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Impact of sickle cell disease on presentation and progression of paediatric HIV: a retrospective cohort study

Joseph Ssenyondwa[1,2], Paul E. George[3], Juan Carlos Bazo-Alvarez[4], Rebecca Mercedes[3], Jacqueline B. Kanywa[1], Ernest Naturinda[1,2], Peter L. M. Wasswa[2,3] and Joseph Lubega[2,3]

1 *Baylor College of Medicine Children's Foundation, Kampala, Uganda*
2 *Texas Children's Hospital – Global HOPE Program, Kampala, Uganda*
3 *Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA*
4 *Instituto de Investigación, Universidad Católica Los Angeles de Chimbote, Chimbote, Perú*

Abstract

OBJECTIVES HIV and sickle cell disease (SCD) are significant causes of morbidity and mortality in sub-Saharan Africa. Given their separate roles in immune dysregulation, our objective was to characterise the impact that SCD has on the presentation and progression of paediatric HIV.
METHODS The study was a retrospective cohort study (study period 2004–2018). Cases of HIV + and SCD-afflicted patients (HIV+/SCD+) were obtained via electronic chart review from a paediatric HIV clinic in Kampala, Uganda and matched 1:3 with HIV + controls without SCD (HIV+/SCD-).
RESULTS Thirty-five HIV+/SCD + subjects and 95 HIV+/SCD- controls were analysed (39% female (51/130), age 3.6 years (SD3.9)). At baseline, WHO clinical stage (64% total cohort Stage III/IV) and nutritional status (9.4% severe acute malnutrition) were similar for both groups, whereas HIV+/SCD + had higher though non-significant baseline CD4 count (1036 (SD713) vs 849 (SD638) cells/microlitre, $P = 0.20$, two-tailed t-test). There were 19 deaths, 6 (17%) HIV+/SCD + and 13 (14%) HIV+/SCD-, with unadjusted/adjusted models showing no significant difference. Nutritional progression and clinical stage progression showed no significant differences between groups. Kaplan–Meier analysis showed a slower rate of treatment failures in the HIV+/SCD + cohort ($P = 0.11$, log-rank survival test). Trajectory analysis showed that in the time period analysed, the HIV+/SCD + cohort showed a more rapid rise and higher total CD4 count ($P = 0.012$, regression analysis).
CONCLUSION The study suggests that SCD does not adversely affect the progression of HIV in patients on ART. Further, HIV+/SCD + achieved higher CD4 counts and fewer HIV treatment failures, suggesting physiological effects due to SCD might mitigate HIV progression.

keywords HIV, sickle cell disease, Uganda, Africa, CD4, paediatric

Sustainable Development Goals (SDGs): SDG 2 (zero hunger), SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)

Introduction

Human immunodeficiency virus (HIV) infection is most prevalent in sub-Saharan African and is an ongoing public health challenge despite extensive efforts towards its prevention and treatment [1]. According to recent data, 36.7 million people are living with HIV worldwide, of whom 25.6 million are in sub-Saharan Africa [1]. In Uganda, 1.5 million people are estimated to be living with HIV, of whom 150 000 are aged between 0 and 14 years [2]. Similarly, sickle cell disease (SCD) is a lifelong illness endemic to sub-Saharan Africa and characterised by chronic anaemia, vaso-occlusive crises, heightened inflammation and splenic dysfunction, increased risk for infections, stroke and end-organ damage [3]. It is most prevalent in people of African and Mediterranean descent with estimates of 75% of the world's SCD patients living in sub-Saharan Africa [4].

In Africa, SCD contributes substantially to mortality in children, especially those under the age of 5 years, with some estimates that SCD contributes to about 15% of under-5 mortality [4-6]. In Uganda, 0.7% (15 000) of newborns are estimated to be born with SCD every year, demonstrating its significant public health burden [7].

