

Evolving Failures in the Delivery of Human Immunodeficiency Virus Care: Lessons From a Ugandan Meningitis Cohort 2006–2016

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Background. Because of investments in human immunodeficiency virus (HIV) care in sub-Saharan Africa, the number of people aware of their status and receiving antiretroviral therapy (ART) has increased; however, HIV/acquired immune deficiency syndrome (AIDS) mortality still remains high.

Methods. We performed retrospective analysis of 3 sequential prospective cohorts of HIV-infected Ugandan adults presenting with AIDS and meningitis from 2006 to 2009, 2010 to 2012, and 2013 to 2016. Participants were categorized as follows: (1) unknown HIV status; (2) known HIV⁺ without ART; (3) known HIV⁺ with previous ART. We further categorized 2006 and 2013 cohort participants by duration of HIV-status knowledge and of ART receipt.

Results. We screened 1353 persons with suspected meningitis. *Cryptococcus* was the most common pathogen (63%). Over the decade, we observed an absolute increase of 37% in HIV status knowledge and 59% in antecedent ART receipt at screening. The 2006 cohort participants were new/recent HIV diagnoses (65%) or known HIV⁺ but not receiving ART (35%). Many 2013 cohort participants were new/recent HIV diagnoses (34%) and known HIV⁺ with <1 month ART (20%), but a significant proportion were receiving ART 1–4 months (11%) and >4 months (30%). Four percent of participants discontinued ART. From 2010 to 2016, meningitis cases per month increased by 33%.

Conclusions. Although improved HIV screening and ART access remain much-needed interventions in resource-limited settings, greater investment in viral suppression and opportunistic infection care among the growing HIV-infected population receiving ART is essential to reducing ongoing AIDS mortality.

Keywords: antiretroviral therapy; cryptococcal meningitis; HIV/AIDS; HIV care continuum; sub-Saharan Africa.

The human immunodeficiency virus (HIV) care continuum is the process by which an HIV-infected individual progresses from initial HIV diagnosis to the end goal of viral suppression—a process that occurs simultaneously with HIV disease progression until reversed by effective antiretroviral therapy (ART) [1]. The continuum consists of a series of states in which an individual can exist: (0) unknown HIV status, (1) known HIV status, (2) linked into regular care, (3) receiving ART, and (4) virologically suppressed [2–4]. An HIV-infected population's distribution within this continuum has important

implications for HIV mortality and for the trajectory of the epidemic [5]. The past decade has seen major efforts to scale up HIV care services with a global investment larger than that for any other disease in history [6]. In Uganda, these efforts have significantly improved HIV status awareness and ART coverage [7]. By 2015, an estimated 57% of the 1.5 million Ugandans living with HIV were receiving ART [7].

However, despite this progress in Uganda, the rate of new infections remains high, and, although absolute HIV-associated deaths decreased by an estimated 58% from 2005 to 2015, HIV is still the leading cause of death in adults with UNAIDS estimating 28 000 acquired immune deficiency syndrome (AIDS)-related deaths in 2015 [7]. These trends are largely mirrored in sub-Saharan Africa as a whole [7]. Data on HIV status knowledge and ART coverage among persons developing AIDS in Uganda and much of sub-Saharan Africa over the past decade and presently is lacking. Without this evidence, decisions about prioritizing HIV investments cannot respond to the needs of the subset of HIV-infected individuals most likely to transmit the virus and to die of AIDS-related infections. *Cryptococcus*

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neoformans accounts for 15%–20% of AIDS-related deaths worldwide, is the most common cause of adult meningitis in Africa, and is a sentinel event marking advanced HIV progression to AIDS and high risk of death [8–11]. Early HIV diagnosis, effective ART, and screening for cryptococcal antigen among late presenters are cost-saving interventions that prevent cryptococcal meningitis [12–14]. Among HIV-infected persons receiving ART, cryptococcal meningitis indicates ART failure, and evidence from South Africa suggests a high incidence of cryptococcal meningitis may persist even with improvements in ART access [15].

We describe characteristics of HIV care that led to AIDS progression and risk of death among HIV-infected Ugandans presenting with meningitis, and we assess how the HIV care history of this key HIV-infected population has shifted over this decade of massive HIV care scale up. We conclude by calling for a re-evaluation of HIV investment priorities to keep up with the evolving needs of HIV-infected Ugandans and sub-Saharan Africans.

