Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 February 1; 62(2): 204–207. doi:10.1097/QAI.0b013e31827ce536.

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

Oche Agbaji, MD[1], **Chloe L. Thio, MD**[2], **Seema Meloni, PhD, MPH**[3], **Camilla Graham, MD**[4], **Mohammed Muazu, MSc**[1], **Ladep Nimzing, MD**[5], **John Idoko, MD**[1,*], **Jean-Louis Sankalé, PharmD, SD**[3], **Ernest Ekong, MD**[3], **Robert Murphy, MD**[6], **Phyllis Kanki, DVM, SD**[3], and **Claudia Hawkins, MD, MPH**[6]

[1]Jos University Teaching Hospital, Jos, Plateau State, Nigeria

[2]Johns Hopkins University, Baltimore MD, USA

[3]Harvard School of Public Health, Boston MA, USA

[4]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

[5]Imperial College London, London, UK

[6]Northwestern University, Chicago IL, USA

Abstract

The effect of HCV on 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 co-infected. A similar proportion of HIV-HCV co-infected and HIV-mono-infected patients achieved HIV RNA <400 cp/ml after 24 and 48 weeks of ART (p values >0.05). Hepatotoxicity was uncommon (0.8% and 0.33% at 24 and 48 weeks, respectively), but was more common in the HIV-HCV co-infected group at 24 (aOR=19.3; 95% CI: 4.41–84.4) and 48 weeks (aOR=56.7; 95% CI: 5.03–636.92). HCV did not significantly impact ART response in this Nigerian cohort.

Keywords

Hepatitis C; HIV; antiretroviral therapy; Africa

Introduction

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

Corresponding Author: Dr Oche Agbaji, Department of Medicine, Jos University Teaching Hospital, P.M.B.2076, Jos, Nigeria. oagbaji@yahoo.com Tel: +234 803 349 1851.
*Currently Director General, National Agency for the Control of AIDS, Abuja, Nigeria.

Presented in part: 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, 3–6th February 2008, Abstract 1058.

Conflicts of Interest: All authors: No reported conflicts.

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.

The prevalence of HCV in HIV-infected individuals in sub-Saharan Africa (SSA) ranges between 0–22% [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 SSA may put HIV-HCV co-infected patients at higher risk of adverse outcomes compared to co-infected populations in the US. In addition, HCV-specific antiviral therapies are rarely available in these settings.

In this evaluation, we studied participants enrolled at one of the largest PEFPAR-supported HIV care and treatment sites in Nigeria, the Jos University Teaching Hospital (JUTH), in order to determine whether chronic HCV infection impacts HIV disease or the early response to antiretroviral therapy (ART) in previously antiretroviral-naïve patients.

Methods

The Harvard/AIDS Prevention Initiative in Nigeria (APIN) PEPFAR program provides ART to eligible HIV-infected patients in Nigeria since June 2004. Eligibility criteria for ART include WHO stage IV, WHO stage III with CD4 <350 cells/mm^3, or WHO stage I or II with CD4 ≤200 cells/mm^3. Patients are assessed by physicians monthly and receive free ART as well as 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 following 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 (HBsAg) negative, and had a minimum of six months of follow-up on ART. This study was approved by the Institutional Review Boards at the JUTH, Harvard School of Public Health and Johns Hopkins University.

HCV antibody was tested with a third generation EIA assay (DIA PRO Diagnostic Bioprobes, Milano, 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 (LLD) of 42 IU/ml (v2.0, Roche Diagnostics GmbH, Mannheim, Germany). HBsAg was determined by EIA assay (Sysmex, Kobe, Japan). HIV RNA was determined using the Roche COBAS Amplicor HIV-1 Monitor Test (Roche Diagnostics GmbH, Mannheim, Germany) with a LLD of 400 cp/mL. CD4+ T-cell count was determined via flow cytometry (Partec GmbH, Munster, Germany). Hepatotoxicity was defined as ALT values (Sysmex, Kobe, Japan) that were at least 5-fold over 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's specifications.

A participant was classified as HIV-HCV co-infected 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-mono-infected. The HIV mono-infected group included participants who were HCV antibody positive with an undetectable HCV RNA, since 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 month 12 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 as well as virologic, immunologic and hepatotoxic outcomes at weeks 24 and 48 between the HIV-HCV co-infected and HIV-mono-infected 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's χ^2-test or Fisher's 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 hepatotoxoicity. 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 (Table 1)

1431 HIV-infected participants were included in this study, of whom 1352 (94%) were HIV-mono-infected (183 HCV antibody positive with undetectable HCV RNA; 1169 HCV antibody negative) while 79 (6%) were HIV-HCV co-infected. The HIV-HCV co-infected group was significantly older than the HIV-mono-infected group (median: 39 vs. 34 years, respectively; $p<0.001$). The gender distribution was similar between the two groups. The median CD4+ T-cell count was 134 cells/mm^3 and there were no statistically significant differences between the two groups (115 cells/mm^3 for HIV-HCV co-infected and 135 cells/mm^3 for HIV-mono-infected, respectively; p=0.43). Likewise, baseline HIV RNA levels were similar between groups (4.9 log cp/ml for HIV-HCV-co-infected and 4.8 log cp/ml for HIV-mono-infected, respectively; p=0.12). HIV-HCV co-infected patients had a significantly higher median baseline ALT than HIV-mono-infected patients (27.3 versus 19.1 U/ml; $p=0.008$). Overall, 0.21% of the participants had an ALT >5X ULN at baseline; there were no statistically significant differences in the proportion of patients with elevated baseline ALT between HIV-HCV co-infected and HIV-mono-infected patients (0% versus 0.23%, $p=1.00$). There were no significant differences in ART regimen by HCV status.

