Community-Acquired Meningitis in HIV-Infected Patients in the United States

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Abstract

We conducted a retrospective study of 549 adults admitted with community-acquired meningitis (CAM) to several hospitals in New Orleans, LA and Houston, TX between 1999 and 2014 to characterize the current epidemiology, clinical manifestations, cerebrospinal fluid (CSF) characteristics, and outcomes of CAM between HIV-infected and uninfected patients and to identify risk factors for adverse outcomes in CAM. Bivariate analysis and logistic regression analysis were used to identify prognostic factors. A total of 1022 patients with CAM were screened. Only 549 (53.7%) subjects had an HIV test and were included in the study. Of those, 138 (25%) had HIV infection. HIV-infected patients presented with less meningeal symptoms (headache, neck stiffness, and Kernig sign), but with higher rates of hypoglycorrhachia, elevated CSF protein, and an abnormal cranial imaging ($p < 0.05$). More than 50% of all the patients had an unknown etiology. Cryptococcal meningitis was the most common identified etiology of CAM in HIV-infected patients followed by neurosyphilis and varicella-zoster virus (VZV). Viral and bacterial etiologies were the most frequent etiologies in non-HIV-infected patients. *Streptococcus pneumoniae* was the most common bacterial pathogen in both groups, but it was rare overall (2%). Adverse clinical outcomes were similar in both groups (27% vs. 24%). Logistic regression identified hypoglycorrhachia and an abnormal neurological examination as independent predictor factors of worse outcome in all patients with meningitis. Our results demonstrate that the etiology, clinical presentation, and CSF findings differ between HIV-infected and HIV-uninfected adults with CAM, but clinical outcomes are similar.

Keywords: HIV, AIDS, meningitis, *Cryptococcus*, *Streptococcus pneumoniae*, outcome

Introduction

COMMUNITY-ACQUIRED MENINGITIS (CAM) is a serious illness associated with high morbidity and mortality. The epidemiology of meningitis varies significantly with the type of host. *Cryptococcus* meningitis is considered the leading cause of meningitis in HIV-infected individuals worldwide.¹⁻⁴ However, the etiology of CAM in HIV-infected patients in the United States (US) remains poorly characterized. In a recent study of 26,429 adults with meningitis and encephalitis in the United States, HIV diagnosis was known only in 4.2% of individuals.⁵ In the Netherlands, only 1% of adults with bacterial meningitis in an 8-year period had HIV and their clinical features were similar to those without HIV.⁶ Unfortunately, the degree of HIV testing in both studies was unknown.

Since the introduction of antiretroviral therapy, the morbidity and mortality of HIV-infected patients have significantly improved. Hospital admissions due to meningitis and cryptococcosis have declined substantially since 1994⁷ and

mortality rates have also significantly decreased.⁸ Despite the availability of antiretroviral therapy, HIV-infected patients continue to be at higher risk of developing bacterial meningitis⁹ and cryptococcal meningitis.¹⁰

The aim of our study was to characterize the epidemiology, clinical manifestations, cerebrospinal fluid (CSF) characteristics, and outcomes of CAM in the posteffective antiretroviral therapy (ART) era between HIV-infected and HIV-uninfected patients and to identify risk factors for adverse outcomes in patients with CAM.

Methods

We conducted a retrospective study of adults (>17 years old) admitted with CAM to several hospitals in New Orleans, LA and Houston, TX, between 1999 and 2014. Patients who underwent HIV testing or known to have confirmed HIV infection were eligible for the study. Patients were identified through ICD-9 codes and laboratory records.

The study was approved by the Tulane University Institutional Review Board, by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects, and by the Memorial Hermann Hospital Research Review Committee.

Case definition

A case was defined as an adult patient (>17 years) with one or more symptom of community-acquired meningitis (e.g., headache, stiff neck, fever, focal neurological deficits, and/or altered mental status) and CSF with pleocytosis [white blood cell count (WBC) >5 cells/mm³], who had an HIV serology test done.

Data collection

Baseline characteristics were obtained, including demographic data (age, sex, and race), concomitant diseases (determined by the Charlson Comorbidity Index¹¹), and signs and symptoms on clinical presentation (including neurologic examination and Glasgow Coma Scale score). Laboratory data (CSF WBC and differential, CSF protein, CSF glucose, CSF microbiology studies, including cultures and molecular diagnostic tests, serum WBC, blood cultures, and serology studies) were also obtained.