METHODS

We performed a retrospective analysis of 3 sequential prospective cohorts of HIV-infected adults presenting with suspected meningitis and consenting to receive a lumbar puncture at 2 public hospitals in Uganda: Mulago National Referral Hospital in Kampala and Mbarara Regional Referral Hospital in Mbarara. Our 2006 cohort included patients from May 2006 to September 2009 [16, 17], and our 2010 cohort included screened patients from November 2010 to December 2012 [9, 18]. The 2013 cohort included screened patients from August 2013 to April 2016, with an institutional review board (IRB)-imposed 6-month gap in screening from September 2014 to February 2015 [19].

In each cohort, we interviewed patients to assess knowledge of HIV status and any previous ART receipt. In the 2006 cohort, we screened all persons with meningitis but interviewed a subset of patients with cryptococcal meningitis who survived hospitalization at their time of entry into outpatient HIV clinic. Cryptococcal meningitis was defined as a positive cerebrospinal fluid (CSF) culture, India ink, or cryptococcal antigen. The 2010 cohort screened patients at time of hospital presentation for the Cryptococcal Optimal ART Timing trial, which was an ART strategy trial of timing of ART initiation [18]. Although there was no ART exclusion to being screened when presenting with suspected meningitis, the clinical trial exclusion criterion of previous ART receipt may have subtly biased the patients who were screened. In the 2013 cohort, we further documented initial HIV diagnosis date and the duration of ART in all participants who were eventually alert and oriented. Participants who did not regain normal mental status before death were unable to provide detailed HIV history and ART duration. All participants, or their surrogates, provided written informed consent

and all relevant IRBs in Uganda and Minnesota approved the prospective cohorts in 2006, 2010, and 2013.

Upon receiving a lumbar puncture, we categorized participants as follows: (1) new HIV diagnosis, (2) known HIV diagnosis without previous ART, and (3) known HIV with previous ART. We compared the proportion in each cohort to describe trends in HIV screening and ART access from 2006 to 2016 in persons who developed AIDS. For the subset of participants of the 2006 cohort and the 2013 cohort who were able to provide more detailed information, we categorized HIV history into groups based on immediate history before in-hospital meningitis screening and review of prescribed outpatient medications, including the last ART refill date. Participants were categorized as follows: (1) New/recent HIV diagnosis: HIV status known <1 month prior; (2) Known HIV with <1 mo ART: HIV status known >1 month but receiving ART <1 month or not receiving ART prior; (3) Stopped ART: Started ART but discontinued >1 month prior; (4) 1–4 months ART: Receiving continuous ART for 1–4 months prior; (5) ART virologic failure: Receiving continuous ART for >4 months prior.

Statistical analysis was done in a descriptive fashion and tested for difference between the 3 cohorts using the χ^2 test and the Kruskal-Wallis test. Analysis was done using Stata version 13.1 (StataCorp, College Station, TX).

RESULTS

We screened 1353 persons with suspected meningitis from 2006 to 2016 including 262 in the 2006–2009 cohort, 469 in the 2010–2012 cohort, and 622 in the 2013–2016 cohort (Table 1). Participant age increased significantly from the 2006 cohort to the 2013 cohort (median 34 years, interquartile range [IQR] 29–39 vs median 35 years, IQR 30–42, respectively; $P < .008$). Proportion of women in the cohorts differed significantly, with 42% women in the 2006 cohort, 48% in 2010, and a decrease to 38% in 2013 ($P = .01$). Before 2013, *Cryptococcus* was isolated in 57% (420 of 731) of patients, bacterial meningitis was diagnosed in 1.6%, and 23% were found to have aseptic or viral meningitis, with the remainder unknown [9]. In the 2013 cohort, cryptococcal meningitis was diagnosed in 71% (439 of 620) using first fingerstick cryptococcal antigen lateral flow assay (LFA) screening followed by CSF analysis, and *Mycobacterium tuberculosis* was isolated in cerebrospinal fluid of 3% ($n = 18$) of a cohort subset ($n = 107$) tested by Xpert MTB/RIF assay (Cepheid, Sunnydale, CA) and mycobacterial growth indicator tube culture [20].