Both HIV and SCD are chronic inflammatory disorders that lead to immune dysregulation. HIV causes

Joseph Ssenyondwa, and Paul E. George are Co-first authors.

destruction of CD4 + lymphocytes, causing a milieu of immune dysregulation and chronic immune suppression that ultimately predisposes to opportunistic infections, malignancy and end-organ damage [8]. SCD is also characterised by immune dysfunction, through pathophysiological mechanisms of which defective splenic function, dysregulated antibody and cytokine response, micronutrient deficiency and tissue infarction are significant factors [9]. Children with SCD are highly susceptible to severe infections, including pneumonia, meningitis, osteomyelitis, septicaemia and severe malaria [3,5].

The pathophysiologic interactions of SCD and HIV are complex and difficult to intuitively deduct [10,11]. This overlap of immune dysregulation may pose significant and unique management challenges as both illnesses independently cause significant morbidity and mortality, especially in the paediatric population [5,8,12,13]. Children and adolescents with HIV infection at Baylor College of Medicine Children's Foundation-Uganda (Baylor-Uganda) received anti-retroviral therapy (ART) in a tertiary specialist paediatric setting with routine CD4 monitoring and management of opportunistic diseases according to the WHO guidelines [14]. Children with SCD are referred to the affiliated national referral centre for management by paediatric haematologists.

The aim of this study was to evaluate the combined impact of co-existence of HIV and SCD on the clinical course and outcomes of children undergoing anti-retroviral therapy (ART). The specific objectives of the study were to determine (a) how SCD affects the baseline (i.e. at ART initiation) characteristics, including disease severity, nutritional, immunologic and haematologic status of patients with HIV and (b) how progression and outcomes of paediatric HIV are influenced by co-existence of SCD, by examining overall survival, ART first-line failure, nutritional, immunologic and haematologic status of the patients.

We hypothesised that SCD synergistically or additively exacerbates the progression, morbidity and mortality of HIV infection. However, conversely, it is plausible that the complex immune interactions between SCD and HIV counteract and mitigate HIV progression because SCD is associated with asplenia and impaired antigen processing both of which are critical to HIV pathogenesis [15].

Methods

Study population and sample

Children with HIV infection with/without SCD were identified from the electronic medical records (EMR) of Baylor-Uganda, a family-centred paediatric and adolescent HIV clinic in Kampala, Uganda. Patients with both HIV infection and SCD (HIV+/SCD+) were identified using the search key words "sickle, sickle cell, sickler, SCD, and SCA." Next, we manually confirmed via chart review these key words corresponded to a diagnosis of SCD in each patient. The standard method of diagnosis of SCD at Baylor-Uganda is haemoglobin electrophoresis. All patients with HIV and SCD who met inclusion criteria were included in the study sample.

Only patients < 19 years old at commencement of ART, who started ART between 1 January 2004 and 1 May 2018, with documentation of a confirmed diagnosis of HIV infection defined as two positive assays were included. Patients who had started ART before enrolling into the Baylor-Uganda COE were excluded. An SCD positive patient was defined as one whose medical record listed him/her as a patient with SCD. For each HIV+/SCD + patient, three patients with HIV but without SCD (HIV+/SCD-) were identified from the EMR, matched for age, sex, age at ART initiation (within six months) and date of ART initiation (within one year). The sampling process is summarised in Figure 1. Our target was to detect a clinically significant difference in mean CD4 that equates to normal *vs.* mild CD4 suppression, that is 500 cells/μl *vs.* 350 cells/μl, as per WHO guidelines [14]. Given this goal, *post hoc* power analysis estimated the available sample size to have> 95% power to detect that difference in CD4 at alpha of 0.05.

Data collection

The following variables were collected from the EMR at baseline and, where applicable, at 1 year and 3 year post-ART commencement: age and date at ART initiation, vital status and date of last follow-up, ART treatment line, treatment failure and date, WHO clinical stage, CD4 counts, haemoglobin levels, weight and height. Briefly, WHO clinical staging is a standardised classification system often used in resource-limited settings that describes the progression of symptomatic HIV infection, with Stage 1 and 2 representing mild to moderate disease, and Stages 3 and 4 representing severe disease [16]. Severe acute malnutrition (SAM) was determined using WHO guidelines based z-scores of less than −3 as follows: weight for height z-score (WHZ) for under 5 years, body mass index for height z-score (BMIZ) for 5 years and older, and height for age z-score (HAZ) for stunting [17].

