Impact of Hepatitis C Virus on HIV Response to Antiretroviral Therapy in Nigeria

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Abstract: The effect of hepatitis C virus (HCV) on antiretroviral therapy (ART) response in patients in sub-Saharan Africa is unknown. We studied 1431 HIV-infected ART initiators in Jos, Nigeria, of whom 6% were HCV coinfected. A similar proportion of HIV/HCV-coinfected and HIV-monoinfected patients achieved HIV RNA <400 copies per milliliter after 24 and 48 weeks of ART ($P > 0.05$). Hepatotoxicity was uncommon (0.8% and 0.33% at 24 and 48 weeks, respectively) but was more common in the HIV/HCV-coinfected group at 24 (adjusted odds ratio = 19.3; 95% confidence interval: 4.41 to 84.4) and 48 weeks (adjusted odds ratio = 56.7; 95% confidence interval: 5.03 to 636.92). HCV did not significantly impact ART response in this Nigerian cohort.

Key Words: hepatitis C, HIV, antiretroviral therapy, Africa

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INTRODUCTION

An estimated 4–5 million patients are coinfected with HIV and chronic hepatitis C virus (HCV) worldwide.[1] In the United States and other developed countries, the majority of studies have found no significant long-term impact of HCV on HIV virologic, immunologic, or clinical outcomes. Overall mortality rates have been shown to be similar in HIV/HCV-coinfected and HIV-monoinfected patients, although HIV-HCV patients are at higher risk of liver-related mortality specifically.[2,3]

The prevalence of HCV in HIV-infected individuals in sub-Saharan Africa ranges between 0% and 22%.[4] The effect of HCV on HIV outcomes in these settings, however, is not well known. Competing risks, such as exposure to liver carcinogens, hepatotoxic therapies, including the antiretrovirals, nevirapine (NVP) and stavudine (d4T), and more advanced HIV immunosuppression in sub-Saharan Africa may put HIV/HCV-coinfected patients at higher risk of adverse outcomes compared with coinfected populations in the United States. In addition, HCV-specific antiviral therapies are rarely available in these settings.

In this evaluation, we studied participants enrolled at one of the largest President's Emergency Plan for AIDS Relief (PEPFAR)–supported HIV care and treatment sites in Nigeria, the Jos University Teaching Hospital (JUTH), to determine whether chronic HCV infection impacts HIV disease or the early response to antiretroviral therapy (ART) in previous antiretroviral-naive patients.

METHODS

The Harvard/AIDS Prevention Initiative in Nigeria PEPFAR program provides ART to eligible HIV-infected patients in Nigeria since June 2004. Eligibility criteria for ART include WHO stage IV, World Health Organization (WHO) stage III with CD4 <350 cells per cubic millimeter, or WHO stage I or II with CD4 ≤200 cells per cubic millimeter. Patients are assessed by physicians monthly and receive free ART and prophylaxis or treatment of opportunistic infections. Every 6 months, they receive immunologic and virologic monitoring. Standard first-line ART regimens include d4T or zidovudine, lamivudine, and efavirenz or NVP. More recently, Truvada (tenofovir and emtricitabine) has been recommended as a first-line alternative nucleoside reverse transcriptase inhibitor combination in Nigeria. Patients were recruited for participation and enrolled in the ART program after written informed consent. For this study, we included participants who initiated ART between October 2004 and June 2006, were HIV antibody positive, had a known HCV status, were hepatitis B surface antigen negative, and had a minimum of 6 months of follow-up on ART. This study was approved by the

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HCV antibody was tested with a third-generation enzyme immunoassay assay (DIA PRO Diagnostic Bioprobes, Milan, Italy) at the time of inclusion into the PEPFAR program. HCV RNA was quantified retrospectively on serum specimens stored at −80°C using the COBAS Amplicor HCV Monitor test, which has a lower limit of detection of 42 IU/mL (v2.0; Roche Diagnostics GmbH, Mannheim, Germany). Hepatitis B surface antigen was determined by enzyme immunoassay assay (Sysmex, Kobe, Japan). HIV RNA was determined using the Roche COBAS Amplicor HIV-1 Monitor Test (Roche Diagnostics GmbH) with a lower limit of detection of 400 copies per milliliter. CD4+ T-cell count was determined via flow cytometry (Partec GmbH, Munster, Germany). Hepatotoxicity was defined as alanine aminotransferase (ALT) values (Sysmex, Kobe, Japan) that were at least 5-fold more than the normal range for the JUTH laboratory (upper limit of normal ALT = 41 IU/mL). All laboratory tests were performed according to the respective manufacturer specifications.

