The Interaction Between Sickle Cell Disease and HIV Infection: A Systematic Review

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Human immunodeficiency virus (HIV) and sickle cell disease (SCD) are regarded as endemic in overlapping geographic areas; however, for most countries only scarce data on the interaction between HIV and SCD and disease burden exist. HIV prevalence in SCD patients varies between 0% and 11.5% in published studies. SCD has been suggested to reduce disease progression of HIV into AIDS. Various interactions of antiretroviral therapy with SCD exist. Both SCD and HIV act as common risk factors for stroke, avascular necrosis, severe splenic dysfunction, pulmonary arterial hypertension, and sepsis, which may result in synergistic increase in risk of developing these diseases. No treatment guidelines regarding SCD with HIV coinfection were identified. Available evidence is mainly based on small clinical studies, thus making strong recommendations difficult. An increased effort to elucidate the precise interactions is warranted to better understand both diseases and effect more adequate treatment approaches, especially in view of their geographical coprevalence.

Keywords: HIV; sickle cell disease; sickle cell trait; disease interaction; systematic review.

Sickle cell disease (SCD) is an inherited severe congenital disorder characterized by the presence of structurally abnormal hemoglobin S [1]. Vaso-occlusive disease and hemolytic crisis are the clinical hallmarks of SCD. Vaso-occlusion results in painful episodes, known as sickle cell crisis, and several organ system complications that can cause long-term disabilities and early death. However, the clinical features of SCD vary markedly among the major genotypes (Supplementary Material I). High hemoglobin S gene frequencies are found in African and Mediterranean populations and populations arising from the slave trade or voluntary emigration from Africa and the Mediterranean [1]. Sickle cell trait (the carrier state of SCD) has a prevalence of 25%–30% in many countries in tropical Africa. Worldwide, there were about 78 million carriers of sickle cell trait in 1992, with most of them (65 million) living in sub-Saharan Africa [2]. Concomitantly, the human immunodeficiency virus (HIV) epidemic has reached every country where SCD is prevalent, and the spread has been particularly alarming in developing countries, especially sub-Saharan Africa where most patients with SCD live (Supplementary Material I). It is therefore to be expected that some degree of interaction will occur between the 2 diseases—SCD and HIV.

Immunosuppression from HIV may affect the natural history of infection with other pathogens by expediting infection, modifying the disease presentation or its course [3]. On the other hand, pathogens and pathogen-derived products may upregulate HIV replication, which can alter the progression of HIV [3]. This includes malaria resulting from infection with Plasmodium species, which is a major cause of sickle cell crisis in SCD patients [3]. Therefore, a plausible hypothesis is that HIV may exacerbate SCD, while SCD speeds up progression of HIV to AIDS. However, available literature on SCD in HIV-infected patients,

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limited as it is, contradicts this hypothesis, as is elucidated in this article. The public health importance of both diseases illustrates the need to examine up-to-date published research on how one disease affects the other. In this review, we aim at providing a comprehensive overview on the interaction of SCD and HIV infection. In addition, we describe the impact of antiretroviral therapy (ART), common risk factors for both diseases, and both disease outcomes in HIV-infected patients with SCD. Gaining more insight into the epidemiology, symptoms, risk factors, and prognosis in those patients is important as it may guide future efforts to improve health outcomes for patients with SCD, especially in resource-limited settings where the treatment of both diseases remains limited.

