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Assessing the impact of HIV status on injury outcomes: A multicenter study of trauma patients in Rwanda[☆,☆☆]

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ABSTRACT

Background: There is conflicting evidence regarding the impact of human immunodeficiency virus serostatus on trauma outcomes in low-resource settings. This study sought to evaluate the impact of human immunodeficiency virus serostatus on mortality outcomes for Rwandan patients presenting after trauma.
Methods: This retrospective review of the University of Rwanda trauma registry captured all adult trauma patients with known human immunodeficiency virus status presenting between March 2011 and July 2015. Confirmed human immunodeficiency virus-positive cases were matched 1:2 with known human immunodeficiency virus-negative controls using a modified Kampala Trauma Score, sex, and district of residence or primary hospital. All-cause mortality was compared using multivariable logistic regression.
Results: In total, 11,280 patients were recorded prospectively in the registry (169 human immunodeficiency virus positive; 334 human immunodeficiency virus negative matches). There was no difference in delay of hospital presentation or time until operation ($P = .50$ and $P = .57$, respectively). Less than 30% of all patients underwent operation during admission ($n = 133$), and the rate of operative intervention was independent of human immunodeficiency virus serostatus ($P = .946$). There was no association between development of any complication and human immunodeficiency virus status ($P = .837$). The overall mortality rate was 8.9% and 3.3% for human immunodeficiency virus-positive and human immunodeficiency virus-negative patients, respectively ($P = .010$). Human immunodeficiency virus positivity was associated with increased 30-day mortality when controlling for potential confounders ($P = .016$; odds ratio 3.60, 95% confidence interval: 1.27–10.2, C statistic 0.88).
Conclusion: Both human immunodeficiency virus and trauma pose substantial public health threats in sub-Saharan Africa. Known human immunodeficiency virus seropositivity in Rwandan trauma patients is associated with early mortality. Further investigation regarding testing, treatment, and outcomes in human immunodeficiency virus-positive trauma patients is warranted and provides an opportunity for leveraging human immunodeficiency virus global health efforts in trauma outcomes assessment.

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Introduction

Efforts to curtail mortality from the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic over the past 20 years have resulted in unprecedented global health and development aid initiatives. Since the HIV epidemic reached its peak in 2006 with more than 2.2 million AIDS-related deaths, the number of patients receiving highly active antiretroviral therapy (HAART) has continued to rise as mortality has simultaneously fallen.[1,2] In 2015, 29.7% of $36.4 billion in development aid was directed at HIV/AIDS treatment and programs.[3] The Ministry of Health of the Republic of Rwanda has prioritized treatment for individuals with HIV, which has resulted in an estimated HIV prevalence among adults 15 to 49 years of 2.9% in 2015 with only an estimated 2,500 AIDS-related deaths among adults older than 15 years during the same year, a figure that has been relatively stable since 2010.[4,5] As recently as June 2016, the Rwandan government in conjunction with the World Health Organization implemented the Treat All program, an initiative to begin all patients with a positive HIV test immediately on HAART.[6,7] Although rates of HIV in Rwanda have been decreasing over the last 20 years,[8] the impact of the disease on outcomes for patients presenting for trauma care and potentially operative intervention has yet to be fully elucidated.[9-12]

There is conflicting evidence regarding whether HIV status, which may or may not include a compromised CD4 count, increases the likelihood of infection or other adverse perioperative events in patients undergoing elective operations.[13,14] The concern may be greater for patients presenting in an emergent setting given the potentially unstable nature of patients presenting for a trauma indication.[15,16] An estimated 973 million individuals worldwide presented with trauma-related injuries requiring treatment in 2013, which accounted for more than 10% of the global burden of disease for the same year.[17] Cherewick et al[18] recently used the Joint United Nations Programme on HIV/AIDS data to estimate that at least 1.5 million operations were needed to meet the surgical needs of individuals living with HIV in sub-Saharan Africa in 2015.[18] A patient presenting in an emergent setting may not have had the benefit of prior HIV testing, and therefore, if the patient is HIV positive, he or she will have not had the benefit of HAART. Very few studies have focused on operative outcomes after trauma for HIV-positive patients, in large part because routine testing is difficult in all settings but especially in low- and middle-income countries (LMICs) where the burden is greater.[19] Because a growing number of LMICs focus on the provision of care for noncommunicable and surgically treatable diseases, understanding the interaction of common comorbidities and surgical outcomes is of ever-increasing importance.[20]

The purpose of the present study was to assess the effects of HIV positivity on post-trauma morbidity and mortality in patients presenting to referral hospitals in Rwanda for acute trauma.

