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Care Continuum and Postdischarge Outcomes Among HIV-Infected Adults Admitted to the Hospital in Zambia

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Background. We characterized the extent of antiretroviral therapy (ART) experience and postdischarge mortality among hospitalized HIV-infected adults in Zambia.

Methods. At a central hospital with an opt-out HIV testing program, we enrolled HIV-infected adults (18+ years) admitted to internal medicine using a population-based sampling frame. Critically ill patients were excluded. Participants underwent a questionnaire regarding their HIV care history and CD4 count and viral load (VL) testing. We followed participants to 3 months after discharge. We analyzed prior awareness of HIV-positive status, antiretroviral therapy (ART) use, and VL suppression (VS; <1000 copies/mL). Using Cox proportional hazards regression, we assessed risk factors for mortality.

Results. Among 1283 adults, HIV status was available for 1132 (88.2%), and 762 (67.3%) were HIV-positive. In the 239 who enrolled, the median age was 36 years, 59.7% were women, and the median CD4 count was 183 cells/mm^3. Active tuberculosis or *Cryptococcus* coinfection was diagnosed in 82 (34.3%); 93.3% reported prior awareness of HIV status, and 86.2% had ever started ART. In the 64.0% with >6 months on ART, 74.4% had VS. The majority (92.5%) were discharged, and by 3 months, 48 (21.7%) had died. Risk of postdischarge mortality increased with decreasing CD4, and there was a trend toward reduced risk in those treated for active tuberculosis.

Conclusions. Most HIV-related hospitalizations and deaths may now occur among ART-experienced vs -naïve individuals in Zambia. Development and evaluation of inpatient interventions are needed to mitigate the high risk of death in the postdischarge period.

Keywords. Africa; care continuum; health systems; HIV infection; hospitalization.

The burden of HIV infection among patients at acute care hospitals in sub-Saharan Africa (SSA) remains high despite scale-up of antiretroviral therapy and substantial progress toward the 90-90-90 targets [1, 2]. In high–HIV prevalence countries, one-third or more of adults admitted to the hospital are HIV-infected [1, 3]. However, data from hospitalizations are rarely fed into HIV program evaluations as most HIV-related activities are centered in outpatient departments and the community, and connections to inpatient services and information are limited [4]. Historically, most hospitalizations were attributed to delayed HIV diagnosis and linkage to care [5]; however, emerging data suggest that the majority of hospitalizations may occur among HIV-infected individuals with substantial time spent in HIV care and on antiretroviral therapy (ART) [6]. Characterizing where hospitalizations occur in the HIV care continuum can help to inform HIV programs.

Hospitalization also presents a window of opportunity to improve retention, viral suppression, and HIV-related mortality. For example, individuals with nonsuppression of HIV RNA could be identified and further evaluated for virological failure and suboptimal retention [7]. Hospitalization also often precedes death, not just during admission [8] but also during the postdischarge period [9, 10]. Mortality during the 6 months after a hospitalization was 23.2% in Uganda [10] and 42.9% in Tanzania [9], and HIV-infected individuals had 1.54 times the odds of postdischarge mortality compared with uninfected individuals [9]. Therefore, hospitalized patients may need more intensive care and follow-up after discharge, although data are scarce and HIV treatment guidelines generally do not address inpatient care.

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In Zambia, we conducted a formative study to characterize the HIV continuum of care for hospitalized patients at a central hospital. We also followed up patients to describe inpatient and postdischarge mortality and engagement in HIV care.

METHODS

Study Context, Population, and Approval

The study was conducted within the Department of Medicine at University Teaching Hospital (UTH) in Lusaka, Zambia, an academic and tertiary care hospital divided into Departments of Medicine, Surgery, Obstetrics and Gynecology, and Pediatrics. Within the Department of Medicine, there are 6 general inpatient wards containing a total of 300 beds, and approximately 20 000 admissions per year are recorded. Each ward is a large open room with up to 75 beds and 1–3 small side rooms (with doors) that can accommodate 2–6 patients for the purposes of TB isolation. Curtains between patient beds provide privacy. Patient files are kept either at the bedside or at the nursing station. Clinical care is free of charge in these wards, although certain laboratory and radiology tests and medications require co-payment.