**METHODS**

Methods of the present review, objectives, and inclusion criteria were specified in advance and documented in a protocol (Supplementary Material II). Recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group were followed. The electronic databases Ovid Medline (1946 to 17 April 2014), Ovid Embase (1947 to 17 April 2014), Cochrane Library including Database of Abstracts of Reviews of Effects and The Cochrane Central Register of Controlled Trials (17 April 2014), Cumulative Index to Nursing and Allied Health Literature Plus with Full Text (1937 to April 2014), Web of Science (1975 to April 2014), Biosis Previews (1993 to April 2014), Population Information Online (1970 to April 2014), African Index Medicus (1993 to April 2014), Latin American and Caribbean Health Sciences Literature (1982 to April 2014), Google Scholar (17 April 2014), and PubMed (non-Medline citations) were searched for studies published up to April 2014, without language restrictions. Also, trial registries (www.clinicaltrials.gov, www.controlledtrials.com, and www.pactr.org) were searched to identify current or future trials. The search strategy consisted of free-text words and subject headings related to SCD and HIV infection. The full search strategies for every database are reported in Supplementary Material III. An experienced clinical librarian (I. M. N.) conducted the actual searches in December 2013. Searches were updated by I. M. N. on 17 April 2014. Bibliographies of relevant studies retrieved from the studies were checked for additional publications. Reference Manager 12.0.3 (Thomson Reuters) was used to manage, de-duplicate, and screen the references for eligibility. There was no exclusion of reports published before a certain point of time. The selection criteria were study population consisting of any group of people with both SCD and HIV of all age groups. All types of original studies, including cross-sectional, case-control, case-report, letters, and cohort studies were included in the qualitative analysis. To determine the prevalence of HIV in SCD patients, we selected cohort studies. Seroprevalence data are mainly derived from studies in blood-transfusion studies. Eligibility assessment of studies found was performed independently in an unblinded standardized manner by 2 reviewers (E. D. A. O., B. J. V.). Titles and abstracts were screened first, and then 1 reviewer (E. D. A. O.) screened and selected relevant full-text articles. For quality control, 1 author (B. J. V.) reviewed 97 (50%) randomly selected full-text articles screened. One author (E. D. A. O.) extracted the following study characteristics: first author, year of publication, language, study site and setting, study design, characteristics of trial participants, objectives/measure of primary outcome, target population and selection criteria, total enrollment, sample size, diagnostic methods, clinical data, risk factors, coinfections, treatment, and mortality. Data were double-checked by B. J. V. for all the included articles (n = 48). Disagreements in the selection process between reviewers were resolved by consensus or in consultation with the senior authors (M. P. G., P. F. M.). The study selection process is summarized in the PRISMA flow diagram (Figure 1). We did not contact authors for further information or confirm the accuracy of information included in our review with the original researchers. No studies were excluded on the basis of quality. The risk of publication bias is most probably larger for observational studies than randomized controlled trials [6], particularly small observational studies as included in this present review. For this reason, the overall publication bias risk for this systematic review is considered substantial. However, we did not investigate publication bias in our review because there is no established method to do this for reviews including only observational clinical studies.

**RESULTS**

The initial search yielded 1698 records, of which 891 remained after removal of duplicates (Figure 1). Forty-eight records met the inclusion criteria (Supplementary Material IV). No current or ongoing trials could be identified in 2 major trial registries (ClinicalTrials.gov and Controlled-Trials.com). One completed study could be identified on pulmonary hypertension in patients with SCD in Nigeria (NCT00367523), of which the data are not yet published.

**Description of Included Studies**

For all articles except 6 the full text paper was retrievable. The majority of records were published in English; however, 15% (7/48) were in another language (mainly French). Fifteen studies took place in sub-Saharan Africa; 27 in Western countries (Europe, United States, Australia); and 6 in other parts of the world (Figure 2). To determine the prevalence of HIV in SCD patients, 14 studies were selected. No meta-analysis could be conducted.
due to insufficient data and clinical heterogeneity of the included studies. Table 1 depicts detailed clinical data of included studies.

**DISCUSSION**

**Prevalence of HIV in Patients With Sickle Cell Disease**

Table 2 depicts studies that investigated the prevalence of HIV in SCD patients. Seroprevalence rates in SCD patients varied between 0% and 11.5%, with the exception of 1 study that had 100% (Figure 3), which can be attributed to the fact that patients selected for the study were mainly those with signs of AIDS-related complexes. The majority of these studies are cross-sectional studies in multiply transfused patients. As the majority of SCD patients in rural or poor parts of the world do not receive blood transfusions, the prevalence reported may be either an underestimation or an overestimation of the true prevalence.