Baseline CD4 counts were low, and we observed no significant difference between cohorts over time. In the 2013 cohort, participants diagnosed with cryptococcal meningitis had lower CD4 counts than those with other forms of meningitis (15 vs 89 cells/ μ L, $P < .001$). The absolute number of patients presenting with meningitis to these 2 public hospitals increased from 18

Table 1. Baseline Characteristics and HIV History of HIV-Infected Meningitis Patients 2006–2016

Baseline Characteristics at Hospital Presentation	2006 Cohort (N = 262)		2010 Cohort (N = 469)		2013 Cohort (N = 622)		P Value, Test for Difference
Age in years, median (IQR)	34	(29–39)	34	(29–40)	35	(30–42)	.008 ^d
Women (%)	109	(42%)	223	(48%)	239	(38%)	.01 ^f
CD4 count cells/ μ L, median (IQR, 90th percentile)	20	(7–40, 77)	19	(9–70, 107)	10	(8–73, 173)	.17 ^d
Aware of HIV status, n (%)	40	(56%) ^a	411	(88%)	578	(93%)	.001 ^f
Receiving/ever received ART, n (%)	0	(0%) ^a	10% (estimate)		366	(59%)	<.001 ^f
Cryptococcal meningitis, n (%)	160	(61%)	260	(55%)	439	(71%)	<.001 ^f
Incident meningitis cases per month of active screening	N/A ^b		18.0		24.0		<.001
HIV History Before Hospital Presentation [3]							
	N = 71			N = 426			
HIV status known <1 month	46	(65%)	N/A		143	(34%)	<.001
HIV status known >1 month but receiving ART <1 month or none	25	(35%)			86	(20%)	
Started but stopped ART >1 month prior	0	(0%)	N/A		15	(4%)	
Receiving continuous ART 1–4 months	0	(0%)	N/A		47	(11%)	
Receiving continuous ART >4 months	0	(0%)	N/A		128	(30%)	
Unknown	0	(0%)			7	(2%)	
Total	71	(100%)			426	(100%)	

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; N/A, not applicable.

^aDenominator n = 71.

^bIn 2006–2009, all persons with suspected meningitis were not enrolled due to limited resources.

^cAmong persons alert and oriented to interview. In 2006–2009, limited to persons with diagnosed cryptococcal meningitis.

^dKruskal-Wallis.

^eNonparametric test for trend across ordered groups.

^f χ^2 test.

per month in 2010–2012 to 24 per month in 2013–2016 (33% increase; 95% confidence interval, 18%–50%; $P < .001$).

We observed a major increase in HIV status knowledge at time of hospital presentation from 56% (40 of 71) in the 2006 cohort to 93% (578 of 622) in the 2013 cohort ($P < .001$) (Figure 1). We observed a large increase in antecedent ART receipt at time

of in-hospital screening as well, from 0% in the 2006 cohort to 59% (366 of 622) in the 2013 cohort ($P < .001$). A subset of 71 participants in the 2006 cohort and 426 participants in the 2013 cohort were interviewed to establish date of previous HIV diagnosis and date of ART initiation, if any. Participants in the 2006 cohort subset had far shorter duration of known HIV status

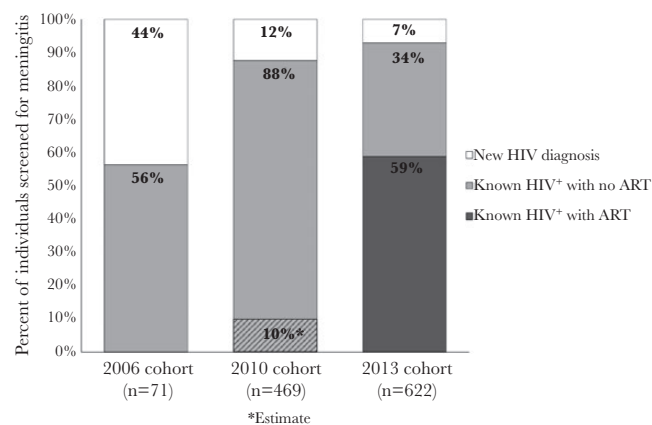


Figure 1. Significant changes in human immunodeficiency virus (HIV) care were observed over the decade. The 32% absolute improvement in HIV status knowledge at time of meningitis presentation from the 2006 cohort to the 2010 cohort indicates significantly increased HIV screening during this time. An estimated 10% of the 2010–2012 persons with meningitis were presenting on antiretroviral therapy (ART). Improvements in ART access have occurred over time. During 2013–2016, 59% were receiving ART among those presenting with acquired immune deficiency syndrome-related opportunistic infections involving the central nervous system.