All patients admitted to the UTH who self-report being HIV-negative or report an unknown HIV status receive diagnostic counseling and testing (DCT), accompanied by 1-on-1 counseling [11]. DCT is provided by counselors on the wards via a point-of-care test for HIV-1/2 antibodies with results provided immediately to patients and documented in the chart. Study approvals were obtained from UTH administration, the University of Zambia Biomedical Research Ethics Committee (Lusaka, Zambia), and the University of Alabama at Birmingham Institutional Review Board (Birmingham, AL).

Sampling Procedures

To recruit a representative sample of inpatients, we adapted a sampling approach used in population-based surveys. We first enumerated the spaces across the wards where patient beds may be located and created a map with each space having a unique number. We then created a randomized list of bed space numbers, allowing for repeats. Using the map, the study nurse or clinician screened consecutive inpatients (using their paper charts) for the following inclusion criteria: age ≥18 years, HIV-positive based on self-report or DCT results, and residence in Lusaka urban district. The reason for admission was extracted from the file as well. If no patient was found at the selected bed space, the screener rotated in a clockwise direction and selected the patient in the nearest bed space. As this was a formative study to gather data for possible interventions to optimize inpatient HIV care, our sample size was dictated by the resources and time available.

Data Collection

If a patient met inclusion criteria per chart review, a study team member spoke briefly with the patient's nurse or clinician and the patient her/himself to assess capacity to provide consent. We excluded those who were too medically unstable to provide consent, usually due to altered mental status and/or comatose state. The remainder were referred to a research assistant who, on the same day or subsequent days, discussed the study in detail with the patient, obtained informed consent, and conducted enrollment procedures. At enrollment, we completed a locator form including participant (and spouse/relatives if possible) phone numbers and directions to their homes.

We collected socioeconomic, HIV care history, and psychosocial data. We asked participants for their dates of HIV diagnosis, initial enrollment in HIV care, and ART initiation. For ART-experienced patients, we asked if they were taking ART at the time of admission. We also assessed disclosure of HIV status to at least 1 relative, structural barriers (time and cost to travel to the nearest HIV clinic), and psychosocial barriers to engagement in HIV care (stigma and alcohol use) [12, 13]. We administered an 11-item version of an established HIV-related stigma scale [14]. Each item was rated on a Likert scale from 0 to 4, and items were weighted equally; therefore, the maximum possible score was 44. We also measured alcohol use by the Alcohol Use Identifications Test-Consumption (AUDIT-C) [15]. Hazardous alcohol use was defined as an AUDIT-C score of 3–12 points for women and 4–12 for men. CD4 count and HIV RNA were also assessed at the time of admission.

We followed patients during the remainder of the hospitalization to ascertain discharge, inpatient mortality, or transfer to another facility. At hospital discharge, we determined the use of ART on discharge based on the discharge summary record. We also ascertained tuberculosis (TB), which was defined as being prescribed multidrug antituberculosis therapy during admission (regardless of the results of TB tests), and cryptococcal meningitis, which was defined by a positive cryptococcal antigen test in cerebrospinal fluid. Three months after discharge, we re-contacted patients/caregivers to assess vital status (alive or dead) and to arrange a home visit. At home visits, we collected additional information on engagement in HIV care since discharge. For patients not on ART at discharge, in the follow-up questionnaire we asked whether they had started/restarted ART since discharge and, if so, if they were currently on it (ie, if they had taken ART in the past 7 days). We assessed the proportion whose medications ran out between discharge and outpatient follow-up. We also assessed the proportion who were re-hospitalized. Finally, we collected a dried blood spot for repeat measurement of HIV VL [16]. Physical tracing was performed up to 2 times for patients who could not be reached by phone call after discharge.

Statistical Analysis

We described the proportion of screened patients with infectious disease vs noncommunicable conditions as the documented reason for admission. To assess selection bias, we

compared enrolled patients with those who were eligible but did not enroll in the study in terms of age, sex, and ward using a rank sum test for continuous variables and chi-square tests for categorical ones. Among enrolled patients, we described an HIV care cascade with the percentages of patients in the following categories: aware of HIV status, diagnosed but never started ART, on ART, on ART for ≥6 months, and VL <1000 copies/mL. Using multivariable Cox proportional hazards regression, we sought to explore possible predictors of postdischarge mortality, including demographics, CD4, TB, ART use, viral suppression, stigma, and alcohol use. Inpatient mortality was considered a competing risk in our analysis. Stata, version 15, was used for statistical analysis (Statcorp, College Station, TX).