**SCD Reduces Progression of HIV Into AIDS**

SCD has been associated with a reduced risk of HIV coinfection and comorbidity [1, 3, 7, 24, 37]. In a study conducted in the United States, a lower rate of HIV comorbidity in African Americans with SCD who were discharged from hospital was observed [7]. Collapsing focal segmental glomerulosclerosis and proteinuria, which is characteristic of HIV type 1 (HIV-1)-associated nephropathy and is concomitant with progressing HIV-1, was observed to be markedly and spontaneously controlled in a patient with SCD in one study [15]. Several hypotheses have been postulated to explain this phenomenon, such as an enhanced immune defence in SCD [7, 24]. This may be

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Figure 1. PRISMA flow diagram: selection of studies. Abbreviations: HIV, human immunodeficiency virus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCD, sickle cell disease.
because of the upregulation of inflammation, iron metabolism, and immunologic changes in SCD that are not favorable for HIV viral replication [37].

In a case-control study of SCD patients in Brazil, 1.3% of the healthy controls possessed the CCR5Δ32 allele, whereas 5.1% of SCD patients had the allele. This CCR5Δ32 mutant allele confers resistance against macrophage-tropic HIV-1 infections [16].

Bagasara and colleagues sought to verify another hypothesis—that the absence of a functional spleen, which is a major site for HIV invasion and replication, and which is characteristic of SCD patients, is a reason for decreased virulence [14]. In their report, they suggested that the long-term nonprogression of HIV-1–infected Haemoglobin SS (homozygosity for the sickle mutation in the beta globin chain of haemoglobin) patients may be attributed to autosplenectomy.

In contrast, there is some evidence in literature that HIV can worsen SCD. In 2001, Lawrence and Nagel suggested a possible deterioration of SCD in patients with HIV [17]. This was because they observed unusually elevated (40 per 1000 red blood cells) intra- and extracellular crystals (reminiscent of hemoglobin C but not to such elevated levels) in a hemoglobin SC patient with HIV, and it was attributed to HIV infection [17].

**HIV and SCD Disease and Drug Interactions**

Various interactions have been documented to occur between chemotherapy of one disease and disease progression of the other, or chemotherapies of both diseases. Prior to ART, iron supplementation was used to manage HIV infections [38]. In the late 1990s and early 2000s, a number of researchers suggested that iron status alters immune function in HIV patients [39]; specifically, iron overload from iron supplementation, blood transfusion, and others, may negatively influence the outcome of HIV-1 infection [39]. This alteration might have been even more severe in thalassemic (major) patients, as they were at higher risk of iron overload [38, 40]. In treating iron overload in HIV patients with SCD or thalassemia, the drug desferrioxamine decreases bioavailability and affects signaling of tumor necrosis factor alpha; this has been attributed to inhibition of HIV replication [13].