Materials and methods

This was a retrospective, case-control study using a 1:2 matching scheme and the University of Rwanda/University of Virginia trauma registry. All entries between March 2011 and July 2015 were reviewed for any patient with known HIV serostatus. Patients with a known HIV status were matched in a 1:2 ratio with known HIV-negative patients using a modified Kampala Trauma Score (KTS), sex, and district of residence or primary hospital, whenever possible. If only one control was available for a given case, the case was matched 1:1 (Fig. 1). Briefly, Weeks et al[21] reported that a modified KTS can be useful in estimating risk of trauma mortality. The modified score uses age, systolic blood pressure, neurologic status, and number of serious injuries, but it excludes respiratory rate.[21] Cases missing age were matched using an additional component—hospital of principal admission. If a case was missing 2 or more of the previously identified variables, the patient was excluded. Matching was employed to eliminate the variables used for matching as confounders. Increasing the ratio of the match from 1:1 to 1:2 was used to increase both the efficiency and the power of the study. The trauma registry is housed at 2 primary referral and teaching hospitals in Rwanda: Centre Hospitalier Universitaire Kigali in the capital city of Kigali, Rwanda, and Centre Hospitalier Universitaire Butare, which is in Butare, Rwanda. Details related to data collection for the trauma registry have been described previously by Petroze et al.[22,23] In brief, the registry used in Rwanda was adapted from regional trauma registries for local use and collects 31 items related to demographic characteristics, prehospital care, initial physiologic parameters, early interventions, comorbid conditions, and outcomes for up to 30 days of an inpatient admission. Trained data managers entered all data into a password-protected database (Microsoft Access, Microsoft Corp, Redmond, WA). Ethical approval to conduct this study was obtained from the University of Virginia Health Sciences Research Institutional Review Board and the Ethics Committee at the Centre Hospitalier Universitaire Kigali.

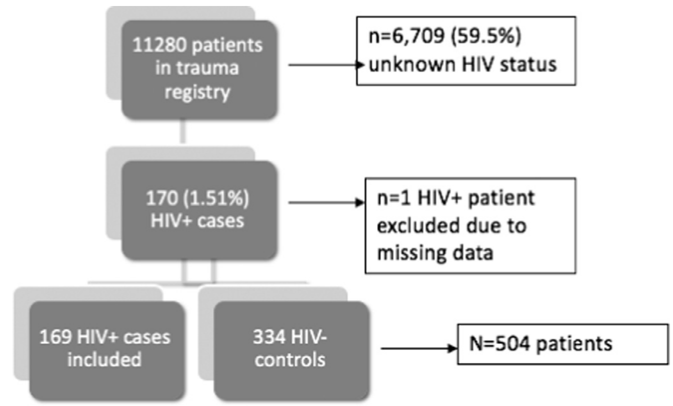

Fig. 1. Flowsheet for case exclusion and inclusion.

Study population characteristics and outcome definitions

We collected peritrauma characteristics for all patients, including age, sex, comorbid conditions, cause of injury, alcohol use, procedures performed, and disposition. All variables, including major comorbidities and postoperative outcomes, were gathered via retrospective data entry from the registry. The primary outcome of the study was 30-day trauma-related mortality, which was defined as any patient dead on arrival, any death occurring on arrival to the accident and emergency department, and any death that occurred within 30 days of trauma admission. HIV status was defined as known HIV-positive, known HIV-negative, or unknown status. Secondary outcomes included determination of 30-day complications and occurrence of any surgical procedure. Complications included surgical site infection (SSI), urinary tract infection, pneumonia, unplanned reintubations, bleeding requiring transfusion, decubitus ulcer or pressure sores, or reoperation, which were abstracted retrospectively from the medical record. Furthermore, a KTS was calculated for each patient. The KTS is an injury severity measurement that has been validated in a developing country, Uganda, but has also been found to be correlated with trauma outcomes in US settings.[21,24] We also calculated a modified KTS for our patient population, which excludes respiratory rate. Less than 15% of our data set had missing variables that precluded calculation of the

Table 1
Study population demographic characteristics and 30-day outcomes ($N = 503$).