RESULTS

From August 25, 2017, to February 28, 2018, during which time an estimated 10 000 adults were admitted to the medical wards, we screened 1283 for inclusion in the cohort. The median age was 38 (interquartile range [IQR], 30–48) years, and 51.2% were women. On admission, 298 (23.2%) were known to be HIV-infected based on report or records, and 982 were eligible for inpatient HIV testing. Of these, 840 (85.5%) received opt-out HIV testing; therefore, only 11.1% of inpatients screened had unknown HIV status. In opt-out testing, 464 additional patients were found to be HIV-infected. Based on reported and tested status, the estimated prevalence of HIV was therefore 67.0% (95% confidence interval [CI], 64.1%–70.0%). Infectious diseases accounted for the majority (63.7%) of reasons for admission among HIV-infected individuals, with pulmonary infections (including TB) being the predominant diagnosed condition. Noncommunicable conditions contributed to only a minority of admissions (30.8% overall and 19.8% among HIV-infected individuals). Among HIV-infected adults, we excluded 67 (8.8%) for home residence outside of Lusaka and 87 (11.4%) for inability to provide consent. We programmatically followed-up 20 of the 82 patients who were deemed critically ill and too sick to provide consent, and 18 (90.0%) of these patients died during hospitalization. Among 608 study-eligible patients, 239 (39.3%) enrolled in the prospective cohort (Figure 1). Most eligible patients did not enroll because they were discharged before enrollment procedures could take place. Men were less likely to enroll compared with women (33.7% vs 44.4%; $P = .007$).

Among the group followed prospectively (Table 1), 223 (93.3%) reported awareness of their HIV status before admission, including 146 patients who underwent inpatient HIV testing. In those with prior awareness, the median time since HIV diagnosis (IQR) was 2.47 (0.47–7.27) years. Of those with prior awareness of HIV status, 206 (92.4%) reported prior ART initiation. Among ART-experienced patients, 53 (25.7%) were recent initiators (<6 months). Among the group with more ART experience (ie, ≥6 months; median, 29.5 months), 74.4% had

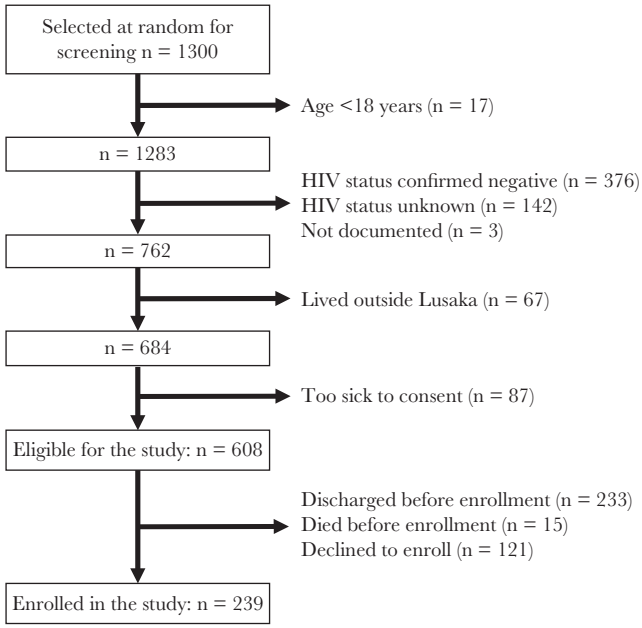

Figure 1. Recruitment flow diagram.

an HIV VL <1000 copies/mL (Figure 2). Therefore, approximately 50% of HIV-infected individuals admitted to the hospital were on ART and virally suppressed. Median CD4+ on admission (IQR) was 181 (52–301) cells/mm^3 among the 143 with available results, 58.7% had a CD4 <200, and 49 (34.3%) had a CD4 <100. Based on CD4 and/or presence of a stage 3 or 4 condition, 170 (71.1%) were considered to have advanced HIV disease. Stigma scores were low on average (median score [IQR], 8 [4–14]) and were similar between patients with prior awareness of status who did and did not openly report it on admission (9 vs 7 points; $P = .41$). Hazardous alcohol use was reported by 34.7% of men and 12.9% of women ($P < .001$).