A participant was classified as HIV/HCV coinfected if they had evidence of chronic HCV infection, which was defined as a positive HCV antibody and detectable HCV RNA. All other participants were considered HIV monoinfected. The HIV-monoinfected group included participants who were HCV antibody positive with an undetectable HCV RNA because they were presumed to either have a past infection with spontaneous clearance or a false-positive HCV antibody.[5,6] For these analyses, data up to 12 months were evaluated. For patients with >12 months of follow-up, data were censored at month 12.

Univariate methods were used to compare demographic and baseline clinical characteristics and virologic, immunologic, and hepatotoxic outcomes at weeks 24 and 48 between the HIV/HCV-coinfected and HIV-monoinfected groups; patients with elevated ALT at baseline were excluded for the hepatotoxic outcome evaluations at weeks 24 and 48. Baseline ALT was included in multivariate models as a continuous variable. The Pearson χ^2 test or Fisher exact test was used for categorical variables, as relevant, and the Wilcoxon test for continuous variables. Variables with a P value of ≤ 0.20 were selected for inclusion into logistic regression modeling, which was conducted to further evaluate factors potentially related to hepatotoxicity. Cox-proportional hazards models were also generated using these data. All analyses were conducted using Stata version 10.1 (College Station, TX).

RESULTS

Baseline Characteristics

One thousand four hundred thirty-one HIV-infected participants were included in this study; of whom, 1352 (94%) were HIV-monoinfected (183 HCV antibody positive with undetectable HCV RNA; 1169 HCV antibody negative), whereas 79 (6%) were HIV/HCV coinfected (Table 1). The HIV/HCV-coinfected group was significantly older than the HIV-monoinfected group (median: 39 vs. 34 years, respectively; $P < 0.001$). The gender distribution was similar between the 2 groups. The median CD4$^+$ T-cell count was 134 cells per cubic millimeter, and there were no statistically significant differences between the 2 groups (115 cells/mm^3 for HIV/HCV coinfected and 135 cells/mm^3 for HIV monoinfected, respectively; $P = 0.43$). Likewise, baseline HIV RNA levels were similar between groups (4.9 log copies/mL for HIV/HCV coinfected and 4.8 log copies/mL for HIV monoinfected, respectively; $P = 0.12$). HIV/HCV-coinfected patients had a significantly higher median baseline ALT than HIV-monoinfected patients (27.3 vs. 19.1 U/mL; $P = 0.008$). Overall, 0.21% of the participants had an ALT >5× upper limit of normal at baseline; there were no statistically significant differences in the proportion of patients with elevated baseline ALT between HIV/HCV-coinfected and HIV-monoinfected patients (0% vs. 0.23%, $P = 1.00$). There were no significant differences in ART regimen by HCV status.

TABLE 1. Cohort Demographics and Baseline Laboratories at ART Initiation

	HIV Monoinfected* (n = 1352)	HIV/HCV$^+$† (n = 79)	P‡
Female, n (%)	—	—	0.38
Median age, yrs (IQR)	35	39	<0.0001
WHO stage, n (%)			
1	37	33	0.50
2	45	46	
3	14	19	
4	4	2	
Drug regimen, n (%)			
NVP containing	95	94	0.80
d4T containing	51	53	0.73
Baseline median CD4 count, cells/mm^3 (IQR)	135	115	0.43
Baseline median HIV RNA, log copies/mL (IQR)	4.8	4.9	0.12
Baseline median ALT, U/mL (IQR)	19.1	27.3	0.008
ALT >5 × ULN, n (%)	0.23	0	1.00

*One hundred eighty-three were HCV antibody positive and HCV RNA <42; 1169 were HCV antibody negative.
†HCV antibody positive and detectable HCV RNA.
‡The P values represent comparison between HIV-monoinfected and HIV/HCV-coinfected subjects.
ULN, upper limit of normal.

Hepatitis C and ART Response

The proportion of HIV/HCV-coinfected and HIV-monoinfected patients achieving an undetectable HIV RNA did not differ at either 24 (65% vs. 70%, $P = 0.40$) or 48 weeks (55% vs. 61%, $P = 0.30$) (Table 2). In addition, there were no significant differences in the median CD4+ T-cell count increase between HIV/HCV-coinfected and HIV-monoinfected patients at either 24 (90 vs. 88 cells/mm^3, respectively; $P = 0.41$) or 48 weeks (111 and 129 cells/mm^3, respectively; $P = 0.32$). Overall, the proportion of HIV/HCV subjects who developed hepatotoxicity was small at 24 weeks (6.35%) and declined further to 2.82% at 48 weeks.