Variable	*HIV-positive cases* (n = *169)*	*HIV-negative controls* (n = *334)*	P
Age (y), median (IQR)	39 (30-51.5)	38 (30-50.5)	.488
Male sex, *n* (%)	112 (66.3)	226 (67.7)	.753
Hospital, *n* (%)			
CHUK (Kigali)	90 (53.3)	186 (55.7)	
CHUB (Butare)	79 (46.8)	148 (44.3)	.604
Mechanism of injury, *n* (%)			
Road traffic injury	76 (45.2)	158 (47.7)	
Burn	9 (5.4)	11 (3.3)	
Fall	53 (31.6)	106 (32.0)	
Blunt force	19 (11.3)	37 (11.2)	.552
Alcohol use, *n* (%)			
Confirmed/suspected	22 (13.8)	29 (9.5)	
Unknown use	4 (2.5)	15 (4.9)	
None	134 (83.8)	263 (85.7)	.192
Disposition from A&E, *n* (%)			
Home	35 (21.7)	81 (25.2)	
Referred	6 (3.7)	9 (2.8)	
Died	12 (7.5)	4 (1.2)	
Admitted	108 (67.1)	225 (69.9)	
Direct to operating theater	22 (20.4)	77 (34.2)	
General ward	80 (49.7)	129 (57.3)	
High-care unit	4 (3.7)	17 (7.6)	
Intensive care unit	2 (1.9)	2 (0.89)	.001
Serious injury, *n* (%)			
One serious injury	141 (83.4)	290 (86.8)	
More than 1 serious injury	19 (11.2)	32 (9.6)	
No serious injury	9 (5.3)	12 (3.6)	.532
Systolic blood pressure (mm Hg), median (IQR)	121 (110-134)	123 (111-135)	.583
Heart rate (beats/min), median (IQR)	84 (72.5-97)	84 (74-95)	.826
Modified KTS, median (IQR)	12 (11-12)	12 (11-12)	.750
Overall 30-day mortality, *n* (%)	15 (8.9)	11 (3.3)	.008
Any operation, *n* (%)	45 (26.6)	88 (26.4)	.946
Overall 30-day complications, *n* (%)	2 (1.2)	6 (1.8)	.604

A&E, accident and emergency; *CHUB,* Centre Hospitalier Universitaire Butare; *CHUK,* Centre Hospitalier Universitaire Kigali; *IQR,* interquartile range.

modified KTS. For these patients, alternative characteristics were used for matching (see details earlier in Methods section).

Statistical analyses

Patient characteristics were aggregated to report demographic and peritrauma factors. The distributions of demographic and clinical variables were analyzed to compare patients based on HIV status using bivariable analysis. Distributional characteristics of categorical variables are expressed as frequencies and percentages for categorical values. The statistical significance of differences in the proportional distribution of categorical variables was assessed using Fisher exact test or χ^2 test, as appropriate. The distributional characteristics of continuous variables are expressed using the median and interquartile range, and the statistical significance of differences in medians was assessed using the Mann-Whitney *U* test. Univariable and multivariable logistic regression analyses were used to test the effect of clinical covariates on the primary study outcome of 30-day mortality. A multivariable model testing the association between covariates and 30-day mortality was performed. Stata Version 14.2 software (Stata Corporation, College Station, TX) was used for data management and statistical analysis.

