

# Seroprevalence of Hepatitis B and C Viruses Among Children in Kilimanjaro Region, Tanzania

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**Background.** Data on human immunodeficiency virus (HIV) and hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection among children in Africa are limited. We evaluated the seroprevalence of both viruses among healthy, HIV-uninfected children and HIV-infected children in the Kilimanjaro region of northern Tanzania.

**Methods.** HBV and HCV markers were assessed using serum and plasma samples from HIV-negative children ages 1 month to 18 years, recruited primarily from 2 hospital vaccination clinics; and HIV-infected children 1–16 years of age, enrolled in care and on highly active antiretroviral therapy (HAART). HBV markers included hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, and hepatitis B core antibody (HBcAb). Evidence of any prior HBV infection was defined as a single positive HBsAg or HBcAb result; presumed chronic hepatitis B infection was defined as a single positive HBsAg result. HCV infection was assessed by anti-HCV enzyme-linked immunosorbent assay.

**Results.** Samples from 547 children were tested. Of 157 children infected with HIV, 9.6% (95% CI: 4.9, 14.2) showed evidence of any HBV infection, compared to 2.1% (95% CI: .6, 3.5) of HIV-negative children. Children with HIV were much more likely to show evidence of HBV infection than children without HIV (odds ratio [OR] = 5.0,  $P < .0001$ ). Prevalence of presumed chronic HBV infection was 2.9% (95% CI: 1.5, 4.3) overall. Again, prevalence was higher among HIV-infected children (7.0% [95% CI: 3.0, 11.0]) compared to HIV-negative children (1.3% [95% CI: .2, 2.4]; OR = 5.8 [ $P = .0003$ ]). Of 546 samples tested for anti-HCV antibody, none were positive.

**Conclusion.** HBV seroprevalence is high among children in the Kilimanjaro Region, with a significantly higher prevalence among children who are infected with HIV. Routine screening for HBV is needed among HIV-infected children. Patients with coinfection require closer monitoring of liver transaminases due to potential for hepatic toxicities, and they may need HAART regimens that will target both viruses. Guidelines for the management of coinfecting children are urgently needed.

**Key words.** HIV; Hepatitis B; Hepatitis C; Children; Sub-Saharan Africa

More than 350 million people worldwide are chronically infected with the hepatitis B virus (HBV), 170 million with the hepatitis C virus (HCV) [1], and 33 million with the human immunodeficiency virus (HIV) [2]. HBV and HCV are more prevalent among HIV-infected individuals due to shared routes of transmission; HIV increases the speed of liver dysfunction among those with coinfection

[3, 4]; and liver disease due to chronic hepatitis is becoming an increasing cause of morbidity and mortality among HIV-infected persons, particularly in resource-limited settings. It has been previously established among HIV-negative cohorts that manifestations of HBV infection vary depending on the age of an individual at the time they acquire infection. Adults who become infected with HBV have up to 5%

risk of acquiring chronic disease; in contrast to a 25%–30% risk with infection before the age of 5 years, and up to a 90% risk of developing chronic hepatitis B with perinatal infection. Furthermore, infants who develop chronic HBV have a 25% risk of dying prematurely due to cirrhosis or liver cancer [5–8]. In contrast to HBV, persistent infection with HCV occurs in 50%–60% of infected children, regardless of age [9]. The relative risk for the development of cirrhosis is doubled in patients with HIV-HCV coinfection [10]. Data on both HIV-hepatitis coinfection and hepatitis monoinfection among African populations, especially children, are limited [11–19].

Although the treatment of hepatitis C in resource-poor settings is still quite limited, there are often treatment options available for those with HBV. For HIV-HBV coinfecting individuals, several nucleotide and nucleoside reverse transcriptase inhibitors are available for the treatment of both viruses, including lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and emtricitabine (FTC). Lamivudine has long been a mainstay of first-line highly active antiretroviral therapy (HAART) for children in sub-Saharan Africa, and although it has potent activity against both HIV and HBV, when used as a single anti-HBV agent resistance develops rapidly [20–23]. Increasingly, TDF and combination TDF/FTC are being rolled out for the treatment of HIV in some sub-Saharan African settings. Tenofovir disoproxil fumarate has potent activity against HBV and a high barrier to resistance [24, 25]. Furthermore, TDF is now approved for use in HIV-infected children down to the age of 2 years [26]. Optimal treatment for HIV-HBV coinfecting children is not established. HIV-infected pregnant women and children in Tanzania are currently not screened for hepatitis coinfection; thus, most clinicians are unaware of coinfecting patients. A better understanding of the prevalence of coinfection is a necessary first step to develop optimal monitoring and treatment approaches.

