and a high prevalence of tobacco and illicit drug use.[3–6] HIV-infected patients with viral suppression still differ from the HIV-uninfected population in important ways that are still being elucidated. Because HIV has a reservoir in the brain and replication can occur and disrupt the blood–brain barrier, much is yet to be learned about virally suppressed HIV-infected groups neurologically. In one study, comparing ≈25 000 HIV-infected to >250 000 HIV-uninfected individuals, the annual incidence of AIS was 1.4× higher in people with HIV.[2] HIV-infected individuals are also at an increased risk of spontaneous intracranial hemorrhage, reportedly 3.4× greater than the general population as shown in a meta-analysis of 190 184 HIV-infected versus 997 778 HIV-uninfected people.[3] Although HIV

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infection is not a contraindication to thrombolysis, there has been limited detailed reporting on the practical use and outcomes of thrombolysis for AIS in this population.[4] Registries, such as Get With The Guidelines, or large cohorts, such as the Framingham Heart Study, do not systematically test HIV.[5] We retrospectively identified HIV-infected patients who received intravenous tPA (tissue-type plasminogen activator) for presumed AIS in 7 large inner-city US academic medical centers.

Materials and Methods

Ethics Approvals

Case files were reviewed with the approval of the institutional review boards at each participating center with individual informed consent waived. We adhered to the Transparency and Openness Promotion Guidelines; however, data cannot be shared because of the small numbers of HIV-infected cases.

Search

We searched the medical records of US teaching hospitals where we worked and had collaborations: 12 patients were found at the New York-Presbyterian/Columbia University Medical Center (January 2001–February 2013); 7 at the Yale-New Haven Hospital (March 2013–March 2017); 6 at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center in Baltimore (January 2000–February 2012); 3 at the Boston University Medical Center (January 2006–March 2017); 3 at the Massachusetts General and Brigham and Women's Hospitals (January 2005–December 2016); 1 at the Cleveland Clinic; and 1 at the University of Miami Hospital. An additional search at Emory University (January 2016–June 2017) in Atlanta revealed 2 cases of intravenous tPA in the setting of thrombectomy who were excluded because of the accompanying procedural interventions. The search strategy varied in time and dates because of the availability of the electronic record and the existence of intravenous tPA, stroke, and HIV patient registries by site. In total, the search spanned from January 2000 to March 2017 (Appendix I in the online-only Data Supplement).

Data Extraction and Collection

Each patient's medical record was reviewed by at least one board-certified neurologist for the accuracy of diagnoses and confirmed use of intravenous tPA. Prespecified variables were extracted from the records by neurologists on a standardized spreadsheet and deposited in a centralized database. Inclusion criteria were as follows: ≥16 years old, documented history of HIV, initial clinical diagnosis of AIS,[7] documented administration of intravenous tPA for AIS, and available data on outcomes at last follow-up in the medical record even if at the time of hospital discharge or if the last follow-up was death. All cases had to have HIV infection before the AIS or documented at the same admission. All AIS cases were confirmed by brain computed tomography or magnetic resonance imaging or both. We defined a stroke mimic as a case in whom stroke was clinically diagnosed, but on follow-up >24 hours later, there was no radiographic evidence for acute stroke, and an alternative clinical diagnosis was determined at discharge.[8]

CD4 count and viral load closest to time of stroke were recorded. Acquired immunodeficiency syndrome was defined as <200 CD4 cells/mm^3.[9] Additional laboratory investigations including cerebrospinal fluid and testing for CNS OIs, such as varicella zoster virus, *Cryptococcus* species, *Mycobacterium tuberculosis*, John Cunningham virus, and *Treponema pallidum*, were reviewed.

The outcomes included (1) stroke versus stroke mimic, (2) modified Rankin Scale score[10] at last follow-up, and (3) intracerebral hemorrhage postintravenous tPA.

Results

We identified 33 HIV-infected patients (24 men [73%], 11 black, 8 white, 4 Hispanic) treated with intravenous tPA for AIS, of whom 10 were stroke mimics (6 men, 60%; Table 1). The remaining 23 (18 men, 78%) had neuroimaging-confirmed AIS. The median age of the entire cohort at the time of stroke presentation was 52 years. Their CD4 counts nearest the time of stroke ranged from 4 to 1340 cells/mm^3 (median, 324). The viral loads were less than the limit of detection in 16 of 33 (48%) and ranged from 32 to 287 000 copies/mL (mean, 52 409; median, 2827) in the remaining 17 patients. Their mean National Institutes of Health Stroke Scale (NIHSS) score was 9 (median, 6; range, 2–24), and the mean time from symptom onset to the administration of intravenous tPA was 144 minutes (median, 159; range, 46–260).