(median 17 days, IQR 0–79 days) than participants in the 2013 cohort (median 134 days, IQR 10 days–38 months), and 34% (146 of 446) of the 2013 cohort subset had received >4 months of continuous ART.

In the 2006 cohort subset with more detailed HIV care information (n = 71), we categorized 65% (46 of 71) as new/recent HIV diagnosis and the remaining 35% (25 of 71) as known HIV with <1 month ART (Figure 2). Among the 2013 cohort subset (n = 426), we categorized 34% (143 of 426) as new/recent HIV diagnosis, 20% (86 of 426) as known HIV with <1 month ART, 4% (15 of 426) as having stopped ART, 11% (47 of 426) as 1–4 months ART, and 30% (128 of 426) as ART virologic failure. Of the 2013 cohort subset, 2% (7 of 426) could not provide dates and were categorized as unknown. Of the 2013 cohort subset, 30% were categorized as ART failure with a median ART receipt of 35 months (IQR 12–71 months).

DISCUSSION

Despite increased HIV screening and ART access in Uganda, HIV-associated infections such as cryptococcal meningitis have

not disappeared. Indeed, our screening indicates that the absolute number of persons presenting with cryptococcal meningitis increased from 2010 to 2016. In the decade from 2006 to 2016, we observed significant changes in HIV care history among such persons presenting with AIDS and meningitis to the public hospitals where we screened. Our point-of-screening assessment of HIV status knowledge and ART receipt showed large increases in HIV screening and ART receipt before participants' presentation with AIDS, and, among the interviewed subsets of our 2006 and 2013 cohorts, we observed a major shift towards the later stages of the HIV care continuum, mirroring trends in the general population [7]. The decreased proportion of women presenting with meningitis in the most recent cohort is likely associated with efforts to prevent mother-to-child transmission and expanded ART access therein through the Option B+ program (of lifelong ART). The increased representation of men among persons presenting with AIDS reflects the current need for interventions to prevent AIDS progression in men.

Data from our 2006 cohort indicate that the most-needed interventions at that time were HIV screening and ART initiation, and the improvements in HIV status knowledge and ART receipt indicate that these interventions were made with relative success over the decade. A push for ART access at Ugandan public clinics from 2010 to 2013 was likely responsible for the substantial improvement in ART receipt after an earlier increase in HIV screening seen in screened participants [21]. However, our data from the recent 2013 cohort indicate a significant current need for investment in the tools required for HIV-infected individuals to reach and maintain viral suppression, which is the ultimate goal of the HIV care continuum. Most disturbing are the 30% of the 2013 cohort subset in the ART failure category who presented with AIDS and high risk of death after receiving more than 4 months of continuous ART, for whom median ART receipt was 34 months. Immediately before presentation with AIDS, this group was receiving ART for sufficient duration to reverse AIDS progression, yet at the time of our screening these individuals had clearly not been virally suppressed for some time.

Human immunodeficiency virus policy and financing is most effective when it can respond to the current needs of the HIV-infected population. Unfortunately, high HIV burden is often accompanied by weak health systems with poor reporting—making it difficult to identify the needs of the subset of HIV-infected individuals developing AIDS. Our screened cohorts are a substitute for this lack of timely information in a key population at high risk of AIDS-related death, and our observations can promote policy changes with the goal of reducing the number of HIV-infected individuals who enter this high-risk group. In our recent 2013 cohort subset, 34% of participants were categorized as recent HIV diagnosis, a major decline from the 2006 cohort's 65% but still significant to warrant prioritization of HIV screening interventions in Uganda and specific