This study aimed to determine the prevalence of HBV and HCV among healthy, HIV-negative children, and HIV-infected children on HAART living in the Kilimanjaro Region of northern Tanzania.

## METHODS

### Study Design and Population

This retrospective, cross-sectional study was conducted using banked serum and plasma samples to determine the prevalence of HBV and HCV among children <18 years of age in the Kilimanjaro Region. Samples were previously obtained from 2 studies conducted in Kilimanjaro Region, the first of which was designed to establish pediatric normal hematologic and immunologic reference ranges [27].

Over 600 healthy, HIV-negative children between the ages of 1 month and 18 years were enrolled between December 2006 and March 2008. Participants were recruited from Kilimanjaro Christian Medical Centre (KCMC) and Mawenzi Regional Hospital (MRH) vaccination clinics in Moshi, Tanzania. Kilimanjaro Christian Medical Centre is a consultant referral hospital with 458 beds serving a catchment area of >1.4 million. Mawenzi Regional Hospital is a 300-bed government hospital also serving the Kilimanjaro Region. Siblings of HIV-infected children in care at the Pediatric Infectious Disease Clinic of KCMC and older children of women attending the KCMC or MRH antenatal care clinics were also recruited. Children were not enrolled if they had a history of acute or chronic illness, were currently receiving any medications, or were pregnant, and data were excluded from study analyses if the child was determined to be HIV antibody seropositive. The second study enrolled HIV-infected children aged 1 to 16 years receiving medical care at the Child Centered Family Care Clinic at KCMC from October 2008 to June 2009, and was designed to assess predictors of virologic failure among Tanzanian children who had taken first-line or second-line HAART for a minimum of 6 months [28].

### Laboratory Methods

Hepatitis B virus status was determined by serologic testing using hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (Monolisa HBsAg ULTRA, Monolisa Anti-HBs PLUS, and Monolisa Anti-HBc PLUS, respectively; Bio-Rad Laboratories, Inc., Hercules, CA). Hepatitis C virus status was determined with anti-HCV enzyme-linked immunosorbent assay (ELISA) (Ortho HCV version 3.0; Bio-Rad Laboratories Inc., Hercules, CA). Laboratory testing was performed at the Kilimanjaro Clinical Research Institute Biotechnology Laboratory, which successfully participates in relevant external quality assurance programs of the College of American Pathologists External Quality Assurance for hematology, the Viral Quality Assurance program of the AIDS Clinical Trials Group, and the United Kingdom National External Quality Assessment Service for flow cytometry. All samples were stored at –80°C and were thawed on the day of testing only.

Validation studies were successfully performed for the HBcAb, HBsAb, and anti-HCV ELISA before testing of patient samples. Hepatitis B surface antigen had been validated previously. All test kits were approved by the US Food and Drug Administration (FDA), testing was performed according to manufacturers' instructions, and all procedures were performed according to good clinical

laboratory practices and followed standard operating procedures.

### Ethics

The study was approved by the Duke University Institutional Review Board and the KCMC Ethics Committee. Informed consent was obtained from all participants as part of the original 2 studies described above.

### Statistical Analysis

Data were entered into a Microsoft Excel database (Microsoft Corporation, Redmond, WA), and all statistical analyses were conducted using SAS software (version 9.3; SAS Institute, Cary, NC) and assumed a 2-sided level of significance of 0.05. Continuous variables were analyzed with nonparametric statistics (Wilcoxon rank-sum test) and categorical variables by the  $\chi^2$  test, with odds ratios (ORs) and 95% confidence intervals (CIs).

Evidence of any prior HBV infection was defined as a single positive HBsAg or HBcAb result; presumed chronic hepatitis B infection was defined as a single positive HBsAg result.