The etiology of meningitis was classified into six categories: bacterial, fungal, viral, parasites, noninfectious, or unknown etiology, according to the final diagnosis at the time of discharge of the patient from the hospital or at the time of death. We defined an urgent treatable etiology as patients who require urgent therapy and hospital admission for cure and survival. Etiologies representing urgent treatable disease included the following: bacterial, fungal, or tuberculous meningitis; Herpes simplex, Varicella zoster, or Cytomegalovirus meningoencephalitis; rickettsial meningoencephalitis; bacteremia; meningeal carcinomatosis; central nervous system vasculitis; parameningeal mass lesions; and subarachnoid hemorrhage.

The primary study end-point for this study was the presence of an adverse clinical outcome at the time of patient discharge using the Glasgow Outcome Scale.¹² A score of 1 indicates death; 2 indicates vegetative state; 3 indicates severe disability; 4 indicates moderate disability (able to live independently, but unable to resume some previous activities); and 5 indicates mild or no disability (able to return to work/school). An adverse clinical outcome was defined as a Glasgow Outcome Scale score of ≤4.

Statistical analysis

The statistical analysis was performed with IBM® SPSS® version 21. Bivariate analysis was performed using Fisher's exact test, Chi square, and Student's *t*-test as appropriate. Significant variables on bivariate analysis ($p \leq 0.05$) were entered into a logistic regression model to identify independent associations with an adverse clinical outcome. Bootstrapping analysis was used to validate the regression model.

Results

Baseline characteristics, clinical findings, and laboratory results

During the 15-year period of the study, a total of 1022 patients with CAM were screened for eligibility. Only 549

(53.7%) of the patients were tested for HIV and were eligible for the study. Of those, 138 (25%) patients had HIV-1 infection.

The demographic, clinical, and laboratory characteristics are shown in Table 1. Patients with HIV were significantly older, with a median age of 50 years, compared to 44 years in non-HIV-infected patients ($p=0.007$). However, there were more patients older than 60 years in the non-HIV group ($p=0.05$). Also, among HIV patients with CAM, there were significantly more African American ($p<0.001$) and more intravenous drug users than non-HIV-infected subjects. The clinical presentation was different between both groups. HIV-infected patients had less meningeal symptoms and signs [e.g., headaches ($p=0.01$), neck stiffness ($p=0.04$), and Kernig sign ($p=0.2$)], but had more malaise ($p=0.04$) and concomitant respiratory symptoms ($p=0.001$). HIV-uninfected adults presented more frequently with seizures ($p=0.02$). There were no significant differences between both groups regarding the proportion of patients presenting with fever, photophobia, mental status changes, skin rash, abnormal neurological examination, or Glasgow Coma Scale.

As shown in Table 2, CSF findings showed that HIV-infected patients were more likely to present with hypoglycorrhachia (glucose <45 mg/dL), a high CSF protein (≥ 100 mg/dL), and a positive CSF Gram stain for yeast or bacteria ($p<0.05$). As expected, due to their immunodeficiency status, HIV-infected patients had less systemic leukocytosis. The median CD4 cell count in those with HIV infection was 89 cells/mm³ (range: 1–593), and 64% of the patients fulfill the definition of AIDS by CD4 cell count (CD4 < 200 cells/mm³). HIV-infected patients were also more likely to have an abnormal head computerized tomography scan ($p=0.05$) and to have urgent treatable etiologies ($p<0.001$). A magnetic resonance imaging of the brain was done in 239 (43.5%) of patients with approximately half of them having an abnormal result with no difference between HIV-infected and non-HIV-infected patients. Empiric antibiotic therapy was more frequently started in HIV-uninfected patients (85% vs. 75%, $p=0.02$).