In logistic regression modelling, after adjusting for age, d4T use, and sex, HIV/HCV coinfection [adjusted odds

TABLE 2. Hepatitis C and ART Response

	HIV Monoinfected		HIV/HCV+		
	n*	%	n*	%	P*
24 Weeks	1344		78		
HIV RNA ≤ 400 copies/mL	1059	70	63	65	0.40
Δ Median CD4 count (cells/mm^3)	1095	88	66	90	0.41
Hepatotoxicity†	1059	0.47	63	6.35	0.001
48 Weeks	1300		76		
HIV RNA ≤ 400 copies/mL	1185	61	71	55	0.30
Δ Median CD4 count (cells/mm^3)	1185	129	71	111	0.32
Hepatotoxicity†	1144	0.17	71	2.82	0.019

*n = number of patients with a value at the observed time (24, 48 weeks).
†Excluded patients who had an elevated ALT level at baseline.

ratio (aOR) = 19.3; 95% CI: 4.41 to 84.4] and baseline ALT (aOR = 1.01; 95% CI: 1.00 to 1.03) were significant predictors of increased risk for hepatotoxicity at 24 weeks. After adjusting for d4T use and baseline ALT, HIV/HCV coinfection (aOR = 56.7; 95% CI: 5.03 to 636.92) increased the risk for hepatotoxicity at 48 weeks, whereas female sex (aOR = 0.05; 95% CI: 0.004 to 0.62) and older age (aOR = 0.81; 95% CI: 0.68 to 0.95) were protective against hepatotoxicity at 48 weeks. Data from survival analysis and Cox proportional hazard models provided similar results (not shown).

DISCUSSION

In one of the few studies to date of the effect of HCV on HIV treatment outcomes in sub-Saharan Africa, we observed comparable HIV and immunologic responses to ART between HIV/HCV-coinfected and HIV-monoinfected populations. The proportion of subjects who experienced an elevated ALT was small, although the HIV/HCV-coinfected group had a significantly higher risk of hepatotoxicity at both 24 and 48 weeks after ART initiation. Thus, we found that HCV does not significantly impact response to ART in the short term in our program population.

The overall prevalence of HCV in this cohort was noted to be similar to United States–based studies and other recent studies in Nigeria.[7] The predominant mode of HCV transmission in sub-Saharan Africa is still unknown although iatrogenic causes such as unsterile injections are thought to be common.[8] Interestingly, HCV antibody was detected in 262 of 1431 (18.3%) patients in this cohort, but the prevalence of chronic HCV, defined as detectable HCV RNA, was only 6%. Few sub-Saharan Africa studies have used molecular methods to determine the prevalence of HCV; these may be important given recent concerns about false-positive HCV antibody testing in sub-Saharan Africa. In a cohort of HIV-infected pregnant women in Malawi, only 2 of 108 women who were anti–HCV positive had a positive recombinant immunoblot assay suggesting recent or past infection and all were HCV RNA negative.[5] In the Rakai Community Cohort Study from Uganda, a high prevalence of HCV seroreactivity (14%) was observed in patients without evidence of HCV viremia.[6] Collectively, these findings suggest that HCV RNA testing is needed to determine the true prevalence of chronic HCV coinfection in HIV cohorts in sub-Saharan Africa.

In this study, there were no significant differences in CD4+ T-cell counts and HIV RNA levels at either baseline or after ART initiation between HIV/HCV-coinfected and HIV-monoinfected groups. The findings are consistent with most other studies on HIV/HCV coinfection in sub-Saharan Africa and developed countries,[2,3,9] but differ from HIV/hepatitis B virus coinfection where CD4+ T-cell counts are lower at baseline with chronic hepatitis B.[10]

Although the finding was not significant, we did observe slightly less robust changes in CD4+ T-cell counts at 24 and 48 weeks after ART initiation in HIV/HCV-coinfected patients compared with HIV-monoinfected patients. Poorer immunologic recovery after ART initiation has been observed in other studies, especially within the first 24 weeks; however, the impact of this initial impaired immune response is thought to have little if any effect on overall morbidity or mortality.[11] Encouragingly, we found that there was no effect of HCV on HIV virologic response after ART initiation, which is consistent with other studies from Nigeria,[12] suggesting there is minimal effect of HCV on the efficacy of ART in controlling HIV viral replication.