Among 33 ART-naïve participants, only 6 (18.2%) were initiated on therapy during admission. Coinfections were common during hospitalization, with 58 (25.5%) diagnosed and treated for tuberculosis, 20% of which was extrapulmonary, and 30 (12.7%) treated for cryptococcal meningitis. The median duration of hospitalization (IQR) was 12 (7–20) days. During hospitalization, 13 (5.4%) died and 3 transferred or withdrew from the study, with the remaining 221 patients discharged home.

Three months after discharge, we obtained vital status information for 212 (95.9%) patients. We learned that 164 were alive and 48 (21.7%) had died. In multivariable analysis, higher CD4 count (adjusted hazard ratio [AHR] per 50-cell increase, 0.78; 95% CI, 0.65–0.95) and TB (AHR, 0.26; 95% CI, 0.08–0.90) were associated with reduced postdischarge mortality (Table 2).

Among the 164 patients who were confirmed alive at 3 months, we conducted in-person interviews with 142 and telephone

Table 1. Demographics, Clinical Features, and Outcomes of HIV-Infected Adults Who Enrolled in a Prospective Cohort at the Time of Hospitalization in Lusaka, Zambia, Stratified by HIV Treatment History

		HIV Treatment History[a]			
	Overall (n = 239)	ART-Naïve (n = 33)	Recent ART Starter[d] (n = 53)	ART-Experienced[b] and VL >1000 (n = 32)	ART-Experienced[b] and VL <1000 (n = 93)
Median age, y	36 (30–42)	35 (32–38)	34 (25–42)	36 (30–40.5)	38 (31–47)
Male sex	96 (40.3)	21 (63.6)	28 (52.8)	13 (40.6)	36 (38.7)
Median CD4 count	181 (52–301)	95 (42–197)	123 (44–229)	40 (10–105)	245 (161–377)
CD4 <200 cells/mm^3	86 (60.1)	20 (76.9)	21 (72.4)	20 (87.0)	24 (38.1)
Median time on ART, mo	—	—	1.8 (0.9–3.8)	37.9 (15.4–70.5)	52.1 (24.9–111.3)
Tuberculosis coinfection	58 (25.5)	7 (21.9)	13 (24.5)	14 (45.2)	20 (22.0)
Cryptococcus coinfection	30 (12.7)	10 (31.3)	6 (11.3)	4 (12.9)	5 (5.4)
Inpatient outcome					
Discharge	221 (92.5)	31 (93.9)	42 (79.2)	31 (96.9)	91 (97.8)
Died	13 (5.4)	1 (3.0)	8 (15.1)	1 (3.1)	2 (2.2)
Other	5 (2.1)	1 (3.0)	3 (5.7)	0	0
Postdischarge outcome					
Alive	164 (74.2)	26 (83.9)	30 (71.4)	20 (64.5)	66 (72.5)
Died	48 (21.7)	4 (12.9)	11 (26.2)	9 (29.0)	20 (22.0)
Other	9 (4.1)	1 (3.2)	1 (2.4)	2 (6.4)	5 (5.5)
Readmitted[c]	39 (23.8)	6 (23.1)	9 (17.0)	6 (30.0)	12 (18.2)
VL <1000 at 3 mo postdischarge[c]	82 (50.0)	9 (34.6)	19 (90.5)	3 (27.3)	41 (97.6)

All values are median (interquartile range) or number (%).

Abbreviations: ART, antiretroviral therapy; VL, viral load.

[a]Twenty-eight patients with time on ART >6 months had missing VL and were not categorized.

[b]ART-experienced was defined as ≥6 months on therapy.

[c]Readmission and VL were only assessed among the group of patients who were alive at 3 months after discharge.