Morbidity and Mortality

No patient died during the hospitalization. All were alive at last available follow-up, which was at a median of 90 days (mean, 79 days; range, 1–420 days). The median follow-up modified Rankin Scale score was 1 (mean, 1.7; range, 0–5) for the 33-patient cohort and 2 (mean, 2.3; range, 0–5) for the 23-patient actual stroke cohort.

Efficacy

Among the 23 patients with true ischemic stroke, discharge NIHSS score was available for 16. These 16 patients showed a decrement of their average NIHSS score from 9 at presentation to 4 at hospital discharge (mean, 9 days; median, 6 days; range, 2–29).

Hemorrhagic Transformation

Two patients (6%) experienced hemorrhagic transformation, both of which were nonfatal and both patients had true AIS. One had hemorrhagic transformation occupying <30% of the infarct size and the other had a hemorrhage size that could not be assessed (Appendix II in the online-only Data Supplement). The discharge NIHSS score and whether hemorrhagic transformation was symptomatic in these cases were unavailable.

Patients With Acquired Immunodeficiency Syndrome

Ten patients (30%) had acquired immunodeficiency syndrome at the time of stroke,[9] 5 of whom were not taking antiretroviral therapy at the time of stroke onset. CNS OIs occurred in a higher proportion in this group (20% versus 4%) compared with those with CD4 counts >200 cells/mL. There were no observed differences in other clinical features or outcomes (Table 2).

Concomitant Infections and Intravenous Drug Use

Cerebrospinal fluid was evaluated in 9 patients and demonstrated varicella zoster virus IgG in 2 (22%) cases and no source of infection in the others. One patient had a highly positive serum Venereal Disease Research Laboratory but no cerebrospinal fluid pleocytosis. These 3 patients (2 with varicella zoster virus CNS vasculitis and 1 with presumed meningovascular syphilis), 7 others who were actively using intravenous illicit drugs (3 cocaine, 1 heroin, and 3 unspecified), and an additional 3 with past intravenous drug use (1 heroin and 2 unspecified) all did not experience hemorrhagic transformation (Table I in the online-only Data Supplement).

Table 1. Demographic and Clinical Features of Study Cohort

Values Given in n (%) or Mean (Range) Unless Otherwise Noted	All Patients (n=33)	Stroke Mimics (n=10)	True AIS (n=23)
Age	51.4 (16–83)	53.0 (42–67)	50.7 (16–83)
Male	24 (73%)	6 (60%)	18 (78%)
Hypertension	23 (70%)	7 (70%)	16 (70%)
Diabetes mellitus	7 (21%)	1 (10%)	6 (26%)
Dyslipidemia	14 (42%)	5 (50%)	9 (39%)
Active smoker	11 (33%)	2 (20%)	9 (39%)
Atrial fibrillation	2 (6%)	0	2 (9%)
Duration of HIV infection, y	12 (1–28)	12 (3–28)	13 (1–28)
Not on ART at time of stroke	9 (27%)	3 (30%)	6 (26%)
NIHSS score	9.2 (2–24)	4.4 (2–8)	11.3 (2–24)
Symptom-to-tPA needle time in minutes	144 (46–260)	160 (50–224)	138 (46–260)
Systolic blood pressure at stroke presentation, mm Hg	142 (85–220)*	136 (110–170)†	145 (85–220)‡
Diastolic blood pressure at stroke presentation, mm Hg	82 (48–118)*	79 (48–100)†	84 (55–118)‡
Blood glucose at stroke presentation	126 (77–344)*	136 (83–344)†	122 (77–283)‡
Hemoglobin A1C	6.1 (4.7–13.6)*	5.8 (5.3–6.5)†	6.2 (4.7–13.6)
Total cholesterol	184 (117–305)*	215 (153–305)†	171 (117–203)
LDL	112 (54–220)*	137 (85–220)†	100 (54–200)
HDL	52 (22–312)*	85 (33–312)†	37 (22–67)
Platelet count (×105/mL)	2.55 (1.57–5.50)*	2.45 (1.67–3.13)	2.60 (1.57–5.50)
CD4 count	461 (4–1340)§	714 (140–1340)	342 (4–1337)
Intravenous drug abuse	10 (30%; 7 active‖)	4 (40%)	6 (26%)
CNS opportunistic infections	3 (9%)¶	0	3 (13%)
Hemorrhagic transformation	2 (6%)	0	2 (9%)
mRS score mean, median, range, (follow-up mean, median days)	1.7, 1, [0–5], (79, 90)	0.4, 0, [0–1], (105, 90)	2.3, 2, [0–5], (68, 90 days)
Stroke mechanism per TOAST criteria[7]			
Cardioembolic	8 (35%)	n/a	8 (35%)
Large artery disease	4 (17%)	n/a	4 (17%)
Small vessel disease	2 (9%)	n/a	2 (9%)
Other	3 (13%)¶	n/a	3 (13%)¶
Undetermined	6 (26%)	n/a	6 (26%)