Etiology of CAM

As shown in Table 3, 345 (63%) of all adults had an unknown etiology. The proportion of unknown etiologies was more commonly seen in the non-HIV-infected patients (69% vs. 43%, $p<0.001$). Viral and bacterial etiologies were the most frequent ones in the non-HIV-infected patients, while fungal and bacterial in HIV-infected patients. Cryptococcosis was the most common cause of CAM in HIV-infected patients, identified in almost one third of the cases ($p=0.0001$). *Streptococcus pneumoniae* was the most common cause of bacterial meningitis in both populations, but it was a rare etiology overall (2%). Among the viral etiologies, HSV was the most common viral infection in non-HIV-infected patients, while varicella-zoster virus (VZV) was the most common one in HIV-infected ones (Table 3). Among HIV-infected patients, patients with cryptococcal meningitis had the lowest median CD4⁺ cell count (41 cells/mm³, range: 1–242), followed by patients with bacterial etiologies (106 cells/mm³, range: 9–315), neurosyphilis (215 cells/mm³, range: 5–556), and viral etiologies (221 cells/mm³, range: 10–593).

TABLE 1. BASELINE CHARACTERISTICS AND CLINICAL PRESENTATION OF 549 ADULTS WITH COMMUNITY-ACQUIRED MENINGITIS WITH OR WITHOUT HIV INFECTION

	HIV infected, n = 138	Non-HIV infected, n = 411	p ^a
Demographic data			
Median age, years (range)	50 (19–74)	44 (18–99)	0.007
Age >60 year, n (%)	5 (3.6)	35 (8.5)	0.05
Gender—male, n (%)	70 (51)	232 (56)	0.2
Ethnicity, n (%)			
White	27 (20)	140 (34)	0.01
African American	89 (63)	186 (45)	<0.001
Hispanic	22 (15)	77 (19)	0.5
Other	3 (2)	8 (2)	0.3
Intravenous drug use, n (%)	26/113 (23)	13/339 (4)	<0.001
Presenting signs and symptoms, n (%)			
Headache	107/130 (82)	354/392 (90)	0.01
Fever	53/116 (46)	137/339 (40)	0.32
Neck stiffness	54/129 (42)	203/385 (53)	0.04
Photophobia	51/122 (42)	172/358 (48)	0.24
Seizures	6/131 (4.5)	44/398 (11)	0.02
Mental status changes	29/121 (24)	66/281 (23)	0.50
Kernig sign	1/67 (1.5)	15/150 (10)	0.02
Brudzinski sign	3/67 (4.5)	11/146 (7.5)	0.5
Skin rash	7/133 (5.2)	20/403 (0.2)	0.8
Abnormal neurological examination ^b	26/63 (41)	73/201 (36)	0.55
Nausea	70/129 (54)	244/390 (63)	0.09
Malaise	64/126 (51)	153/379 (40)	0.04
Respiratory symptoms	41/130 (32)	69/388 (18)	0.001
Glasgow Coma Scale <15	26/121 (21)	53/337 (16)	0.16

^ap Value comparing HIV-infected versus non-HIV-infected adults.

^bAbnormal neurological examination: seizures, abnormal mental status (disorientation or Glasgow Coma Scale <15), cranial nerve abnormality, focal motor deficit, or aphasia.

HIV, human immunodeficiency virus.

Clinical outcome

Of the 549 patients, 26% had an adverse outcome at discharge (Glasgow Outcome Score ≤4), but there was no significant difference between both groups (27% in HIV patients

vs. 24% in non-HIV patients; $p = 0.56$). Only 13% of the HIV-infected patients with cryptococcal meningitis had an adverse clinical outcome (data not shown in table). As shown in Table 4, clinically relevant variables that were associated to an adverse clinical outcome on bivariate analysis included

TABLE 2. DIAGNOSTIC STUDIES AND OUTCOMES IN 549 ADULTS WITH COMMUNITY-ACQUIRED MENINGITIS WITH OR WITHOUT HIV INFECTION

	HIV infected, n = 138	Non-HIV infected, n = 411	p ^a
Laboratory examinations			
CSF gram stain positive, n (%)	16/122 (13)	4/346 (1.1)	<0.001
CSF protein (≥100 mg/dL), n (%)	77/112 (60)	160/330 (48%)	0.04
CSF glucose (<45 mg/dL), n (%)	46/112 (41)	53/330 (16)	<0.001
CSF WBC (median, range)	45 (6–53,790)	133 (6–22,900)	0.77
Leukocytosis (>12,000 cells/μL), n (%)	12/112 (11)	101/330 (31)	<0.001
CD4 ⁺ cell count median (range, cells/mm ³)	89 (1–593)	—	
CD4 < 200 cells/μL, n (%)	75/118 (64)	—	
Imaging studies, n (%)			
Abnormal CT head	25/128 (20)	44/359 (12)	0.05
Abnormal brain MRI	33/67 (49)	82/172 (48)	0.88
Outcomes, n (%)			
Urgent treatable etiologies ^b	61/138 (45)	69/411 (16)	<0.001
Empiric antibiotics	90/120 (75)	285/337 (85)	0.02
Glasgow outcome score ≤4	36/133 (27)	90/371 (24)	0.56