## RESULTS

Of 655 HIV-uninfected children and 230 HIV-infected children enrolled in the 2 original studies, a total of 554 children had samples available. Of these, 394 were HIV-negative and 160 were HIV-positive subjects. Seven

subjects were subsequently excluded due to insufficient sample for testing or indeterminate HBsAg results, resulting in a final analysis of 390 and 157 samples from HIV-negative and HIV-positive children, respectively (Figure 1). Enrollment was balanced across genders with 281 (51.4%) female subjects, and the mean age (standard deviation [SD]) of participants was 7.9 ( $\pm$ 4.8) years. Evidence of any HBV infection was present in 4.2% (95% CI: 2.5, 5.9) overall and in 9.6% (95% CI: 4.9, 14.2) of HIV-infected children compared to 2.1% (95% CI: .6, 3.5) of HIV-negative children. Table 1 shows HIV infection status by age group. Children with HIV infection were more likely to have evidence of any HBV infection than HIV-negative children (OR = 5.0 [95% CI: 2.1, 12.2];  $P < .0001$ ). Resolved infection (HBcAb and HBsAb positive) was found in 5 patients overall, 2 with HIV infection and 3 without. Two of these 3 were infants, both 5 months of age, likely representing maternal antibody transmission. Isolated HBcAb was found in 2 patients, both of whom were infected with HIV.

Prevalence of presumed chronic HBV infection was 2.9% (95% CI: 1.5, 4.3) overall. Again, prevalence was higher among HIV-infected children (7.0% [95% CI: 3.0, 11.0]) compared to HIV-negative children (1.3% [95% CI: 1.5, 4.3, .2, 2.4]; OR = 5.8;  $P = .0003$ ). Of 546 patients whose samples were screened for anti-HCV antibody, all were negative.

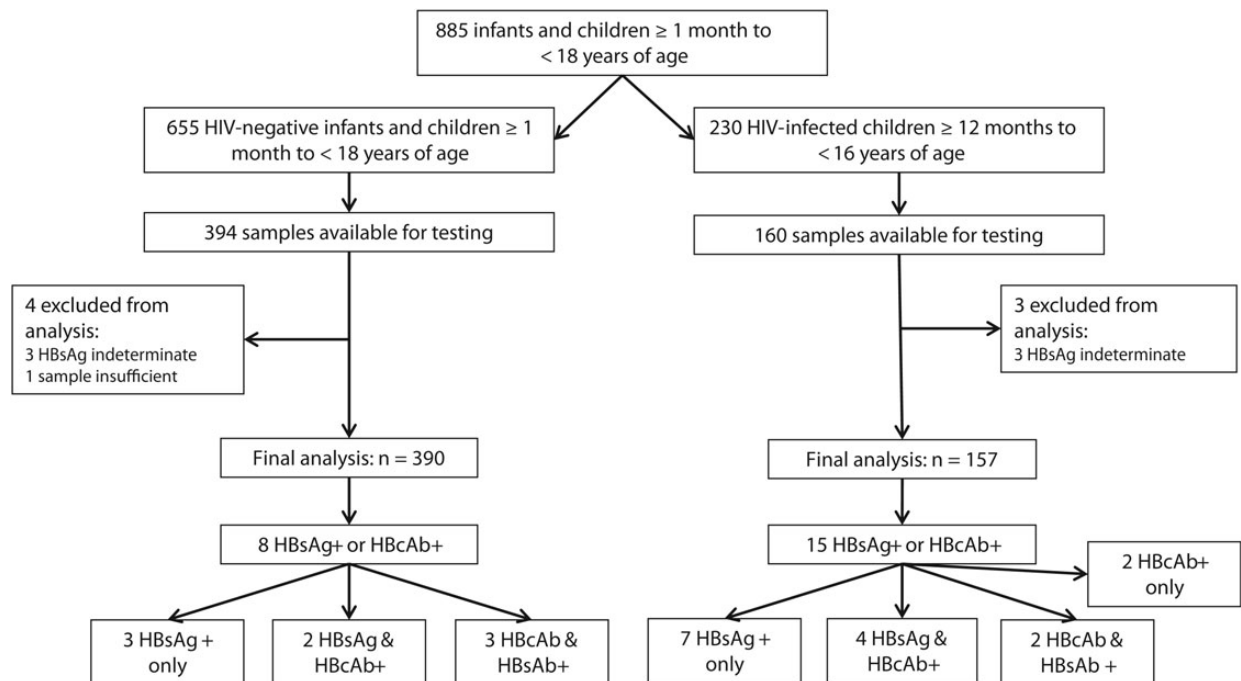


Figure 1. Flowchart of study participants included in the analysis: children ages 1 month to <18 years. Abbreviations: HbsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HIV, human immunodeficiency virus.