AIS indicates acute ischemic stroke; ART, antiretroviral therapy; CNS, central nervous system; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; mRS, modified Rankin Scale; n/a, not applicable; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue-type plasminogen activator; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*Data not available in n=10.

†Data not available in n=3.

‡Data not available in n=7.

§At or closest to time of stroke.

‖Three cocaine, 1 heroin, and 3 unspecified.

¶Two with varicella zoster virus vasculitis diagnosed with cerebrospinal fluid IgG and 1 with hypercoagulability.

Discussion

Our report is relevant to the care of HIV patients presenting with presumed AIS who are eligible for intravenous tPA. We observed no fatalities. Hemorrhagic transformation of the ischemic stroke occurred in 6% of HIV-infected patients with presumed AIS. Although this percentage seems within the range observed in the general population,[11] our small sample size means this point estimate has a wide range of confidence (1%–20%). No patient with CNS OI or current or past illicit drug use experienced hemorrhagic transformation.

Table 2. Demographic and Clinical Differences Between Patients: CD4 <200 Versus CD4 >200 Cells/mL

	CD4 <200 (n=10)	CD4 >200 (n=23)
Age, y, mean (range)	44.5 (19–58)	54.4 (16–83)
Male, n (%)	9 (90%)	15 (65%)
Duration of HIV infection, y, mean (range)	11.5 (3–17)	13.2 (1–28)
Not on ART at time of stroke, n (%)	5 (50%)	4 (17%)
NIHSS score mean (range)	10.4 (2–22)	8.7 (2–24)
Symptom-to-tPA needle time in minutes, mean (range)	128 (73–210)	151 (50–260)
CD4 count, mean (range)	93.6 (4–200)	637 (205–1340)
IV drug abuse, n (%)	3 (30%)	7 (30%)
CNS opportunistic infections, n (%)	2 (20%)	1 (4%)
Hemorrhagic transformation, n (%)	1 (10%)	1 (4%)
mRS score mean, median, range, (mean, median follow-up)	1.9, 2, [0–4], (71,75 days)	1.7, 1, [0–5], (83, 90 days)

ART indicates antiretroviral therapy; CNS, central nervous system; HIV, human immunodeficiency virus; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

We report the safe use of tPA in 10 HIV patients who did not have ischemic strokes. Although other studies have reported the safe administration of intravenous tPA to patients with stroke mimics,[12,13] we extend this finding to the population with potential CNS OIs. Although efficacy data were not available for the entire cohort, there was a clinically significant reduction in NIHSS score post-thrombolysis (decrement from 9 to 4 on average).

We acknowledge several limitations. We depended on retrospective data collection at multiple large US academic medical centers that have differences in population characteristics, HIV prevalence, and likely physician decision-making patterns over time. In some cases, there were missing data on the variables of interest. The follow-up duration and search years could not be unified across sites because of different medical records systems, registries, and software searching programs. We were unable to obtain long-term follow-up on all patients but had a reasonable observation time for short-term outcomes with a median of 90 days. If patients were followed for longer, more uniform amounts of time, we would be better able to comment on outcomes, fatality, and safety. It is possible that other patients had HIV and were untested for it, undercounting the number of cases. Because HIV testing is not routine in patients with AIS, it is likely some cases were unrecognized or undisclosed and therefore uncoded and not included here. The impact of this undercounting is uncertain, that is, whether this increases or decreases the true hemorrhagic conversion rate. Data on whether the hemorrhagic transformation was symptomatic versus only radiographic was not available. In addition, by using *International Classification of Diseases* codes to identify most patients, we relied on the accuracy and completeness of the hospitals' billing records.