Results

Review of the University of Rwanda/University of Virginia trauma registry indicated that there were 11,280 patients with an acute trauma admission during the nearly 4.5-year study period. Of these, most patients had an unknown or missing HIV status ($n = 6{,}709$, 59.5%). Of the remaining patients with a known HIV status ($n = 4{,}571$, 40.5%), 170 were HIV positive (1.51% of the registry population) and 4,400 were HIV negative (39.0% of the registry population). One of the known HIV-positive patients was excluded because of missing data precluding a match. For 4 known HIV-positive patients, there was only 1 available control HIV-negative match, and these patients were matched 1:1. The final cohort included 503 patients, 169 HIV-positive cases and 334 HIV-negative matched controls. Demographic and clinical variables were similar between HIV-positive cases and HIV-negative controls, as described in Table 1. Patients in both groups were well matched for age, sex, hospital where initial care received, and mechanism of injury ($P >$ .488). In total, 333 patients were admitted to the hospital (66.2%). Patients who were HIV-negative were more likely to be admitted to the hospital ($n = 225$, 69.9%, vs $n = 108$, 67.1%; $P = .001$) and were also more likely to receive admission to the high care or intensive care units ($n = 19$ vs $n = 6$). Physiologic parameters, including systolic blood pressure and heart rate obtained on admission, were not statistically different between HIV-positive and HIV-negative patients (all $P >$ .583). Median modified KTS scores were similar between HIV-positive patients and HIV-negative patients ($P = .750$).

Table 2
Operations received among patients presenting for trauma ($n = 503$).

Operation	*HIV positive* (n = *169)*	*HIV negative* (n = *334)*
Craniotomy	3	1
Laparotomy	1	4
Open fracture reduction	30	49
Operative wound debridement	14	37
Total operations	48	91

Just under one-third of all patients in our cohort underwent any operative procedure. Operations received included craniotomy, laparotomy, open fracture repair, and operative wound debridement (Table 2). There was no significant difference in receipt of

Table 3
Outcomes among patients still admitted at 30 days ($n = 72$).

Variable	HIV positive ($n = 38$)	HIV negative ($n = 151$)	P
Any 30-day complication, n (%)	1 (10.0)	5 (8.1)	.837
Any operation, n (%)	6 (60.0)	25 (40.3)	.244
30-day inpatient mortality, n (%)	0 (0)	0 (0)	n/a

n/a, Not applicable.

Table 4
Independent association between 30-day mortality and perioperative factors.

Variable	Odds ratio	95% CI	P*
HIV-positive status	3.60	1.27–10.2	.016
Age (y)	1.02	0.99–1.05	.244
Glasgow Coma Scale score (3–15)	0.56	0.47–0.66	<.001
Any operation	0.17	0.021–1.42	.102

* P value < .05 considered significant by multivariable logistic regression.†C statistic for model is 0.88.

operative intervention based on HIV status ($P = .946$). Among patients admitted to the hospital, 72 patients remained in-hospital for at least 30 days ($n = 72$ of 333, 21.6%). The 30-day complication rate for patients still admitted at 30 days was similar for HIV-positive cases ($n = 1$, 10%) and HIV-negative controls ($n = 5$, 8.1%, $P = .837$). The only complication among HIV-positive cases was an SSI ($n = 1$) compared with SSI ($n = 2$) and other complication ($n = 2$), which were the most common complications among HIV-negative controls. In addition, HIV-positive cases and HIV-negative controls were equally likely to undergo any operation ($n = 6$, 60% vs $n = 25$, 40.3%, $P = .244$ [Table 3]). No patients remaining in-hospital at 30 days experienced an inpatient mortality.