There have been a few case reports of suspected ART-induced sickle cell crisis [11]. In their correspondence, Lowe and colleagues suggested 2 possible explanations: either the drugs directly cause the red blood cells to sickle, or the drugs affect cytokine concentrations in the body, which in turn causes the sickle cell crisis [11]. However, this was noticed only in some specific antiretroviral regimes. In another case, an HIV patient with sickle cell trait and on ART developed osteomyelitis and musculoskeletal-type chest pain, which is common in both SCD patients (but not sickle cell trait) and HIV patients [19]. Patients with sickle cell trait have also been observed to be adversely affected by certain antiretrovirals. For instance, Lawson and colleagues in 1999 observed acute renal insufficiency in an HIV patient with sickle cell trait on oral acyclovir [21].
<table>
<thead>
<tr>
<th>Author and Year of Publication</th>
<th>Country (Study Site), Time Frame</th>
<th>Study Design</th>
<th>No. of Participants</th>
<th>Mode of HIV Transmission</th>
<th>Measure of Outcome</th>
<th>Main Findings (Main Point of Study in Bold)</th>
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<tbody>
<tr>
<td>Nouraie et al, 2012 [7]</td>
<td>US, 1997–2009</td>
<td>Retrospective</td>
<td>423 (3370 SCD patients)</td>
<td>Horizontal</td>
<td>Association between SCD and HIV</td>
<td>The lower risk of HIV comorbidity with SCD is consistent with the possibility that SCD has a unique effect in altering the risk of HIV infection or progression. “In multiple logistic regression and adjusting for age, gender, geographic location, marital status and other co-morbidities (including infectious, neoplasm, endocrine, haematological, mental, nervous, cardiovascular, respiratory, digestive, genitourinary, skin, musculoskeletal disease and injuries), SCD was associated with an OR of 0.24 (95% CI 0.18 to 0.32) for concurrent HIV diagnosis in the 1997–2003 period and with an OR of 0.31 (95% CI 0.22 to 0.42) in the 2004–2009 period” [7]. HIV comorbidity was lower in SCD, but an increased risk on hepatitis B and C was observed. Mechanisms explaining the beneficial effect of SCD on HIV progression (adapted from [7]): 1. Chronic hemolysis upregulates heme oxygenase-1, which blocks HIV-1 infection in macrophages and T cells treated with hemin. 2. Hypoxia related to anemia and vaso-occlusive episodes may contribute to inhibition of HIV. 3. Higher expression of inflammatory cytokines may be associated with enhanced innate immunity and protection from HIV infection. 4. HIV transcription is inhibited when cellular iron is reduced with iron chelators or when the iron export protein ferroportin is overexpressed. 5. Duffy antigen receptor for chemokine-negative status and CCR5 blockage could slow HIV progression. 6. Hydroxyurea, widely used in patients with SCD to reduce vaso-occlusive episodes, is a virostatic drug against HIV.</td>
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<tr>
<td>Barnett et al, 2008 [8]</td>
<td>US, 2008</td>
<td>Case report</td>
<td>1</td>
<td>Horizontal</td>
<td>Clinical case description</td>
<td>Pulmonary arterial hypertension (PAH) (a common risk factor in SCD and HIV) should be recognized early and treated. A man with homozygous SCD and HIV positive treated with exchange transfusion and ART ( stavudine, lamivudine, and efavirenz). He developed PAH, treated with sildenafil (Viagra). It is estimated that 10% of patients with hemoglobinopathies and 0.5% of patients with HIV infection develop moderate to severe pulmonary hypertension.</td>
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<td>Derchi et al, 2010 [9]</td>
<td>Italy, 1989–2008</td>
<td>Case report</td>
<td>1</td>
<td>Horizontal</td>
<td>Clinical case description</td>
<td>Both β-thalassemia and HIV can cause PAH, but mechanisms are largely unknown. 43-year-old woman, HIV-positive and β-thalassemia major, adequately treated with antiretroviral and transfusion-chelation therapy, that develops progressive right ventricular dysfunction due to severe PAH, in absence of symptoms. • &quot;A possible physiopathological link may be a chronic immune activation indirectly caused by HIV that increases secretion of cytokines and growth factors. These agents can create platelet activation promoting micro-thrombosis and can cause oxidative damage and interstitial fibrosis by free radical production: well-known mechanism of iron induced damage of cardiovascular system in thalassaemia.&quot; (Adapted from Derchi et al [9])</td>
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<td>Eholié et al, 2009 [10]</td>
<td>Ivory Coast, 2009</td>
<td>Case series</td>
<td>3</td>
<td>Horizontal</td>
<td>Clinical case description</td>
<td>Avascular osteonecrosis of the femoral head is a common complication for both SCD and HIV-infected patients on ART. Three men with heterogeneous Hb AS sickle cell disease (33, 44, and 45 y and CD4+ T-cell counts 243, 245, and 8 cells/µL, respectively). They all received ART for &gt;4 y including lopinavir and ritonavir. All diagnosed with avascular osteonecrosis of the femoral head. • This small case report study shows the importance of recognition of clinical symptoms of avascular osteonecrosis of the femoral head and the clinical management in SCD patient with HIV. No association between osteonecrosis and SCD and ART is proven, but described is a common complication of both SCD and ART.</td>
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  • Hospitalized 5 times in 1 y since the start of ART (without clear cause), whereas before crises occurred only occasionally.  
  • Suggestive that ART played a role, possible causes: (1) A direct effect by 1 or more of the drugs (stavudine or didanosine) or (2) HAART might indirectly lead to sickle cell crises through changes in cytokine concentrations: “It is currently thought that the increased adhesiveness of erythrocytes and leukocytes to the (postcapillary venule) endothelial wall is an important step in a sickle vaso-occlusive event, and that cytokines (TNF, IL-1, IL-6, and IL-8) are of importance. In (late stage) HIV infection, there is a change in cytokine profile, which is reflected in a switch from a Th type 1 profile (cellular immune response) to a Th type 2 profile (humoral immune response). Th1 cells produce IL-2, IFN-γ, and TNF-β. Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13. ART is accompanied by a (rapid) change in the concentrations of cytokines and cytokine receptors.” (Adapted from Lowe et al [11]) |