**Table 1.** Evidence of Any Hepatitis B Virus Infection by HIV Status and Age Group

Age	<12 Months	≥1 < 5 Years	≥5 < 13 Years	≥13 < 18 Years	Total
HIV-positive	0 of 0 (0.0%)	4 of 32 (12.5%)	9 of 108 (8.3%)	2 of 17 (11.8%)	15 of 157 (9.6%)
95% CI	–	(.4, 24.6)	(3.0, 13.6)	(0.0, 28.8)	(4.9, 14.2)
HIV-negative	2 <sup>a</sup> of 41 (4.9%)	0 of 110 (0.0%)	2 of 151 (1.3%)	4 of 88 (4.6%)	8 of 390 (2.1%)
95% CI	(0.0, 11.8)	–	(0.0, 3.2)	(.1, 9.0)	(.6, 3.5)
Overall	2 <sup>a</sup> of 41 (4.9%)	4 of 142 (2.8%)	11 of 259 (4.3%)	6 of 105 (5.7%)	23 of 547 (4.2%)
95% CI	(0.0, 11.8)	(0.0, 5.6)	(1.8, 6.7)	(1.2, 10.2)	(2.5, 5.9)

Abbreviations: CI, confidence interval; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HIV, human immunodeficiency virus.

<sup>a</sup>These 2 patients were HBcAb and HBsAb positive, likely reflecting maternal antibody transmission.

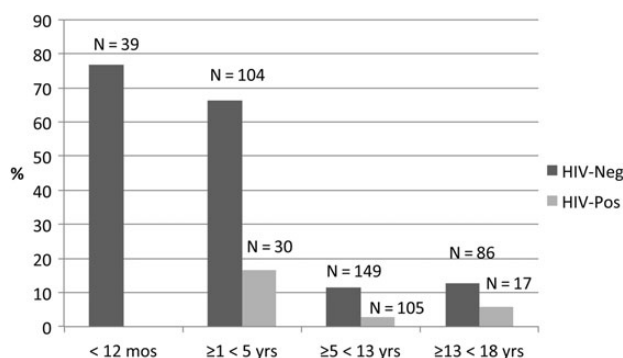
**Table 2.** Characteristics of HIV-Infected Patients With Hepatitis B Virus–Coinfection

Number	Age (years)	Sex	HBsAg	HBcAb	HBsAb	CD4 (cells/L)	CD4%	HIV-1 RNA (cp/mL)	Time on HAART (years)	3TC-Based Regimen
1	2.1	M	Neg	Pos	Neg	1134	21	235	1.1	Yes
2	3.5	M	Neg	Pos	Pos	1335	32	ND	3.2	Yes
3	3.8	M	Pos	Neg	Neg	1724	33	ND	3.3	Yes
4	5.0	F	Neg	Pos	Neg	849	28	285	1.2	Yes
5	6.8	F	Pos	Neg	Neg	743	28	87	0.6	Yes
6	9.5	F	Neg	Pos	Pos	1113	36	ND	0.8	Yes
7	9.8	M	Pos	Pos	Neg	208	25	535	5.0	No
8	9.9	M	Pos	Neg	Neg	1154	37	44	3.4	Yes
9	10.1	F	Pos	Neg	Neg	298	7	89	2.8	No
10	11.2	F	Pos	Neg	Neg	390	24	249	0.6	Yes
11	11.3	M	Pos	Neg	Neg	895	34	<40	3.3	Yes
12	11.5	M	Pos	Neg	Neg	474	19	<40	0.6	Yes
13	12.8	F	Pos	Pos	Neg	666	21	ND	2.3	No
14	13.3	M	Pos	Pos	Neg	307	10	ND	2.3	Yes
15	13.5	F	Pos	Pos	Neg	926	38	<40	0.6	Yes

Abbreviations: 3TC, lamivudine; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; ND, not detected; Neg, negative; Pos, positive.