The primary outcome of interest, 30-day mortality, was investigated in relation to relevant clinical covariates using both univariable and multivariate logistic regression analyses (Table 4). Overall mortality for the patient population was 5.2% ($n = 26/503$); mortality rate was 8.9% ($n = 15$) and 3.3% ($n = 11$) for HIV-positive and HIV-negative patients, respectively ($P = .010$). The primary diagnoses for HIV-positive patients who died included 8 patients with head injury, 2 with burn injuries, and 2 with chest trauma; 5 sustained multisystem trauma. Among HIV-negative patients who died, primary diagnosis included 8 patients whose injuries included head trauma and 4 whose injuries involved chest trauma; only 3 total patients sustained multisystem trauma. There was no statistical difference in mechanism of injury (ie, falls, burns, road traffic injury, blunt force) between HIV-positive patients who died and HIV-negative patients who died ($P = .655$). One HIV-positive patients who ultimately died underwent an operative procedure compared with no HIV-negative patients ($P = .382$). When controlling for potential confounders, including receipt of a peritrauma operation, patients with HIV-positive status were 3.60 times more likely to experience any 30-day mortality event compared with HIV-negative controls (95% confidence interval [CI]: 1.27–10.2, $P = .016$). The multivariable model also revealed that patients with a lesser Glasgow Coma Scale (GCS) score on admission were more likely to experience a 30-day mortality event (odds ratio [OR] 0.56, 95% CI 0.47–0.66, $P < .001$). A C statistic of 0.88 indicates a good capacity of the multivariable logistic regression model to discriminate between patients who did and did not experience a 30-day mortality event.

Discussion

Using short-term data from a trauma registry and multivariate analysis, we found that HIV-positive patients were 3.60 times more likely to experience a mortality compared with their HIV-negative counterparts. There are minimal data regarding outcomes for HIV patients presenting for trauma care—indeed, most prior data examined outcomes for elective orthopedic indications only.[11] Findings from the present study have clinically important implications for the triage and planning of care for patients living with HIV in Rwanda and underscore the importance of the Treat All approach mandate currently being implemented in-country.[6,7] The 1.51% HIV-positive rate for our study population is well under the known population prevalence of HIV, particularly in the capital city of Kigali, where the best estimate of HIV positivity is currently ~3%.[4] This may be because seropositive status in our study reflects only patients with a known status and not those who had been tested prospectively. In Rwanda there is ample funding for HIV, and total HIV spending in fiscal year 2011–2012 was USD $234.6 million. This massive funding effort resulted in greater than 90% of eligible adults and children receiving antiretrovirals in 2013. [4] In Rwanda there is increased access to medical care for HIV-positive patients; although we suspect known HIV-positive patients in our study may be a subset who are on HAART, this figure is unknown because of limitations of our study design as a retrospective analysis. An important caveat to understanding HIV treatment in Rwanda is that virus genotype and drug susceptibility are not tested before commencement of HAART. In general, first-line drugs are used for new diagnoses and viral load is checked at 1 year. At that time, depending on response to treatment, the cycle of genotype testing may begin and subsequent second-line or third-line drugs initiated. Therefore, if trauma patients have a new diagnosis within the past year, they may be more susceptible to HIV-related mortality if they are on a resistant HAART regimen.

Given the high percentage of eligible patients receiving treatment in Rwanda, we hypothesized that a large proportion of patients in our cohort with known HIV-positive status were likely receiving antiretroviral therapy, but despite this possibility, we found a robust association with increased overall and inpatient mortality among this group. Unlike the ample funding for HIV care, there is little funding for trauma and other related noncommunicable diseases.[25] In 2000, mortality from HIV/AIDS was growing by nearly 10% per year in LMICs. After the creation of the Millennium Development Goals in 2001, an unprecedented global aid effort has unfolded, with $10.8 billion USD, or 30% of development assistance for health, being directed toward HIV/AIDS care in 2015. At the same time, only 1.3% of funding was directed toward noncommunicable disease.

This is true despite the fact that trauma is the most common cause of surgically treatable disease in LMICs.[3] Since the year the trauma registry was initiated in 2011, multiple studies have reported the cost-effectiveness of tackling surgically treatable illnesses in LMICs.[25,26] Building HIV status into future trauma or general surgical registries could be a bridge to linking efforts that target both communicable diseases, like HIV and noncommunicable diseases. Linking funding for these seemingly disparate issues enhances communication and collaboration with the existing stakeholders in global health who have previously been skeptical regarding funding for efforts targeting operations performed in LMICs. Furthermore, findings of our present study are in line with those of prior authors from Malawi who investigated barriers to implementing universal HIV testing and counseling (HTC) on surgery wards using existing infrastructure and found that it was feasible, despite a much greater recent HIV rate of 11%.[27,28] Rwanda's HIV rate is much less with a smaller overall population, which would ease implementation of such a program.