  Case of an 18-month-old Kenyan girl with SCD and HIV who developed a severe hypersensitivity reaction to first-line ART. She started ART that included abacavir, lamivudine, and nevirapine. She was also given daily co-trimoxazole prophylaxis. Two weeks later, she developed features of a severe hypersensitivity reaction; these included generalized rash, diarrhea, vomiting, and abdominal pain. ART was stopped and symptoms resolved. An alternative regimen of ZDV, 3TC, and LPV/r was chosen.  
  • Given the possibility of worsening anemia or an aplastic crisis with the patient’s underlying SCD, initiating this regimen was to be done with close monitoring of her Hb level [12]. |
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| Bellocq et al, 1999 [13]       | France, 1999                    | Observational clinical study | 10 (7 patients with thalassemia major and 1 patient with SCD) | HIV-seronegative subjects | Measurement of TNF-α and soluble TNF-α receptor levels | • DFX may delay progression of HIV-1 by reducing TNF-α bioavailability.  
  Background of study: “Evidence indicates that the rate of progression of the HIV-1 disease is significantly reduced in thalassemia major patients upon treatment with high doses of desferrioxamine (DFX).” Previously Bellocq et al demonstrated that in vitro exposure of mononuclear cells to DFX decreases the bioavailability of TNF-α which has a stimulatory effect on HIV-1 replication.  
  Methods: TNF-α bioavailability from mononuclear cells isolated from 10 patients with thalassemia or sickle cell anemia given DFX compared with 10 untreated subjects has been evaluated.  
  • DFX treatment reduces TNF-α bioavailability ($P < .05$) by inhibiting its steady state ($P < .05$) and by enhancing its inactivation through binding to soluble TNF-α receptor type ($P < .05$).  
  • Thus, TNF-α bioavailability and signaling are impaired in patients upon DFX treatment. This mechanism may contribute to delayed progression of the HIV-1 infection in vivo. |
| Bagasara et al, 1998 [14]      | US, 1998                        | Case-control, retrospective | 54                                | Horizontal | HIV-1 RNA quantification by branched DNA signal amplification | Dysfunction of the spleen, common in adults with SCD, may account for the observation that a significant proportion of HIV-1–seropositive SS patients are asymptomatic long-term nonprogressors.  
  Background: The spleen and lymph nodes are major sites of HIV-1 replication, mutation, and genetic variation in vivo. If a major portion of the lymphatic tissue, such as the spleen, is removed or otherwise is unavailable for invasion by the HIV-1 virus, will the course of the infection be altered, resulting in a prolonged symptom-free interval or even increased survival?  
  Results: Evaluation of a limited number of adult individuals suggests that a significant proportion of HIV-1-seropositive SS patients (44%) may be asymptomatic long-term nonprogressors. In these patients, the CD4 $^+$ T-lymphocyte counts remained high and their viral burdens were remarkably lower than in non-SS HIV-1-seropositive individuals. |
  A 23-year-old man with SCD and HIV-1-associated nephropathy (progressive disease characterized by collapsing focal segmental glomerulosclerosis and proteinuria) showed improvement of renal function correlated with the decline in viral load (without ART). |
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<tr>
<td>Chies et al, 2003 [16]</td>
<td>Brazil</td>
<td>Case-control</td>
<td>79</td>
<td>NA</td>
<td>Prevalence (%) of the CCR5Δ32 allele</td>
<td>A higher prevalence of the CCR5Δ32 allele was identified in homozygous sickle cell patients compared to health controls. The CCR5Δ32 allele confers relative resistance to macrophage-tropic HIV infection, which could lead to better survival of SCD patients carrying this specific allele. In this case study, the investigators showed that a relatively higher prevalence (5.1%) of the CCR5Δ32 allele was identified, by PCR amplification using specific primers, in 79 SCD patients (Afro-Brazilians) compared to healthy controls (1.3%). “Based on a hypothesis that considers SCD as a chronic inflammatory condition, and since the CCR5 chemokine receptor is involved in directing a Th1-type immune response, it is suggested in this study that a Th1/Th2 balance can influence the morbidity of SCD. If the presence of the null CCR5Δ32 allele results in a reduction of the chronic inflammation state present in SCD patients, this could lead to differential survival of SCD individuals who are carriers of the CCR5Δ32 allele.” [16]</td>
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<tr>