Our report improves on the overall lack of information on acute stroke treatment for HIV-infected adults. Given the small number of cases at any one center, we collectively gathered all available data on HIV-infected tPA use for AIS, including the range of HIV-infected patients from severely immunosuppressed to treated with highly active antiretroviral therapy. Overall, our data are reassuring that both stroke and stroke mimic HIV-infected patients received intravenous tPA without short-term fatalities, even in the setting of CNS OIs, high degrees of immunosuppression, and other comorbidities. We hope this work will lead to the eventual development of a shared patient registry and improved documentation of HIV infection in existing registries for future patients.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Appendix I: Search strategy per individual medical center:

At the New York-Presbyterian/Columbia University Medical Center, the medical records were searched from January 2001 to July 2016 for individuals carrying the *International Classification of Diseases* 9th edition (ICD-9) diagnosis codes 042 or V08, which is a 99% sensitive and 89% specific method for the detection HIV-infected individuals.[1] The results were cross-referenced with those carrying the ICD-9 codes 432 to 436 for *cerebrovascular diseases*, coded at any level of diagnosis (primary or otherwise) in the same patient. HIV/AIDS had to precede the diagnosis of stroke in all cases. The resultant cohort of 115 patients was searched manually by an American Board of Psychiatry and Neurology-certified neurologist for those who received tPA, producing 10 HIV-infected individuals that received tPA for acute ischemic stroke.

A similar search method at the MGH and BWH from January 2005 to December 2016 produced 3 individuals and from January 2000 to December 2012 at the JHH and JHBMC produced 6 individuals. A similar search produced 1 individual from each of the Cleveland Clinic and the University of Miami.

An additional 2 patients were identified at the New York-Presbyterian/Columbia University Medical Center by manually screening a database of all admitted patients with acute ischemic stroke who presented within 12 hours following symptom onset from January 2011 to February 2013 for the presence of HIV infection and tPA use.

At the Yale-New Haven Hospital, the electronic medical record was searched for all admitted patients from March 2013 to March 2017, filtered by a diagnosis of HIV and one of the ICD billing codes associated with tPA for stroke and non-stroke indications (ICD-9 code V45.88 or ICD-10 code Z92.82). The 30 identified patients were then reviewed for stroke to obtain 7 HIV-infected patients that received tPA for acute ischemic stroke.

At the Boston University Medical Center, a database of 182 acute ischemic stroke patients who received tPA from January 2012 to March 2017 was searched for HIV-infected individuals, 2 were found. An additional case was found in a database of 27 HIV-infected patients that suffered acute ischemic stroke identified through the ICD-9 search method described above conducted from 2005 to 2010.

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Appendix II: Description of Hemorrhagic Transformation of Cases post-TPA

The first was a man in his 80s who was an active smoker with hypertension and atrial fibrillation that presented with an NIHSS score of 17, had a CD4 count of 395 cells/mm^3 with undetectable viral load on ART. He was given IV-tPA at 90 minutes from symptom onset but developed hemorrhagic transformation rated as *parenchymal hemorrhage 1* according to the European Cooperative Acute Stroke Study (ECASS) radiographic classification for hemorrhagic transformation, indicating hemorrhagic transformation occupying <30% of the infarct size with some mass effect. He had an mRS score of 5 at 24 days. The second was a man in his 50s with hypertension and dyslipidemia that presented with an NIHSS score of 10, had a CD4 count of 159 cells/mL with a viral load of 90,000 copies/mL on nevirapine, abacavir, and lamivudine. He was given IV-tPA at 75 minutes from symptom onset and had a mRS score of 4 at 16 days follow-up. He had parenchymal hemorrhagic transformation at the site of his infarct, the extent of which was not available for our review.

Table I: Patients with Concomitant Opportunistic Infection or IV Drug Use	**n=10**
Stroke age mean, range	49, [37-58]
Male (n, %)	8, 80%
Hypertension (n, %)	7, 70%
Diabetes (n, %)	3, 30%
Dyslipidemia (n, %)	4, 40%
Active Smoker (n, %)	6, 60%
Atrial Fibrillation (n, %)	0
Duration of HIV Infection (mean in years, range)	11, [3-23]
Not on ART at time of stroke (n, %)	3, 30%
NIHSS score mean, range	11, [2-23]
Symptom-to-tPA needle time in minutes mean, range	148, [73-240]
CD4 count mean, range*	364, [4-1340]
Active Intravenous Drug Abuse at time of Stroke	7, 70%**
Opportunistic Infections at time of Stroke (n, %)	3, 30%***
Hemorrhagic Transformation (n, %)	0
mRS score mean, range, (mean days of follow-up)	1.6, [0-4], (64 days)

*At or closest to time of stroke.
** 3 cocaine, 1 heroin and 3 unspecified.
*** 2 with VZV vasculitis diagnosed with positive CSF IgG and 1 with positive hypercoagulable work-up.
ART=antiretroviral therapy, CNS=central nervous system, mRS=modified Rankin scale, NIHSS=national institute of health stroke scale, tPA=tissue plasminogen activator