[d]Recent was defined as ART start <6 months before admission.

interviews for the remaining 22. Readmission to the hospital was reported by 39 (22.2%) at a median (IQR) of 74 (48–108) days after discharge. Among 128 who reported being on ART at the time of discharge, 29 (22.7%) reported running out of pills before their outpatient follow-up. Among treatment-naïve patients, 5 died during or after hospitalization, and 21 of 22 (94.5%) who were interviewed at 3 months postdischarge reported having started ART. Among 32 patients suspected to have disengaged from ART (>6 months since initiation and VL >1000), 10 died and 17 of 18 were on ART at 3 months postdischarge.

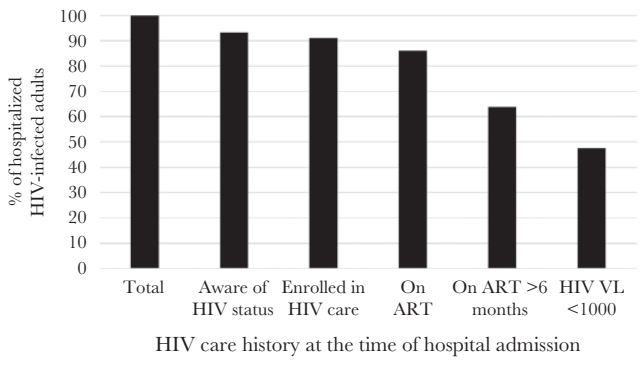

Figure 2. HIV care continuum at the time of admission for hospitalized adults. Abbreviations: ART, antiretroviral therapy; VL, viral load.

DISCUSSION

At a central hospital in Zambia, opt-out inpatient HIV test reached approximately 90% of adults admitted to internal medicine, including many who already knew their HIV-positive status. Among HIV-infected individuals, the majority had already initiated ART, and half were virally suppressed. Advanced HIV disease was common, and at least one-third had either TB or cryptococcal meningitis. After discharge home, early mortality was strikingly high (22%) at 3 months, particularly in those with low CD4. Those diagnosed with tuberculosis had reduced post-hospital mortality. Hospitalization is an opportunity to intervene in HIV-related mortality.

Among hospitalized patients, high levels of awareness of HIV status and prior treatment with ART were observed, building on several other reports. In other studies, 21.7% of hospitalized HIV-infected adults in the Democratic Republic of Congo, 35.4% of hospitalized HIV-infected adults in Kenya, and 65% of hospitalized HIV-infected adults in South Africa had prior ART use [6]. In these studies, the average time from ART start to hospitalization was 3–4 years, similar to our sample. These data are also aligned with data from outpatient HIV programs in Zambia, where most deaths occurred after 1+ years on ART [17]. Our finding that one-quarter of inpatients with >6 months since ART start were not virally suppressed builds on data from a South African emergency department where 32.8% were

Table 2. Factors Associated With Early Postdischarge Mortality Among Hospitalized HIV-Infected Adults in Zambia

	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Age, per 5-y increase	1.00 (0.97–1.03)	0.97 (0.92–1.02)
Female sex	1.02 (0.57–1.82)	1.28 (0.50–3.27)
CD4 count, per 50-cell increase	0.88 (0.81–0.97)	0.83 (0.74–0.95)
ART-experienced[b]	1.75 (0.62–4.97)	1.82 (0.31–10.85)
HIV VL <1000 copies/mL	0.67 (0.36–1.23)	1.04 (0.43–2.53)
On TB therapy at discharge	0.78 (0.39–1.58)	0.29 (0.09–0.95)
Stigma score, per 1-unit increase	0.99 (0.95–1.04)	0.99 (0.92–1.06)
Hazardous alcohol use	0.98 (0.48–2.00)	0.98 (0.35–2.71)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis; VL, viral load.

[a]Cox proportional hazards regression was performed considering inpatient mortality as a competing risk for postdischarge mortality.

[b]ART-experienced was defined as having taken antiretroviral drugs for any duration of time before admission.

not suppressed [7]. Nonsuppression may be more common at inpatient settings, as only 10.8% of patients reporting ART use were not suppressed in a population-based door-to-door survey in Zambia [18]. As expected, patients without viral suppression had lower CD4 counts compared with those with suppression; however, the proportion diagnosed with tuberculosis and *Cryptococcus* was similar across groups. Guidelines for advanced HIV disease were derived from data from outpatients and ART-naïve individuals starting therapy; however, these data suggest the need to develop additional guidelines for co-infection screening even once ART is well established [19].