<td>Lawrence et al, 2001 [17]</td>
<td>US, 2001</td>
<td>Case report</td>
<td>1</td>
<td>Horizontal</td>
<td>Case description</td>
<td>Observation of possible deterioration of SCD in a patient with HIV, explained by the observation of an unusually elevated (40/1000 RBC) intra- and extraerythrocytic crystals (reminiscent of Hb C but not to such elevated levels), which was attributed to the HIV infection. A 35-year-old woman with Hb S and C disease and HIV (CD4+ count 17 cells/µL and viral load 8276 copies of viral RNA/mL). Admitted with fever for 2 wk and 3 d of increasing shortness of breath and pleuritic chest pain. Diagnosed with <em>Pneumocystis jiroveci</em> pneumonia and acute chest syndrome. She was transfused and was discharged after 11 d on Bactrim, tapering prednisone, and fluconazole.</td>
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<td>Kourtis et al, 2007 [18]</td>
<td>US, 1994–2003</td>
<td>Retrospective study</td>
<td>686 (children)</td>
<td>Vertical</td>
<td>Multivariate logistic regression, odds ratio</td>
<td>Hospitalized children with SCD and HIV infection have higher odds of infection (e.g., pneumonia) than those with SCD alone. Their inpatient case-fatality rate is lower than that of children with HIV infection alone. Their average length of stay was longer than that of children with SCD alone (8.0 d vs 4.3 d, respectively), and the mean charges associated with the hospitalization were also higher (US $18 291 vs $9584). Compared with patients with SCD without HIV, HIV infection conferred a higher risk for hospitalizations for bacterial infections and sepsis (OR, 2.75; 95% CI, 1.66–4.6), but less of a risk for vaso-occlusive crises (OR, 0.32; 95% CI, .22–.48). Inpatient case-fatality rate of children with SCD and HIV was no different from that of children with SCD alone, but lower than that of the rest of children with HIV infection.</td>
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<td>Godeau et al, 1992 [20]</td>
<td>France, 1985–1990</td>
<td>Retrospective cohort study</td>
<td>283</td>
<td>Horizontal</td>
<td>The clinical course of HIV in adults with SCD.</td>
<td>Pneumococcal infection appears to occur frequently and is often serious in HIV-infected adults with SCD. Oral penicillin and vaccination are probably warranted. Retrospective study to determine the clinical course of HIV infection in adults with SCD. During a 6-y period, 283 adults with SCD were screened for HIV infection. 8 (2.8%) patients were HIV positive. Five episodes of severe pneumococcal infection were observed in 4 of these 8 patients (septic shock in 2 patients and 3 episodes of meningitis in 2 patients); 2 patients died of meningitis. Only 1 severe pneumococcal infection was observed in the 275 non-HIV-infected participants with SCD [20].</td>
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<td>US, 1999</td>
<td>Case report</td>
<td>1</td>
<td>Horizontal</td>
<td>Case description</td>
<td>Renal disorders in SCD and HIV are not uncommon. HIV patients are likely to receive acyclovir during their lifetime. When such patients have raised creatinine levels or hyperkalemia in conjunction with acyclovir, the acyclovir should be considered as a potential cause. A 40-year-old man with HIV (CD4+ 601 cells/µL), sickle cell trait and IV drug abuse, was admitted with fever and abdominal pain. For herpes simplex 1 and 2 infection, he received oral acyclovir (baseline creatinine clearance 88 mL/min). He developed acute renal insufficiency, most probably due to oral acyclovir. Conceivably, competition with a cephalosporin for renal tubular elimination predisposed the patient to nephrotoxic levels of acyclovir. In addition, the sickle cell trait might have contributed to a disproportionate degree of hyperkalemia and acidosis seen early in the patient’s clinical course.</td>
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Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CI, confidence interval; DFX, desferrioxamine; HAART, highly active antiretroviral therapy; Hb, hemoglobin; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; IV, intravenous; LPV/r, ritonavir-boosted lopinavir; MRI, magnetic resonance imaging; NA, not applicable; OR, odds ratio; PAH, pulmonary arterial hypertension; PCR, polymerase chain reaction; RBC, red blood cell; SCD, sickle cell disease; Th, T-helper cell; TNF, tumor necrosis factor; US, United States; ZDV, zidovudine.
The case of an 18-month-old Kenyan girl with SCD and HIV who developed a severe hypersensitivity reaction to first-line ART illustrates the challenges and possible management dilemmas encountered in choosing an appropriate ART regimen [12].