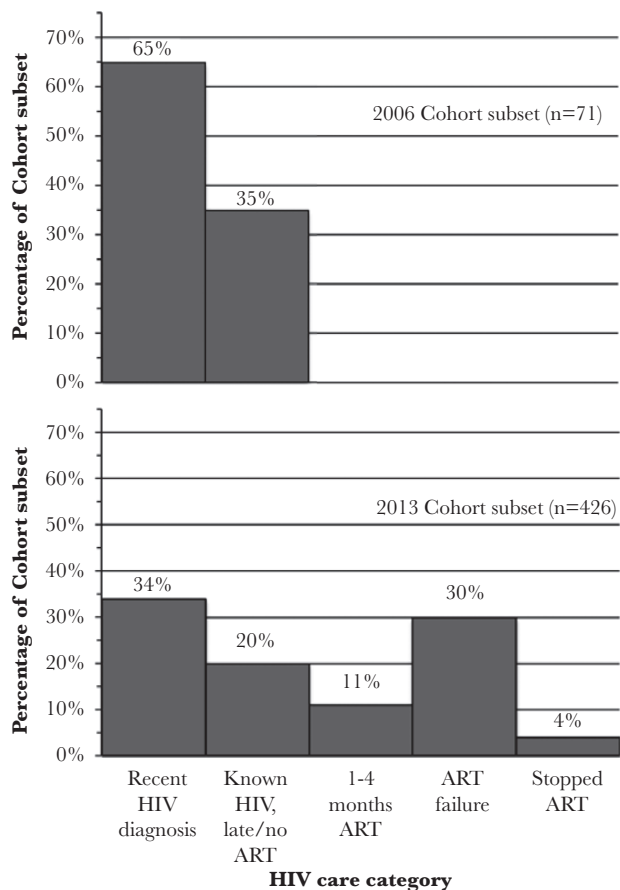


Figure 2. Meningitis patients exhibited a changing experience with human immunodeficiency virus (HIV) care over the decade. Whereas HIV screening and antiretroviral therapy (ART) initiation were key interventions needed in 2006–2009, our 2013–2016 cohort's experience indicates the increasing need for interventions to prevent or address ART failure as well as pre-ART cryptococcal antigen screening.

interventions for late presenters, such as baseline CD4 testing to gauge the degree of immunosuppression and opportunistic infection care to reduce deaths.

However, our 2013 cohort's ART failure group, at 30%, was nearly as significant. This observation underscores the critical need for investment in virologic monitoring, access to newer-generation antiretrovirals, and patient support to ensure that individuals receiving ART achieve virologic suppression, instead of failing treatment and developing AIDS. Policymakers and HIV financiers should be concerned that this group will continue to grow as more of the HIV-infected population is diagnosed with HIV and receives ART. Our 2013 cohort's known HIV with <1 month ART group (20%) and 1–4 months ART group (11%) also illustrate the importance of continued ART scale-up in Uganda. Only 4% of the 2013 cohort subset had started but stopped ART, indicating that the ART program default is not a common event immediately before AIDS hospital presentation. Of note, the most common reason cited for discontinuing ART in this group was adverse medication effects.

Cryptococcal meningitis was by far the most common pathogen directly responsible for hospital presentation in our screened patients. Unlike many opportunistic infections, cryptococcosis can be diagnosed with point-of-care cryptococcal antigen LFA (Immy, Norman, OK) in any locale. Regarding meningitis in particular, our data indicate that investment in cryptococcal antigen screening and preemptive antifungal therapy for early, disseminated cryptococcal infection is another much-needed step to reduce this frequent cause of AIDS-related death. Participants in the known HIV with <1 month ART, 1–4 months ART, and ART failure categories (together 61% of the 2013 cohort subset) could have been eligible for this cost-effective intervention [12, 13].

CONCLUSIONS

This study has several limitations. Our point-of-screening assessment of HIV status knowledge and any ART receipt was a blunt tool that relied on participant self-reporting and medication review. However, previous HIV diagnoses and ART receipt were sufficient to categorize participants into the broad HIV care categories used to identify system failures and areas of improvement. The size of our 2006 interviewed cohort subset was small due to limited resources, but the experiences were consistent with the time period of persons presenting late with opportunistic infections and unknown HIV status. Our 2010 cohort's focus on predominantly ART-naive participants likely yields a slight underestimation of ART coverage among individuals with AIDS in the middle of the decade.

The large size of the 2013–2016 cohort allows for a comprehensive assessment of the current situation among persons presenting with AIDS-related opportunistic infections of the central nervous system. Our assessment of patients failing ART leaves important questions unanswered and requires further exploration, especially given that 30% were receiving >4 months

of continuous ART. From our data, we cannot infer the relative contributions toward ART failure from program factors, patient factors, or whether primary ART resistance was present. However, our data indicate that an area of growing priority for preventing AIDS deaths is achieving and maintaining viral suppression in persons receiving ART. The observed trends and current HIV care needs identified in Uganda likely are generalizable to other sub-Saharan African settings.

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