The 15 HIV-infected children with past or current HBV infection were evaluated in more detail; clinical data are displayed in Table 2. Two of these children showed evidence of resolved infection (HBcAb positive, HBsAg negative), 2 had isolated HBcAb, and the remainder were HBsAg positive and presumed to have chronic infection. The mean (SD) age for these 15 children was 8.9 (3.8) years, 7 (46.7%) were female, the mean (SD) CD4-lymphocyte count was 814 (434) cells/L, and all had an HIV-1 RNA < 1000 copies/mL. Of the 11 who were HBsAg positive, all had received 3TC-containing HAART: 8 were receiving 3TC at the time of the study, and 3 were on second-line regimens but had previously received 3TC. Thus, all children had at some point received monotherapy against HBV as part of their antiretroviral (ARV) treatment regimen. There were no statistically significant differences among HIV-infected children with and without evidence of HBV infection in terms of age, sex, CD4 lymphocyte count, and use of 3TC-containing HAART (data not shown).

Evidence of seroprotection from previous vaccination was relatively uncommon. Of 535 children with HBsAb results, and after excluding 5 children showing natural resolved infection, 138 of 530 (26.0%) were HBsAb



**Figure 2.** Prevalence of hepatitis B surface antibody without hepatitis B core antibody among HIV-positive and -negative children.

positive. Thus, just over one-quarter had evidence of seroprotection from vaccine. Seropositivity was most common in younger children (Figure 2). Tanzania incorporated the hepatitis B vaccine into its national immunization program in 2002; thus, only children in the younger age groups would likely have had access to vaccine. Among children in the <12-month age group, none were HIV-infected. Among the 134 children between 1 and 5 years of age with HBsAb results, 30 (22.4%) were HIV-infected. In this age bracket, 74 (55.2%) were positive for HBsAb with a titer



$\geq 10$  mIU/mL, the World Health Organization (WHO) reference standard for demonstrating post-vaccination protection. Evidence of immunity was 16.7% among children with HIV, compared to 66.4% among children without HIV (OR = .10 [95% CI, .04 to .29];  $P < .0001$ ).

## DISCUSSION

To our knowledge, this is the largest HBV/HCV seroprevalence study to date among children in East Africa. Few studies worldwide have reported the prevalence of HBV and HCV infection among children with and without HIV coinfection. Our data demonstrate that HBV coinfection is common among HIV-infected children in Kilimanjaro Region, with an HBsAg prevalence of 7.0%, and evidence of any current or prior HBV infection in 9.6%. Conversely, HCV infection was not found among 546 patient samples screened. Our study is in contrast to a recent study conducted among HIV-infected children in Dar es Salaam, where only 1.2% of 167 HIV-infected children were positive for HBsAg, and 13.8% had anti-HCV IgG antibodies [14]. Other pediatric hepatitis studies conducted in Tanzania include 1 in Iringa Region and Pemba Island, which found an HBsAg seroprevalence rate of 3.9% among children <3 years of age; HIV testing was not performed [17]. A Dar es Salaam study among children <5 years of age, 89.5% of whom were HIV-negative, found an HBsAg prevalence of 1.7% [18]. Other recent studies elsewhere in sub-Saharan Africa have shown HBV prevalence rates among HIV-infected children ranging from 4% to 19% [11–13, 19, 29]. Asian countries highly endemic for HBV with successful vaccination programs in place, notably China and Thailand, have reported relatively low HIV-HBV prevalence rates of 4.9% and 3.3%, respectively [30, 31].

In our study, we also found isolated HBeAb among 2 patients, both of whom were HIV-infected. The significance of this is unclear, because we were unable to perform HBV DNA testing. Both patients had detectable HIV-1 RNA levels, although only at 235 and 285 copies/mL; 1 had a CD4-lymphocyte percentage below threshold for age (21%); and both were receiving 3TC-containing HAART for just over 1 year. The presence of isolated HBeAb is common among HIV-infected individuals and has been associated with the presence of concurrent HCV infection [32–34]. Whether the results for these 2 patients reflect immunity with undetectable HBsAb, occult HBV infection, or a false-positive HBeAb result is unclear.

Of 530 children with HBsAb results and without prior infection, only 138 (26.0%) were positive at a value  $\geq 10$  mIU/mL, showing evidence of protection. Interestingly, within the age group  $\geq 1 < 5$  years, all of whom should