^ap Value comparing HIV-1-infected vs. non-HIV-infected adults.

^bUrgent treatable etiologies are expressed as a ratio of HIV-1 infected to non-HIV infected and include the following: *Cryptococcus* (41:3), *Streptococcus pneumoniae* (3:9), *Mycobacterium tuberculosis* (2:5), other bacteria (13:42), HSV encephalitis (2:6), VZV (5:4), toxoplasmosis (3:0), noninfectious (i.e., malignancy and bleeding; 2:6), others (1:2).

CSF, cerebrospinal fluid; CT, computerized tomography; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MRI, magnetic resonance imaging; VZV, varicella-zoster virus; WBC, white blood cell count.

TABLE 3. ETIOLOGY OF COMMUNITY-ACQUIRED MENINGITIS IN 549 ADULTS WITH OR WITHOUT HIV INFECTION

	HIV infected, n=138	Non HIV infected, n=411	p ^a
Bacterial	16 (12%)	51 (12%)	0.76
<i>Streptococcus pneumoniae</i>	3 (2%)	9 (2%)	1.00
<i>Staphylococcus aureus</i>	0	9 (2%)	0.12
<i>Mycobacterium tuberculosis</i>	2 (1.4%)	5 (1.2%)	1.00
<i>Streptococcus</i> Group B	0	4 (1%)	0.57
<i>Mycoplasma</i> spp.	1 (0.7%)	4 (1%)	1.00
<i>Escherichia coli</i>	0	4 (1%)	0.57
<i>Enterococcus</i> spp.	0	3 (0.7%)	0.57
<i>Listeria monocytogenes</i>	0	2 (0.5%)	1.00
<i>Neisseria meningitidis</i>	0	2 (0.5%)	1.00
<i>Haemophilus influenzae</i>	0	2 (0.5%)	1.00
<i>Treponema pallidum</i>	6 (4%)	1 (0.2%)	0.001
Other bacteria ^b	4 (2.8%)	6 (1.2%)	0.27
Viral	15 (11%)	63 (15%)	0.25
Herpes simplex virus	3 (2.1%)	24 (5.8%)	0.11
Enterovirus	0	15 (3.6%)	0.01
West Nile virus	1 (0.7%)	14 (3.4%)	0.13
Varicella Zoster virus	5 (3.7%)	4 (1%)	0.04
Epstein Barr virus	2 (1.4%)	3 (0.7%)	0.60
St Louis encephalitis	0	3 (0.7%)	0.57
Acute HIV	3 (2.1%)	0	0.015
HIV encephalitis	1 (0.7%)	0	0.25
Fungal	42 (30%)	3 (0.7%)	0.0001
<i>Cryptococcus neoformans</i>	41 (30%)	3 (0.7%)	0.001
<i>Histoplasma capsulatum</i>	1 (0.7%)	0	0.26
Parasites	3 (2%)	1 (0.2%)	0.050
<i>Toxoplasma gondii</i>	3 (2%)	0	0.0156
Cysticercosis	0	1 (0.2%)	1.00
Noninfectious ^c	2 (1%)	8 (2%)	1.00
Unknown	60 (43%)	285 (69%)	0.0001

^ap Value comparing HIV-1 infected versus non-HIV-infected adults.

^bOther bacteria: Non-HIV-infected patients (one case each of the following: *Streptococcus milleri anginosus*, *coagulase-negative staphylococcus*, *Brucella* spp., *Fusobacterium* spp., *Campylobacter* spp., and Lyme disease); HIV-infected patients (one case each of the following: *Streptococcus* Group A, *Bartonella* spp., *Pseudomonas* spp., and leptospirosis).