Patients were considered lost to follow-up (LTFU) per Uganda Ministry of Health guidelines if they (a) missed an appointment and had not returned to clinic for> 90 days after the missed appointment and (b) if the clinic staff was unable to reach the family through phone

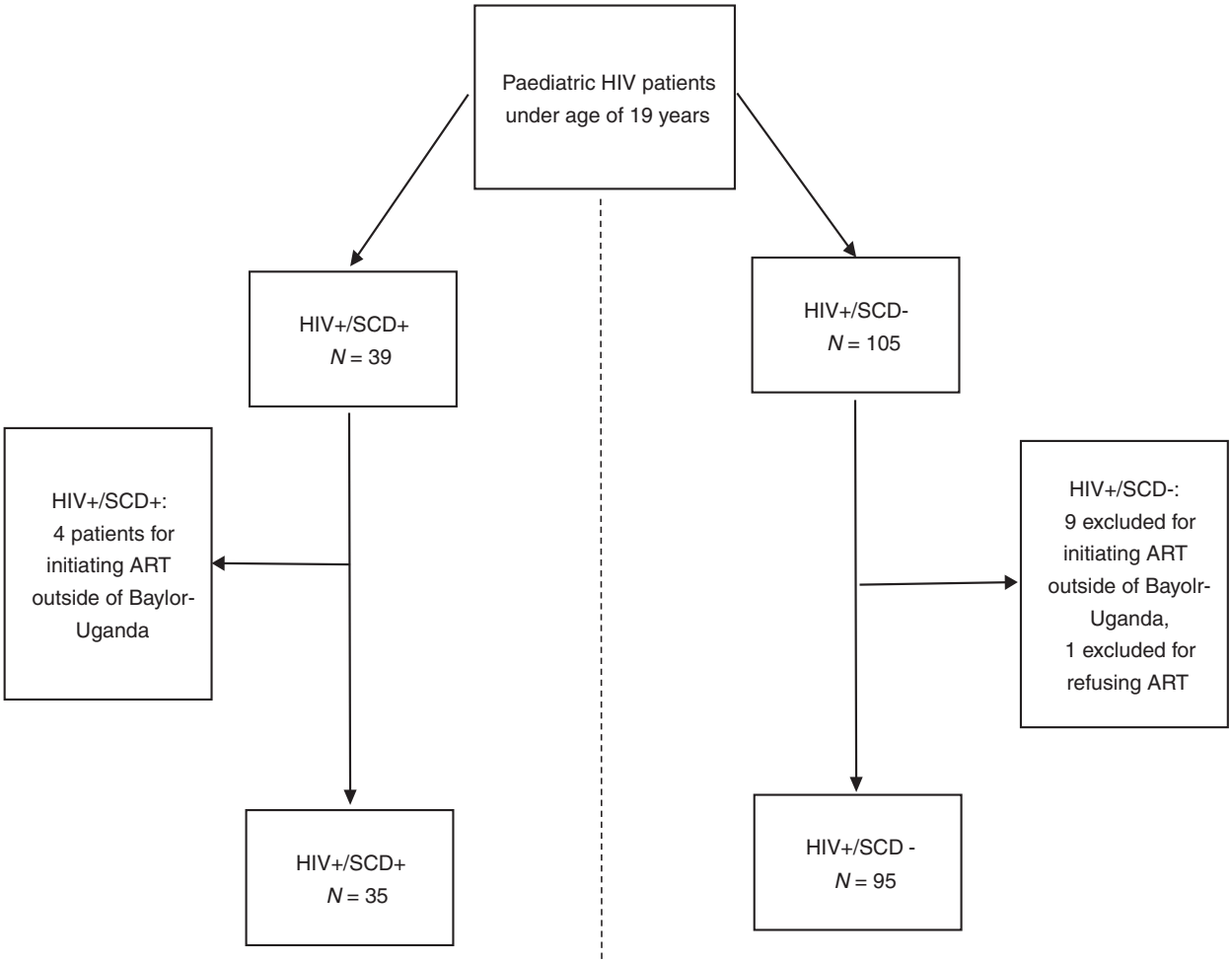

Figure 1 Flow chart for patients included in the analysis and reasons for exclusion.