Both SCD and HIV May Act Synergistically to Increase Risks for Certain Diseases and Complications

An increase in frequency and severity of certain conditions in SCD patients living with HIV has been observed [20, 41]. For instance, in Africans especially, both SCD and HIV are risk factors for stroke [42]. Hypothetically, having both conditions could predispose a patient to more frequent and severe stroke episodes.

HIV and SCD have each been associated with pulmonary arterial hypertension (PAH) [8, 9, 41, 43], with a likelihood that interactions between both will result in a higher prevalence of PAH [41].

In a nationwide study across the United States, an increased risk of infection was observed in hospitalized children with HIV and SCD [18]. However, they had a reduced inpatient case-fatality rate compared to that of children with only HIV.

Pneumococcal infections, especially drug-resistant types [44], have also been observed to frequently occur in SCD adults infected with HIV [20]. Individuals with hemoglobin SS have an increased risk of infection because of defective complement activation, hyposplenism, and diminished cell-mediated immunity. *Streptococcus pneumoniae* and *Salmonella* species are the most common bacterial organisms in SCD patients [45].

The rate of community-acquired bacterial bloodstream infection in HIV patients presenting to healthcare services is 21% in adults and 26% in children, whereas HIV-negative patients have rates of 10% and 12%, respectively [46]. Globally, nontyphoidal salmonellae, *S. pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus* are the main pathogens found in HIV patients [46]. Combination of both high-risk factors in an individual might increase the severity of such infections in HIV patients with SCD [20, 47].

HIV and ART are risk factors for avascular necrosis [10]. This condition was observed to be worse in patients with sickle cell trait in West Africa. The authors thus suggested SCD, and sickle cell trait also might be potential risk factors [10].

Both HIV and SCD on their own have been associated with severe splenic dysfunction; functional hyposplenism occurs in many people living with unmanaged HIV infections, while autosplenectomy and irreversible hyposplenism are common in SS or Sβ0-thalassemia SCD patients [48].

Bone marrow transplant could possibly be the next mode of treating HIV and SCD coinfection. This is because, on the one