^cNoninfectious etiologies: Lymphoma, neurosarcoidosis, endocarditis, cerebral aneurysm, other malignancies, SLE, and multiple sclerosis.

HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

Charlson Comorbidity Score, an abnormal neurological examination, leukocytosis (white cell count $\geq 12,000$ cells/ μ L), hypoglycorrhachia (CSF glucose <45 mg/dL), and elevated CSF protein (≥ 100 mg/dL) at the time of diagnosis. As shown in Table 5, a multivariable logistic regression analysis showed that only an abnormal neurological examination and hypoglycorrhachia (CSF glucose <45 mg/dL) were independent predictor factors of an adverse clinical outcome in the total cohort of patients. These two variables were internally validated by using bootstrapping ($p < 0.05$).

Discussion

To our knowledge, this is the largest study to date comparing meningitis in HIV-infected and non-HIV-infected adults and the only one in the United States. Previous studies

TABLE 4. BIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH AN ADVERSE CLINICAL OUTCOME IN 549 ADULTS WITH COMMUNITY-ACQUIRED MENINGITIS

Baseline variables	Odds ratios (95% CI)	p
Male gender	1 (0.6–1.4)	1.0
Charlson comorbidity index score ≥ 1	2.6 (1.4–4.5)	0.001
Immunosuppressed	0.9 (0.6–1.4)	1.0
HIV infection	1.159 (0.7–1.8)	0.56
Abnormal neurological examination ^a	8.0 (3.3–19.3)	<0.001
Glasgow Coma Scale <15	3.5 (1.9–6.6)	<0.001
Age >60 years old	1.7 (0.8–3.5)	0.1
Serum WBC $\geq 12,000$ cells/ μ L	2.4 (1.3–4.4)	0.006
CSF protein ≥ 100 mg/dL	3.9 (1.9–7.7)	<0.001
CSF glucose <45 mg/dL	3.1 (1.6–5.7)	<0.001

^aAbnormal neurological examination: seizures, abnormal mental status (disorientation or Glasgow Coma Scale <15), cranial nerve abnormality, focal motor deficit, or aphasia.

CI, confidence intervals; HIV, human immunodeficiency virus; WBC, white blood cell count; CSF, cerebrospinal fluid.

have had smaller sample sizes, not documented the degree of HIV testing, included only patients with bacterial meningitis or cryptococcal meningitis, or evaluated patients in developing countries with high incidence of tuberculosis or cryptococcal meningitis.^{1–4,6,9,10} In contrast to previous studies of meningitis in HIV-infected patients, we analyzed data of all-cause etiologies of CAM over a 15-year period and evaluated prognostic factors.

The demographic characteristics of our HIV-infected cohort correlate with our HIV epidemic. The majority of the patients were younger than 60 years, with a higher prevalence of African American and intravenous drug users in the HIV-infected patients compared to non-HIV-infected patients. We also found that cryptococcal meningitis continues to be the most common cause of meningitis in HIV-infected patients, despite the widespread availability of antiretroviral therapy. Neurosyphilis and VZV were also seen more frequently in HIV-infected patients. Tuberculous meningitis remained a

TABLE 5. LOGISTIC REGRESSION OF PREDICTORS OF ADVERSE OUTCOME IN PATIENTS WITH COMMUNITY-ACQUIRED MENINGITIS

Baseline variables	Odds ratios (95% CI)	p
Charlson comorbidity index score ≥ 1	2.01 (0.88–4.5)	0.10
Abnormal neurological examination ^a	5.76 (2.25–14.74)	0.001 ^b
Serum WBC $\geq 12,000$ cells/ μ L	1.97 (0.83–4.71)	0.11
CSF protein ≥ 100 mg/dL	2.22 (0.90–5.48)	0.09
CSF glucose <45 mg/dL	2.88 (1.20–6.90)	0.02 ^b

^aAbnormal neurological examination: seizures, abnormal mental status (disorientation or Glasgow Coma Scale <15), cranial nerve abnormality, focal motor deficit, or aphasia.

^bValidated internally by bootstrapping ($p < 0.05$).