calls or home visits during the same 90-day period. Baseline date was defined as the ART initiation date. The 1-year time point included data from 6 months to 18 months post-ART initiation, and the 3-year time point included data from 30 months to 48 months. If more than one data point was available for the given time frame, the data point closest to the 12- or 36-month time point was chosen.

Statistical analysis

Descriptive statistics were used to show the main characteristics of the HIV+/SCD + *vs*. HIV+/SCD- patients at baseline, 1st year and 3rd year of follow-up. The descriptive variables included age, sex, WHO stage, CD4 count, nutritional status and haemoglobin. For CD4 count, we made comparisons at baseline, 1st year and 3rd year of follow-up between both groups of patients, by using a two-tailed t-test for independent samples.

We performed survival analysis to compare time to event for HIV+/SCD + *vs*. HIV+/SCD-. The events of interest were death, lost to follow-up and change to second-line therapy. For each outcome, we computed log-rank test and estimated unadjusted hazard ratios (HR). We also estimated these HR adjusted for nutritional status, CD4 absolute count, WHO clinical stage, treatment line, sex and age, all at baseline. To handle missing values, we performed a multiple imputation procedure on covariates only.

We performed a longitudinal analysis over three time points (baseline, 1st year and 3rd year) for three outcomes: CD4 count, nutritional status (WHZ/BMIZ and

HAZ) (all treated as continuous variables), and WHO treatment stage (treated as dichotomous, Stages I/II versus Stages III/IV). To model each outcome trajectory over time, we fitted random intercept and slope models to account for the within-individual correlation (unstructured) and handle missing outcome records over time by using a restricted maximum likelihood (REML) function. Results reported with beta values or odds ratios (OR) come from these random-effects models.

A more detailed explanation of the statistical analysis is provided in the appendix. We used Stata 14 for all the statistical analyses and reported *P*-values and 95% confidence intervals for the main estimates.

Results

In total, 35 HIV+/SCD + subjects and 95 HIV+/SCD- controls were identified that met inclusion criteria (Figure 1). The mean age of the two groups was similar, 3.6 years for HIV+/SCD + and 3.6 years for HIV+/SCD-. The age structure of both groups was also similar with most patients in the 1– 4 years (pre-school children) age group (Table 1). At presentation, 64% of patients had advanced HIV (WHO Stage III or IV). Other than lower baseline haemoglobin in HIV+/SCD + than HIV+/SCD- patients (7.3 g/dl (SD 1.7) *vs.* 9.9 g/dl (SD 2.0)) respectively, the cases (HIV+/SCD+) and controls (HIV+/SCD-) arms of the cohort had similar characteristics at baseline.

Table 1 Baseline characteristics of the study population

	Exposed (HIV+/SCD+)	*n*	Control (HIV+/SCD-)	*n*
Gender (Female)	43%	35	38%	95
Mean Age (SD) years	3.57 (3.88)	35	3.55 (3.92)	95
Age categories		35		95
<1 years	3%	1	6%	6
1–4 years	71%	25	71%	67
5–12 years	20%	7	17%	16
13–19 years	6%	2	6%	6
WHO Stage		34		92
I and II (Non-severe)	38%	13	35%	31
III and IV (Severe)	62%	21	65%	57
CD4 count (SD) cells per microlitre	1036 (713)	33	849 (638)	91
Nutritional status				
WHZ/BMIZ (SD)	−1.1 (1.8)	35	−0.8 (1.7)	94
HAZ (SD)	−2.7 (1.2)	35	−2.4 (2.3)	94
Severe malnutrition	11.4%	4	8.6%	8
Severe stunting	40.0%	14	41.5%	39
Haemoglobin	7.3 (1.7)	28	9.9 (2)	84

Baseline refers to values at anti-retroviral therapy initiation. *n* = number of subjects for whom there is data available at each time point; SD = Standard deviation; WHZ = weight for height z-score; BMIZ = body mass index z-score; HAZ = height for age z-score. Severe acute malnutrition is WHZ/BMIZ < −3; Severe stunting is HAZ < −3.