have had access to universal HBV vaccine, children with HIV were significantly less likely to show evidence of protection compared to children without HIV infection. It is possible that the HIV-infected children in this age group were less likely to receive vaccine, perhaps because of illnesses resulting in missed visits. Or, more likely, these children received vaccine but experienced a primary vaccine failure due to immunosuppression from their HIV disease. Standard 3-dose HBV vaccine regimens confer protection in >95% of immunocompetent children [35], but HIV-infected children have lower seroconversion rates. Even when seroconversion does occur, attrition of antibody with time, even among the immunocompetent, is also possible [30–33]. Tanzania's national immunization program does not include a birth dose of hepatitis B vaccine, but rather a 3-dose regimen beginning at 4 weeks of life in conjunction with other routine vaccinations. A study among HIV-infected children in Tanzania found a seroconversion rate of 59.5% after 3 doses of HBV vaccine; children on HAART before receipt of vaccine were more likely to develop an adequate immune response to HBV [36]. All HIV-infected children in our study were on HAART for a minimum of 6 months at study entry, but few or none would have been on HAART at the time of receiving vaccine. Finally, the potential impact of antiviral drug-associated vaccine escape mutants (VEMs) has been described as a possible mechanism for HBV vaccine failure among immunized populations. In populations where 3TC has been used as a single anti-HBV drug, as is often the case with HIV-infected individuals in sub-Saharan Africa, viruses with surface antigen alterations may occur. Thus, if a mother developed VEMs as a result of treatment with 3TC, her virus may be capable of escaping the infant's vaccine-generated antibody response [37].

The high prevalence of HIV-HBV coinfection among children in Tanzania underscores the need for treatment guidelines for this special population. Currently, the WHO recommends starting TDF and 3TC or FTC-containing ARV regimens for HIV-infected adolescents and adults with HBV coinfection "needing treatment" [38]. There are no guidelines for how to treat coinfecting children. One of the primary dilemmas in developing such recommendations is because children with chronic HBV are usually in the immune-tolerant phase of infection, often for years or even decades. During this phase, there is little to no liver inflammation or fibrosis. Treatment of HBV is typically optimal during the immune clearance or reactivation phases, when there is active liver inflammation [39]. Furthermore, in most sub-Saharan African countries, first-line HAART regimens include 3TC, which quickly leads to 3TC-resistant HBV strains when used as a single agent against HBV. The recent

approval of TDF down to the age of 2 years, combined with its rollout in many African countries, should provide an alternative for coinfecting children. Still, whether this should be used immediately for all coinfecting children or reserved for later when they show signs of active HBV disease is unclear and requires further study.

Currently, Tanzania, like many resource-poor countries, offers no guidelines for screening pregnant women for HBV infection; thus, most coinfecting women are unaware of their status, providing little opportunity for prevention of mother-to-child transmission and optimal maternal health. Although there are no FDA-approved HBV antiviral agents for use in pregnant women, safety data is increasingly accumulating [40], and potent antiviral drugs such as tenofovir may be a good option in many circumstances. Furthermore, although Tanzania includes universal HBV vaccine as part of its expanded program on immunizations, a monovalent birth dose of the vaccine would likely reduce the number of new infections as well. Although children in sub-Saharan Africa were traditionally believed to acquire their HBV infection horizontally in the early childhood years, more recent transmission data are lacking, particularly among women who are HIV-HBV coinfecting. A birth dose of HBV vaccine given within 24 hours is 70%–95% effective in preventing mother-to-child transmission [41]. High coverage with the primary vaccine series among infants has the greatest overall impact in preventing chronic HBV infection in children [6].

Our study had several limitations. First, chronic hepatitis B infection could not be confirmed, because samples were tested at a single timepoint; however, it is likely that most of the children with positive HBsAg were chronically infected. Second, the significance of 2 patients with isolated HBcAb is unclear because HBV DNA levels were not obtained. Third, we have no information on maternal HBV status or proof of HBV vaccine, both of which would certainly influence transmission risk. Finally, false-negative anti-HCV antibody results have been reported to occur among HIV-infected patients with immune suppression, although this is less likely with third-generation assays [42] such as the one used in our study.

In conclusion, our study demonstrates that HBV infection is a significant problem for HIV-infected children in the Kilimanjaro Region. HBsAg screening should be implemented for all HIV-infected children before starting HAART. Although most of these children will likely have immune-tolerant HBV disease, they will require closer monitoring for signs of liver inflammation and potential hepatotoxicities from their HAART regimens. Identifying HIV-infected children with HBV infection would also afford the opportunity to vaccinate susceptible household

members or other close contacts, and revaccination or booster doses for HIV-infected patients could be considered. Further study of how best to manage HIV-HBV coinfecting children in resource-poor settings is required, as pediatric guidelines are urgently needed.

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