### Table 2. Studies Reporting the Prevalence of HIV Infection in Patients With Sickle-Cell Disease

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Country</th>
<th>Study Design and/or Setting and No. of Patients</th>
<th>Reported Prevalence of HIV Infection Among SCD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>[22]</td>
<td>DRC</td>
<td>Cross-sectional transfusion security study; N = 140 SCD patients, of which 127 transfused</td>
<td>1/127 (0.9%)</td>
</tr>
<tr>
<td>[23]</td>
<td>Turkey</td>
<td>Cross-sectional overview of thalassemia patients; N = 388 total, 20 (5.1%) with SCD; 23 with SCD + β-thalassemia (5.9%)</td>
<td>0/43 (0%)</td>
</tr>
<tr>
<td>[24, 25]</td>
<td>Mali</td>
<td>Prospective study of the seroprevalence of HIV in sickle cell anemia patients. N = 133 total with SCD</td>
<td>2/133 (1%)</td>
</tr>
<tr>
<td>[26]</td>
<td>Congo-Brazzaville</td>
<td>Cross-sectional evaluation of homozygote SCD patients; N = 112</td>
<td>0/112 (0%)</td>
</tr>
<tr>
<td>[27]</td>
<td>Zambia</td>
<td>20 repeatedly transfused sickle cell anemia patients</td>
<td>20/20 (100%)</td>
</tr>
<tr>
<td>[28]</td>
<td>Brazil</td>
<td>Cross-sectional study in sickle cell anemia patients N = 1415</td>
<td>11/1415 (0.8%)</td>
</tr>
<tr>
<td>[15, 29]</td>
<td>Turkey</td>
<td>Cross-sectional seroprevalence study in patients with thalassemia and SCD N = 399</td>
<td>0/399 (0%)</td>
</tr>
<tr>
<td>[30]</td>
<td>Nigeria</td>
<td>Retrospective study in sickle cell anemia patients N = 55</td>
<td>1/55 (1.8%)</td>
</tr>
<tr>
<td>[31]</td>
<td>Togo</td>
<td>Cross-sectional seroprevalence study in patients with SCD N = 119</td>
<td>6/199 (5.04%)</td>
</tr>
<tr>
<td>[32]</td>
<td>Gabon</td>
<td>Cross-sectional study; data of hospitalization and management of children with SCD N = 79</td>
<td>1/79 (1.3%)</td>
</tr>
<tr>
<td>[33]</td>
<td>Zaire</td>
<td>Two series of 251 hospitalized SCD patients and 340 SCD outpatients. N = 591</td>
<td>68/591 (11.5%)</td>
</tr>
<tr>
<td>[34]</td>
<td>DRC</td>
<td>Blood transfusion rate in SCD patients N = 150</td>
<td>17/150 (11.3%)</td>
</tr>
<tr>
<td>[35]</td>
<td>Guadeloupe (France)</td>
<td>Retrospective seroprevalence study in sickle cell patients N = 331</td>
<td>0/331 (0%)</td>
</tr>
<tr>
<td>[36]</td>
<td>Nigeria</td>
<td>Cross-sectional seroprevalence of HIV among transfused children with sickle cell anemia. N = 69</td>
<td>2/69 (2.9%)</td>
</tr>
</tbody>
</table>

Abbreviations: DRC, Democratic Republic of the Congo; HIV, human immunodeficiency virus; SCD, sickle cell disease.
In contrast, a patient with acute myeloid leukemia and HIV-1 in 2009 received transplanted stem cells from a donor who was homozygous for the allele CCR5 32 had no viral rebound 1 year 8 months afterward [53], and is still HIV negative with no antiretrovirals [54].

Mouse and human models have been successfully corrected [49], and clinical trials are currently under way in France [50] and the United States [37, 55], with promising results thus far.

**Strengths and Limitations**

This review triangulates data from quantitative, qualitative, and mixed-methods studies to increase the content validity and comprehensiveness of the review. A systematic search yielded an initial search of 1638 results, with almost 50% duplicates, which indicates a good-quality literature search. To minimize bias, eligibility assessment was performed independently in an unblinded standardized manner by 2 authors (E. D. A. O., B. J. V.). Even though most of the burden of both diseases lies with Africa, only 27% (13/48) of the studies originated from Africa; this is an important limitation of the results. For the literature review, the main limitation was the fact that unpublished studies were not searched for, which may have introduced bias. However, by searching clinical trial registries for ongoing or unpublished studies, this risk of bias was significantly reduced. Although there were no language restrictions for the selection of papers, and no studies were excluded on the basis of language, the focus of the majority of the used search engines (Medline and Embase being the primary source of studies) to date has been on the European family of languages, and predominantly English. Unfortunately, the full text for 6 studies could not be retrieved, which may have introduced bias. The majority of the studies included in this review are observational or case series, which will have a high publication bias compared to randomized controlled trials. Therefore, the overall publication bias risk for this review is considered as substantial and warrants further clinical research in better-designed randomized controlled trials.

**CONCLUSIONS**

This systematic review demonstrates the interaction between HIV and SCD. These interactions affect the diagnosis, treatment, prognosis, and general healthcare of the patients with both conditions. Although HIV and SCD coexist, few properly designed studies show systematic investigation into their interaction. The evidence that is available and is presented in this review shows that SCD slows the progression of HIV into AIDS but that, on the other hand, HIV worsens SCD; drugs for treating both diseases interact with each other and the respective diseases; and both diseases are risk factors for certain diseases such as...
as stroke, avascular necrosis, severe splenic dysfunction, PAH, and sepsis, which could synergistically increase the odds of getting those diseases. Properly documented information on this has the potential to inform national health policies in these areas, many of which are developing countries. There is therefore the need for further research on the impact of this contemporaneity on the health and well-being of individuals and their families, as well as society as a whole.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes


Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References