We found no difference in overall complications or in complications among patients still admitted to the hospital at 30 days. This observation is consistent with previous research investigating outcomes for HIV-infected and noninfected individuals in both low- and high-income countries.[29] We found that patients with lesser GCS scores are significantly more likely to experience a 30-day mortality event. This is consistent with previous analysis from the Rwanda trauma registry, which found that an initial GCS score of 3 to 8 had the greatest association with mortality.[30] In one of the largest studies comparing outcomes among patients undergoing various general surgery procedures, Horberg et al[12] reported increased complications only for individuals with a CD4 cell count less than $50/\mu L$. Their study did not include patients presenting for trauma indications. Unfortunately, data on outcomes for this population in LMICs are mostly limited to patients undergoing operations for orthopedic indications rather than an overall trauma population.

Finally, patients who are HIV negative may be more likely than those who are HIV positive to require complex post-trauma care in the intensive care unit (ICU) or high-dependency unit (HDU), given a greater likelihood of survival among HIV-negative patients. It is possible that patients had equivalent need for ICU/HDU admission regardless of HIV status, but there was a reason that HIV-positive patients were admitted at a lesser rate to the ICU/HDU. If so, this could have contributed to their morbidity and mortality. We must ask the following question: How does being HIV positive in an acute trauma setting influence clinical decision-making?[31,32] Practitioners caring for patients in Rwanda have reported rare instances where HDU/ICU admission was refused for HIV-positive patients even when the HIV disease was well-controlled, and this serves as a potentially confounding factor for the present study. It should be noted that delayed care for HIV-positive patients has not been reported or studied among trauma patients in Rwanda. Future studies should focus on this aspect of patient care and added barriers to care for HIV-positive trauma patients.

Although we believe that HIV is an important factor to examine for trauma patients in Rwanda, we also acknowledge the high rate of in-emergency department mortality. In total, 16 patients died in the emergency department, which represents just more than 60% of total mortalities in the current data set. Furthermore, the most common primary diagnosis for patients who died regardless of HIV status included head trauma, raising the possibility that severe traumatic brain injury or hemorrhage played a primary role in hospital mortality. Despite the association between HIV status and mortality, there are likely many other factors related to early mortality in this study population, and therefore this outcome should not be attributed to HIV alone. To incriminate HIV, one would need more clinical, biologic, and virologic parameters, such as CD4, viral load, or clinical stigmata of self-neglected disease such as oral thrush, Kaposi sarcoma, tuberculosis, and so on, which is not available for the present study.

Our study had several limitations, the first of which is that HIV status was self-reported by patients or found in prior chart documentation, such as insurance records from an NGO providing HIV care. In fact, HIV status was initially added to the registry to provide background information for eventual prospective HIV testing and to provide opportunities for grant funding within the better funded HIV realm. Unfortunately, at present, the trauma registry is unfunded. Additional limitations of the present study include a lack of data on comorbidities, such as hepatitis C, HAART therapy, and CD4 counts, for HIV-positive patients. Although there is limited information regarding short- and long-term outcomes for HIV-positive patients experiencing trauma in LMICs, studies examining outcomes for an overall ICU-admitted population of HIV-positive patients have reported only weak associations between CD4 counts and worse outcomes for these patients.[13,33-35] Regardless, the need for inclusion of HIV-specific variables in future registries is of the utmost importance to aid in increasing accuracy of risk stratification and prediction. In addition, most registry patients did not know their HIV serostatus, which places them at greater risk for disease transmission regardless of their overall risk of experiencing a trauma event.[36]

In conclusion, although there is no association between HIV serostatus and delayed presentation or likelihood of operative intervention among trauma patients in this study, there is a definite association with early mortality. Further investigation regarding testing, treatment, and outcomes in HIV-positive trauma patients in low-resource settings is warranted. Studies investigating HIV seropositivity in trauma patients in LMICs provide a unique opportunity for collaboration in global health funding and a way to potentially leverage HIV/AIDS development assistance for noncommunicable diseases such as trauma.

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