Overall survival and treatment failure-free survival

Figure 2 shows Kaplan–Meier overall survival curves in the cohort. In total, there were 19 deaths, 6 (17%) of the HIV+/SCD + patients and 13 (14%) of the HIV+/SCD- patients. HIV+/SCD- patients had slightly higher overall survival at 12 years with an HR = 0.81 (95% CI: 0.31–2.1; $P = 0.67$; $n = 130$). On the other hand, HIV+/SCD + patients had better treatment failure-free survival of 97% at 5 years and 84% at 12 years compared to 89% at 5 years and 70% at 12 years for HIV+/SCD- (Figure 3), with a hazard ratio 3.1 (95% CI: 0.72–13.6; $P = 0.13$; $n = 130$). The differences in overall survival and treatment failure-free survival between HIV+/SCD + and HIV+/SCD- were not significantly influenced by baseline nutritional status, CD4 absolute count, WHO clinical stage, treatment line, sex and age in a multi-variable regression model. One factor that strongly determined mortality was baseline WHO stage; those with advanced HIV (WHO Stage III or IV disease) at baseline accounted for 64% of the entire cohort and 90% of the overall deaths/lost to follow-up. Similarly, independently of being in the case (HIV+/SCD+) or control (HIV+/SCD-) group, patients with SAM at baseline also had six times higher risk of dying than those patients with normal nutrition at baseline (HR = 6.2, 95% CI: 2.1–18.1).

WHO treatment stage

WHO treatment stage showed dramatic improvement from baseline and throughout the study period for both

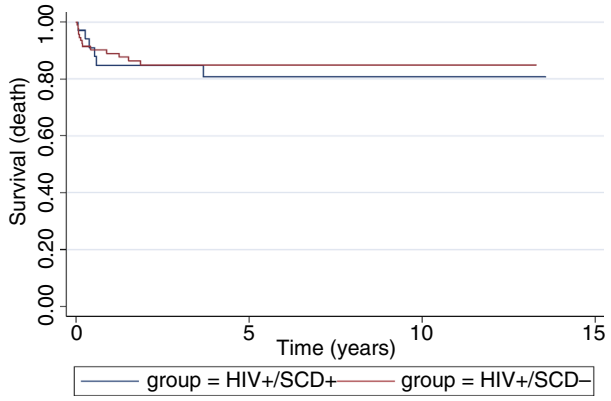

Figure 2 Kaplan–Meier curve for overall survival analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

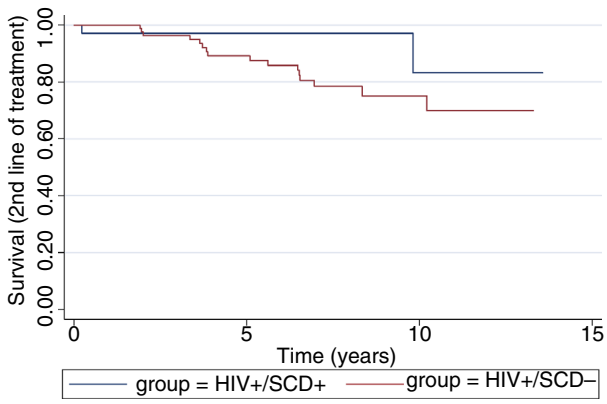

Figure 3 Kaplan–Meier curve for analysis of switch to 2nd line. [Colour figure can be viewed at wileyonlinelibrary.com]

arms of the cohort (Table 2). By the third year, 85% of the HIV+/SCD + arm and 98% of the HIV+/SCD- arm were WHO treatment stage I/II. There was no significant difference between the HIV+/SCD + and HIV+/SCD- groups in terms of improvement in WHO treatment stage (OR = 0.84; 95% CI: 0.2–3.3; P = 0.80; n = 126).