CI, confidence intervals; CSF, cerebrospinal fluid; WBC, white blood cell count

rare cause of CAM in our study with only two HIV-infected and five non-HIV-infected microbiologically proven cases. This is in sharp contrast to studies from South Africa. Jarvis and Britz found that *Cryptococcus* spp. and *Mycobacterium tuberculosis* were the most common causes of meningitis in HIV-infected patients in Cape Town and Gauteng with >85% of cases.^{2,4} Although these studies were conducted in cities with high prevalence of HIV, no definitive diagnosis of HIV was obtained in all cases. Therefore, it could not be considered a true reflection of HIV prevalence.

The epidemiology of bacterial CAM in the general population has had changing patterns in the last few years.¹³ Although bacterial meningitis is not one of the most common bacterial infections in HIV-infected patients,¹⁴ the risk of bacterial meningitis in HIV-infected patients has been reported higher than the rest of the population.^{6,9,15} We found very few cases of bacterial meningitis in our cohort, but *Streptococcus pneumoniae* was the leading cause underscoring the importance of the use of steroids to improve morbidity and mortality if bacterial meningitis is highly in the differential.

In contrast, in non-HIV-infected patients, viral etiologies were the most commonly followed by bacterial etiologies. This correlates with the more florid clinical presentation with meningismus of non-HIV-infected patients (headaches, nuchal rigidity, and seizures) due to the acuity of the infection. However, more severe CSF findings such as hypoglycorrhachia and an elevated protein concentration were seen in the HIV-infected group, most likely due to the higher frequency of cryptococcal meningitis.

Twenty-seven percent of all HIV-infected patients had an adverse clinical outcome. In a recent study in Tanzania,¹⁶ the mortality of HIV-infected patients with meningitis was 36%, primarily due to cryptococcal meningitis, whereas a study in Denmark¹⁷ reported a mortality of 20% in patients with cryptococcal meningitis. In our study, only 13% of the patients with cryptococcal meningitis had an adverse clinical outcome. This difference is most likely due to the lack of resources and access to healthcare for prompt treatment in Africa compared to the United States. A low CD4 cell count has been found to be a predictor of poor prognosis in HIV-infected patients with meningitis.¹⁶ Logistic regression analysis did not identify any prognostic factor in our HIV cohort (data not shown in tables). However, among all patients, hypoglycorrhachia and an abnormal neurological physical examination on admission correlated with a poor outcome. This was expected, as both are traditional hallmarks of cryptococcal meningitis and bacterial meningitis.

The Center for Disease Control and Prevention recommends HIV testing as part of routine medical care in all healthcare settings unless HIV seroprevalence rate is documented to be <0.1%.¹⁸ Moreover, the UK joint specialist societies guideline on the diagnosis and management of meningitis recommends HIV testing in all patients presenting with acute meningitis as part of the initial workup.¹⁹ It is surprising that in our cohort, only half of the patients presenting with meningitis (54%) were tested for HIV. Hanson et al. found an alarming 5% of patients admitted to the hospital with acute meningitis not appropriately diagnosed with HIV infection.²⁰ Therefore, it is imperative to test for HIV in patients presenting with meningitis to provide appropriate treatment and linkage to care.

Our study had several strengths. This is the largest study of CAM comparing HIV-infected to non-HIV-infected adults in the United States. Second, only patients who underwent HIV testing were included in the study. Other studies that did not report on the proportion of patients tested for HIV could suffer from diagnostic bias. Last, the large amount of outcomes resulted in a strong multivariable analysis that was internally validated with bootstrap. Despite the strengths, our study had several limitations. First, due to the retrospective nature of the study, some missing data could limit the conclusion of the analysis. There was a high proportion of unknown etiologies indicating an underutilization of currently available diagnostic techniques. Last, the study was conducted in Houston and New Orleans and the results might not be generalizable to other cities in the United States as the epidemiology of HIV is different.

In conclusion, the etiology and clinical presentation of meningitis in HIV- and non-HIV-infected patients is different; however, the clinical outcomes are similar. Hypoglycorrhachia and an abnormal neurological examination at the time of diagnosis are associated with worsening outcome. Despite the availability of ART, cryptococcal meningitis continues to be the most common cause of CAM in HIV population in Houston and New Orleans, but there is still a large amount of patients without an identified etiology. This finding highlights the importance to continue our efforts to improve early diagnosis and access to ART to improve outcomes of HIV-infected patients.

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