Although there was a significantly higher rate of hepatotoxicity among HIV/HCV-coinfected patients compared with HIV-monoinfected patients at 24 and 48 weeks after ART initiation, the percentage of patients with hepatotoxicity was low. We were not able to correlate these hepatotoxic events with clinical status, and it is unknown if severe elevations in ALT resulted in any significant morbidity or mortality. A number of studies have found HCV and hepatitis B virus to be associated with increased risk for elevated transaminases after ART initiation in HIV-infected individuals.[13,14] Notably, the overall incidence of severe elevations (>5× upper limit of normal) even in resource-limited settings is small and most cases are asymptomatic.[13] Several mechanisms of hepatotoxicity after ART initiation have been proposed, including: immune-mediated damage to HCV-infected hepatocytes from immune reconstitution syndrome, direct effects of drug toxicity, and steatosis from antiretroviral agents resulting in accelerated inflammation and fibrosis. Of particular concern is the effect of more hepatotoxic ART drugs, such as d4T, didanosine, NVP, and lopinavir/ritonavir, which may also contribute to hepatic damage in HIV-infected populations.[15] In this cohort, we did not find an association between specific ART and hepatotoxic events in the short term (see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A372). Additional research is needed into pathogenesis of these hepatotoxic events and the effect of these events on long-term liver-related outcomes.

To our knowledge, this is the largest study of HIV/HCV-coinfected individuals in sub-Saharan Africa, where HCV infection was confirmed by both serologic and molecular methods, providing more accurate data about the true prevalence of chronic HCV infection in HIV-infected populations in these settings. We were also able to assess HIV virologic endpoints in a setting where HIV RNA testing is not

routinely available, further confirming the findings from developed countries of minimal effect of HCV on response to ART. Limitations of this study included the relatively short follow-up period after ART initiation, which prevented us from determining whether HCV has any long-term effect on HIV outcomes. Data on important confounders such as alcohol consumption, status of underlying liver disease, and TB therapy were not available. Furthermore, we could not determine whether there was any significant effect of HCV on mortality or other morbidities in HIV-infected individuals including long-term liver-related complications.

In summary, HCV RNA testing is important for the diagnosis of chronic HCV infection in sub-Saharan Africa. Our data demonstrate that HIV/HCV-coinfected patients respond as well to ART as HIV-monoinfected subjects. Because the risk of severe hepatotoxicity was small, ART should not be withheld from HIV/HCV-coinfected patients in sub-Saharan Africa, but coinfected patients should be monitored more closely for hepatotoxicity.

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REFERENCES

1. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol.* 2006;44(suppl 1):S6–S9.
2. Turner J, Bansi L, Gilson R, et al; UK Collaborative HIV Cohort (UK CHIC) Study. The prevalence of hepatitis C virus (HCV) infection in HIV-positive individuals in the UK—trends in HCV testing and the impact of HCV on HIV treatment outcomes. *J Viral Hepat.* 2010;17:569–577.
3. Sullivan PS, Hanson DL, Teshale EH, et al. Effect of hepatitis C infection on progression of HIV disease and early response to initial antiretroviral therapy. *AIDS.* 2006;20:1171–1179.
4. Barth RE, Huijgen Q, Taljaard J, et al. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. *Int J Infect Dis.* 2010;14: 1024–1031.
5. Charles C, and the BAN Study Team. Prevalence of hepatitis C virus infection among human immunodeficiency virus Type-1 infected pregnant women in Malawi: the BAN study. Paper presented at: 17th Conference on Retroviruses and opportunistic infections, February, 2010; San Francisco, CA. Oral Presentation # 693.
6. Kirk GD, Ocama P, Stabinski L, et al. High prevalence of seroreactivity to hepatitis C virus without detectable viremia in rural Ugandans. Presented at: 13th International Symposium on Viral Hepatitis and Liver Disease; March 2009; Washington, DC.
7. Otegbayo JA, Taiwo BO, Akingbola TS, et al. Prevalence of hepatitis B and C seropositivity in a Nigerian cohort of HIV-infected patients. *Ann Hepatol.* 2008;7:152–156.
8. Madhava V, Burgess C, Drucker E. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. *Lancet Infect Dis.* 2002;2:293–302.
9. Moore E, Beadsworth MB, Chaponda M, et al. Favourable one-year ART outcomes in adult Malawians with hepatitis B and C co-infection. *J Infect.* 2010;61:155–163.
10. Idoko J, Meloni S, Muazu M, et al. Impact of hepatitis B virus infection on human immunodeficiency virus response to antiretroviral therapy in Nigeria. *Clin Infect Dis.* 2009;49:1268–1273.
11. Miller MF, Haley C, Koziel MJ, et al. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: a meta-analysis. *Clin Infect Dis.* 2005;41:713–720.
12. lsa SE, Gwamzhi LN, Akolo C, et al. A prospective cohort study of immunologic and virologic outcomes in patients with HIV/AIDS and hepatitis virus co-infection in Jos, Nigeria. *Niger J Med.* 2010;19: 279–285.
13. Núñez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. *Hepatology.* 2010;52:1143–1155
14. Jones M, Núñez M. HIV and hepatitis C co-infection: the role of HAART in HIV/hepatitis C virus management. *Curr Opin HIV AIDS.* 2011;6:546–552.
15. Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *J Hepatol.* 2006;44:S132–S139.