Treatment line

Figure 3 shows Kaplan–Meier curves for first-line treatment failure. A lower percentage of patients from the HIV+/SCD + cohort, 6% (2/35), were switched to second-line treatment regimens as compared to the HIV+/SCD- cohort, 17% (16/95), though statistical significance was not reached (Log-Rank: $chi^2(1)=2.5$, P = 0.11). Unadjusted HR = 3.1 (95% CI: 0.72–13.6; P = 0.13; n = 130) and adjusted HR = 2.9 (95% CI: 0.62–13.9; P = 0.18; n = 130) also showed a trend towards the HIV+/SCD- cohort having an association with higher treatment failure rates. Of note, SCD did not impact which ART regimen to use per Ugandan national guidelines; instead, year of ART initiation was the determining variable for which first-line medication was used. Given that we controlled for year of ART initiation, the cases cohort and control cohort were on equivalent first-line ART.

Immunological response (CD4 count)

Baseline, 1-year and 3-year CD4 counts are presented in Table 2. The mean CD4 count at baseline was higher in the HIV+/SCD + vs HIV+/SCD- patients (1036 cells/μl vs 849 cells/μl, P = 0.195, two-tailed t-test). This tendency to higher CD4 counts in the HIV+/SCD + group became more apparent during ART at both 1 year (2004 cells/μl vs 1339 cells/μl, P = 0.003, two-tailed t-test) and 3 years (1838 cells/μl *vs.* 1287 cells/μl, P = 0.01, two-tailed t-test) (Figure 4). The average difference of the CD4 counts trajectory between HIV+/SCD + vs HIV+/SCD- was β_{group}=−333(95% CI: −591.4 to −74.7; P = 0.01), with the HIV+/SCD + group showing a more robust CD4 increase in response to ART. Of note, the total white blood cell count of the HIV+/SCD + group was significantly higher than the HIV+/SCD- group at all time points as well (baseline 1211 cells/μl *vs.* 8139 cells/μl; 1-year 1377 cells/μl *vs.* 6843 cells/μl, 3-year 1270 cells/μl *vs.* 6311 cells/μl, P < 0.001, two-tailed t-test, for all time points).

Discussion

This study examined the impact of SCD on presentation and longitudinal outcomes amongst paediatric patients with HIV, both of which are independently significant causes of morbidity and mortality in sub-Saharan Africa. Contrary to the complex systemic pathophysiology and morbidity associated with each of SCD and HIV that putatively results in synergistically or additively worse clinical outcomes, these results show no significant

Table 2 Changes in WHO treatment stage and CD4 count between HIV+/SCD + and HIV+/SCD-

	Baseline				1 year				3 year			
	Exposed HIV+/SCD+	n	Control HIV+/SCD-	n	Exposed HIV+/SCD+	n	Control HIV+/SCD-	n	Exposed HIV+/SCD+	n	Control HIV+/SCD-	n
WHO Treatment Stage		34		92		22		57		20		47
I and II (Non-severe)	38%	13	35%	31	91%	20	86%	49	85%	17	98%	46
III and IV (Severe)	62%	21	65%	57	9%	2	14%	8	15%	3	2%	1
CD4 count (SD) cells per microlitre	1036 (713)	27	849 (638)	91	2004 (1067)	22	1339 (801)	64	1838 (992)	15	1287 (652)	52