Another major finding in this study was that the risk of death remains very high after hospitalization [20, 21]. This builds on data from other countries in Africa [9, 10] and postdischarge mortality is more problematic in HIV-infected individuals. In Tanzania investigators concluded that suboptimal engagement in HIV care after discharge was the major driver of post-hospital mortality [9]. Although our study design prevented us from carefully measuring engagement in care in those who died after discharge, survivors of the post-hospital period reported gaps in adherence and/or retention, and several other similar reports have noted major lapses in transitions in care after discharge [9, 22], further supporting the need for strong engagement in HIV care after hospital discharge. Low CD4 was associated with increased risk of postdischarge death, and there was a trend toward lower mortality among those on TB therapy, suggesting opportunistic infections as major causes of death after discharge.

This study also supports the critical role of opt-out HIV testing at clinical settings in SSA (ie, provider-initiated counseling and testing) to identify undiagnosed individuals and to reveal the status to providers. It was interesting that nearly half of HIV-infected adults who knew their status and were taking ART were retested upon admission because they did report being HIV-positive. This builds on a population-based survey in Zambia where 15.3% of HIV-infected adults who reported no prior HIV diagnosis had ART in their blood. Similarly, in emergency departments in the United States and South Africa, HIV-infected patients often failed to report their status to providers [23, 24]. Anecdotally, participants in our study reported not disclosing their status due to lack of rapport with inpatient staff and the presence of family members to whom they had not yet disclosed.

These data have several important implications. Hospitalization should be considered a window of opportunity to make interventions to reduce HIV-related death in SSA. For example, interventions are needed at inpatient settings to diagnose and rapidly start ART at inpatient settings and to identify patients who disengaged from ART or are failing therapy and in some cases re-initiate ART through the "side door" [25], a concept that acknowledges that achieving viral suppression may not occur following a traditional linear care continuum but may include intermittent gaps in retentions. Further, hospitalization provides the opportunity to intervene on causes of death in advanced HIV such as TB and cryptococcal coinfections [19]. Although promising, providing additional interventions at inpatient settings may be challenging as the HIV response has focused on outpatient and community environments. Inpatient units in Zambia and other SSA settings often do not have dedicated pharmacies, labs, and record systems to support HIV-related interventions and often have to rely on nearby outpatient facilities. Our data also provide a rationale to identify ways for HIV programs to use hospitalization surveillance data [4]. As many deaths are preceded by a hospitalization and death is very often underascertained, use of hospitalization data could improve the understanding of program impact.

Major strengths of the study were our use of a rigorous sampling strategy to characterize and recruit participants and our nearly complete follow-up on patients who were discharged from the hospital. However, the study had several limitations. First, the study site was a tertiary care hospital that likely has a higher proportion of HIV-infected patients with advanced disease and ART experience than other facilities, and we excluded critically ill patients. Therefore, our data might not be representative of all hospitalized patients, and we may have over- or underestimated post-hospital mortality. Also, only 40% of eligible inpatients agreed to enroll in the cohort, with men being less likely to enroll than women. This may have led us to overestimate awareness of HIV status and underestimate postdischarge mortality, as Zambian men are less likely to take an HIV test [18] and have increased HIV-related mortality [17]. Despite these limitations, we feel that our data remain informative. Our results also would have been strengthened by less missing CD4 and VL data, although missing data appeared to occur at random. Finally, we did not perform drug resistance testing on patients with high VL, which could be an explanation for nonsuppression [26].

In conclusion, at a central hospital in Zambia, we observed that many HIV-related hospitalizations and deaths in Zambia occur among individuals with substantial prior ART experience. On admission, opt-out HIV testing is critical to raise clinician awareness of a patient's status and provide the opportunity to intervene in suboptimal HIV care. Postdischarge mortality was high, providing rationale to develop and evaluate models of care for hospitalized patients in SSA settings to support appropriate transition to HIV outpatient services and reduce the overall risk of death from HIV infection.

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