Hepatitis C and ART Response (Table 2)

The proportion of HIV-HCV co-infected and HIV-mono-infected 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). In addition, there were no significant differences in the median CD4+ T-cell count increase between HIV-HCV co-infected and HIV-mono-infected patients at either 24 (90 versus 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 co-infection (aOR=19.3; 95% CI: 4.41–84.4) and baseline ALT (aOR=1.01; 95% CI: 1.00–1.03) were significant predictors of increased risk for hepatotoxicity at 24 weeks. After adjusting for d4T-use and baseline ALT, HIV-HCV co-infection (aOR=56.7; 95% CI: 5.03–636.92) increased the risk for hepatotoxicity at 48 weeks whereas female sex (aOR=0.05; 95% CI: 0.004–0.62) and older age (aOR=0.81; 95% CI: 0.68–0.95) 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 SSA, we observed comparable HIV and immunologic responses to ART between HIV-HCV co-infected and HIV-mono-infected populations. The proportion of subjects who experienced an elevated ALT was small, although the HIV-HCV co-infected 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 US-based studies and other recent studies in Nigeria [7]. The predominant mode of HCV transmission in SSA is still unknown although iatrogenic causes such as unsterile injections are thought to be common [8]. Interestingly, HCV antibody was detected in 262/1431 (18.3%) of patients in this cohort, but the prevalence of chronic HCV, defined as detectable HCV RNA, was only 6%. Few SSA 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 SSA. 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 (RIBA) 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 co-infection in HIV cohorts in SSA.

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 co-infected and HIV-mono-infected groups. The findings are consistent with most other studies on HIV-HCV co-infection in SSA and developed countries [2, 3, 9], but differ from HIV-HBV co-infection 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 co-infected patients compared to HIV-mono-infected 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 co-infected compared to HIV-mono-infected 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 HBV 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 (>5xULN) 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 [supplementary table]. 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 co-infected individuals in SSA, 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 SSA. Our data demonstrate that HIV-HCV co-infected patients respond as well to ART as HIV mono-infected subjects. Since the risk of severe hepatotoxicity was small, ART should not be withheld from HIV-HCV co-infected patients in SSA, but co-infected patients should be monitored more closely for hepatotoxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding: This publication was supported by NIH U01 AI38858, the Northwestern University AIDS International Training and Research Program (NU-AITRP, Grant number 5D43TWOO7995-02, and Cooperative Agreement No. U51HA02522 from the Health Resources and Services Administration). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Health Resources and Services Administration. CT was additionally supported by NIH grants R01AI071820 and R56AI060449.

The authors are thankful to the staff and patients of the HIV Clinic at Jos University Teaching Hospital (JUTH), Harvard PEPFAR and AIDS Prevention Initiative in Nigeria (APIN) programmes for supporting the care of HIV patients at JUTH.

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Table 1

Cohort demographics and baseline labs at ART initiation

	HIV mono-infected[a] n=1,352	HIV/HCV+[b] n=79	P value[c]
Female, n (%)			0.38
Median age, years (IQR)	35	39	<0.0001
WHO Stage, n (%)			0.50
1	37	33	
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 cp/ml (IQR)	4.8	4.9	0.12
Baseline median ALT, U/ml (IQR)	19.1	27.3	0.008
ALT >5x ULN, n (%)	0.23	0	1.00

[a] 183 were HCV antibody positive and HCV RNA <42; 1169 were HCV antibody negative

[b] HCV antibody positive and detectable HCV RNA

[c] *p*-values represent comparison between HIV-mono-infected and HIV-HCV co-infected subjects

Table 2

Hepatitis C and ART response

	HIV mono-infected		HIV/HCV+		P value*
	N[a]	%	*N*[a]	%	
24 weeks	1344		78		
HIV RNA ≤400 cp/ml	1059	70	63	65	0.40
Δ median CD4 count (c/mm^3)	1095	88	66	90	0.41
Hepatotoxicity[b]	1059	0.47	63	6.35	0.001
48 weeks	1300		76		
HIV RNA ≤400 cp/mL	1185	61	71	55	0.30
Δ median CD4 count (c/mm^3)	1185	129	71	111	0.32
Hepatotoxicity[b]	1144	0.17	71	2.82	0.019

[a] N= number of patients with a value at the observed time (24, 48 weeks)

[b] Excluded patients that had an elevated ALT level at baseline