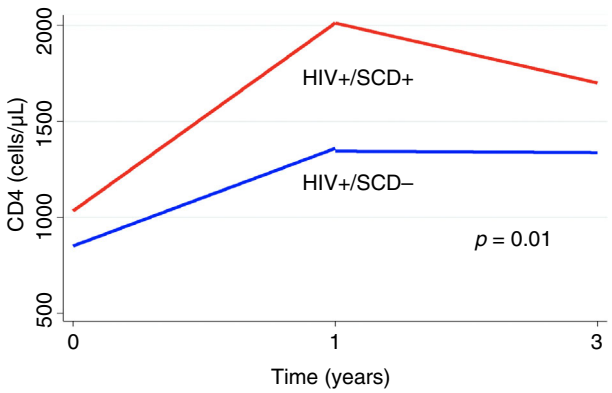

Figure 4 Population trajectory of CD4 count over time by exposed (red) and control (blue) cohorts. [Colour figure can be viewed at wileyonlinelibrary.com]

differences in overall survival between patients with HIV+/SCD + and those with HIV+/SCD-. Interestingly, HIV+/SCD + patients were found to have better HIV-related outcome parameters, namely higher CD4 counts and lower probability of first-line ART failure resulting in change to second-line ART. Overall, the findings suggest that co-existence of SCD and HIV results in counteraction and mitigation of some of the pathophysiological and clinical effects of HIV disease.

The potentially protective effect of SCD against HIV progression is consistent with some previous studies. A multicentre study of 18 HIV+/SCD + adults and 36 HIV+/SCD- adults examined virologic and CD4 progression of a group of HIV + adults not receiving ART, finding that compared to those without SCD, adults with SCD maintained higher CD4 counts and lower viral loads [18]. Another study found that hospitalised HIV+/SCD + patients had a lower case-fatality rate than HIV+/SCD- patients [10].

There are several mechanisms which could explain the protective effect of SCD on HIV progression. While the lack of proper splenic function predisposes to bacterial infections that increases morbidity and mortality in SCD patients, it could be protective against HIV progression. The spleen is one of the key sites for HIV replication and concentration in CD4 lymphocytes [19]; thus, the limitation of splenic function in SCD patients may curtail HIV progression [18]. Another potential explanation of the protective role of SCD is the elevated inflammatory status associated with SCD [9]. For example, haem oxygenase, which has been shown to substantially inhibit HIV-1 replication, is induced by a number of inflammatory factors, including cytokines, hypoxia and haem, that are known to be elevated in SCD patients [20-22]. Further, due to this constant inflammation in the context of ongoing red blood cell production, the bone marrow of sickle cell patients is hyperactive at baseline, as noted in our study with higher baseline total white blood cell counts. Thus, this hyperactivity may be an underlying factor contributing to higher CD4 counts and thus relative protection from the morbidity associated with low CD4 counts.

Medications used for management of SCD have also been shown to significantly impair HIV replication [23]. Cyclin-dependent kinase 2 (CDK2) is one of the key enzymes in HIV-1 transcription, and it has been shown that iron chelators such as deferasirox inhibit CDK2 hence inhibiting HIV-1 replication [23]. Hydroxyurea, another therapy used in management of SCD, inhibits ribonucleotide reductase a rate-limiting enzyme in DNA synthesis. It has been shown that hydroxyurea has both antiviral and immune modulating properties and when used in combination with ART, significant viral suppression is achieved [24-26]. While medications could plausibly further support why SCD patients had better immunologic outcomes, it is unlikely as iron chelation therapy is not readily available in Uganda and hydroxyurea has only recently become widely available. However, we were unable to retrieve data on SCD-specific medications SCD patients were taking, which represents an important limitation of this study.

Genetic factors could also provide a protective mechanism for SCD. CCR5 is one of the receptors that HIV utilises to enter into the CD4 lymphocyte to proliferate; CCR5Δ32 gene mutations have been found to be protective against HIV infectivity in the homozygous state and have also been found to significantly hamper HIV progression in the heterozygous state [27]. Chies et al, while investigating the frequency of CCR5Δ32 allele in a Brazilian admixed population, found that the frequency was higher in SCD population compared to general population [28].

In this study, we found that HIV+/SCD- patients were threefold more likely to fail on first-line ART. Although not statistically significant due to a small sample size, the trend is in keeping with the differences observed in the changes in immunological status while on ART between the two patient groups. It is important to note that Ugandan clinical HIV guidelines call for changes to second-line therapy only with evidence of HIV disease progression, typically with declining CD4 counts and/or detectable viral load values over consecutive visits. Thus, the fewer changes to 2nd line amongst the HIV+/SCD + cohort provide additional evidence that SCD may slow the virologic and immunological progression of HIV. Both HIV and SCD have been shown to increase caloric demand and cause more frequent infections contributing to the development of malnutrition [29-31]. Given the negative impact of both

SCD and HIV on nutritional status, the logical assumption would be to see a compounding effect with HIV+/SCD + group having worse nutritional outcomes but 40% of the HIV+/SCD + patients were stunted at baseline compared to 41.5% of the HIV+/SCD- patients, indicating comparable rates of chronic malnutrition [32].

At baseline, HIV+/SCD + patients were comparably similar to HIV+/SCD- patients in terms of WHO stage, and both groups showed similar initial trends in improvement on treatment. However, at year 3 follow-up, the HIV+/SCD + cohort had relatively fewer patients with non-severe WHO stage I/II (non-severe stages) (85% vs 98%), despite their immunologic and treatment line characteristics. It is plausible that even if SCD leads to better immunological response, the significant comorbidities uniquely associated with SCD outweigh the immunologic benefits [3,4].

This study has several limitations. Most importantly, the study data were taken retrospectively from an electronic medical record of a clinic whose primary function is patient care, not research, and our HIV+/SCD + cases were a sample of convenience. While this method has the benefit of following patients' outcomes as demonstrated in clinical practice and outside the confines of strict clinical trials, it has several important downsides. For one, we only have access to data routinely collected at the paediatric HIV clinic in the clinical management of patients with HIV. Thus, much data that could be relevant to our outcomes are lacking. Most notably, we did not have access to: SCD parameters, such as SCD-specific medications and rates of complications of SCD such as pain crises and acute chest syndrome, consistent HIV viral load data, genotype analyses and causes of death. Furthermore, patients with SCD were defined by a diagnosis of SCD based on haemoglobin electrophoresis in medical records; we did not review the patients' laboratory reports. It is possible that some patients with SCD were misclassified as HIV+/SCD-, which would blunt the observed effect of SCD on HIV. The lack of data on specific organ dysfunction, opportunistic infections and treatment adherence in this cohort limits the ability to correlate morbidity or mortality in this study to specific pathophysiological processes.

Notably, our study size is an important limitation. It was a sample size of convenience in that we took every patient with SCD and HIV from our available database. The small number of cases, 35, represents an important limitation. However, despite the high prevalences of both HIV and SCD, our study is the largest longitudinal study to date of paediatric patients with both SCD and HIV. Furthermore, even with the small sample size, we found significant correlations and trends, notably CD4 counts and death/LTFU, that warrant further investigation.

Finally, population size at baseline suffered a reduction across the years (i.e. outcome records missing over time), which is not addressed in the t-test statistic. However, we fitted mixed-effects models with REML for addressing this issue by its implicit imputation of missing outcomes, which provides unbiased estimates under missing at random assumptions [33].

In conclusion, our study demonstrated that HIV+/SCD + patients on ART had better immunological outcomes and similar clinical outcomes to their HIV+/SCD- counterparts. However, these findings should be validated in a larger prospective and multi-specialty setting of HIV and SCD care and by laboratory comparison of specific pathophysiological pathways in SCD and HIV. Such findings are likely to guide the clinical management of patients with co-existence of these two endemic diseases in sub-Saharan Africa while also providing insights into the complex interaction of other forms of immune dysregulation with HIV disease.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1.
PART 1: Statistical Methods
PART 2: Figures and Tables
PART 3: Strobe Checklist
PART 4: Study Protocol

Corresponding Author **Paul E. George**, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77054, USA. Tel.:+1 314 278 6855; Fax: +1 832 798 1479; E-mail: paul.george@bcm.edu