DR. MICHAEL JEFFREY VINIKOOR (Orcid ID : 0000-0002-3862-7795)

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TITLE PAGE

Title:

Hepatitis B therapy as HIV prevention in Africa: a case series from Zambia

Authors:

Michael J. Vinikoor[1,2], Edford Sinkala[3], Belinda Chihota[1], Annie Kanunga[3], Gilles Wandeler[4]

Institutions:

[1]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

[2]Department of Medicine, University of Alabama at Birmingham, Birmingham, USA

[3]Department of Medicine, University Teaching Hospital, Lusaka, Zambia

[4]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland

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Background:

In East and Southern Africa, where 5-10% have chronic hepatitis B virus (HBV) infection, incidence of human immunodeficiency virus (HIV) infection remains unacceptably high. This introduces challenges and opportunities for implementation of HBV care and treatment. We now describe new HIV diagnoses made within an HBV monoinfection cohort in Zambia and their relevance to broader HBV policy implementation.

HBV monoinfection cohort in Zambia:

At a hospital in Lusaka, adults (18+ years) who were hepatitis B surface antigen-positive and HIV-negative (based on an antibody assay ≤12 months prior) enrolled in a prospective cohort. At enrollment, a physical examination was performed and we measured HBV DNA, hepatitis B e antigen (HBeAg), and ALT, which was repeated every 3-6 months thereafter. HBV therapy initiation, with fixed-dose combination tenofovir disoproxil fumarate (TDF) and lamivudine – the recommended regimen in Zambia, was based on World Health Organization (WHO) criteria (1). All patients were followed-up every 3-6 months, and HIV testing was repeated yearly.

Description of new HIV diagnoses:

Among 160 participants (median age 33 years, 71.9% male), 5 (3.1%) tested HIV-positive during follow-up (Table 1). Patient 1 was a 28-year-old man with HBeAg-negative hepatitis (HBV DNA 23,017 IU/ml and ALT 79 U/L) at baseline. He initiated HBV therapy 6 months post-enrollment and at 1 year, HBV DNA was undetectable

(<20) and ALT had reduced to 33 U/L. However, repeat HIV testing was positive. HIV RNA was undetectable. Patients 2-4 were men, aged 23-38 years-old, non-cirrhotic, and presumed inactive HBV carriers (HBV DNA <2,000 IU/ml and ALTs of 26-33 U/L) who did not meet criteria for HBV therapy. At their 1-year visits, HIV-positivity was ascertained. Patient 5 was a 45-year-old man with HBeAg-positive hepatitis (HBV DNA >170,000,000 IU/ml and ALT 100 U/L) who initiated HBV therapy 2 months post-enrollment. Medication adherence was good per pharmacy records and HBV DNA was undetectable at 2 years. However, at 3.5 years on therapy, HIV-positivity was diagnosed. At that time HBV DNA was 3,417 IU/ml and HIV-1 RNA was 4,523 copies/ml. Sanger sequencing of HIV-1 revealed M184V, a mutation that confers high-level resistance to lamivudine, and the thymidine analog mutations (TAMs) M41L and T215Y, which, when combined, confer low-level resistance to TDF.

Discussion:

Current WHO HBV guidelines lack guidance on the timing and frequency of HIV testing (1), nor do they mention the potential of HBV therapy to prevent new HIV infections, i.e., pre-exposure prophylaxis (PrEP). In an HBV cohort in Zambia, 3.1% became HIV positive, providing insights for HBV therapy in high HIV prevalence settings. Patient 1 seroconverted between enrollment and HBV therapy initiation and although he suppressed HIV RNA on HBV therapy, this scenario could have spawned HIV drug resistance (HIVDR). On the basis of this case, we now re-confirm HIV status at the first dispensation of HBV therapy, regardless last negative HIV test date. Patients 2-4 were ineligible for HBV therapy, posing potential missed opportunities to prevent HIV infection. Only a small fraction (5-25%) of chronic HBV

cases in Africa meet HBV therapy criteria (2). HIV incidence could potentially be reduced by expanding eligibility for HBV therapy, for example, to immune tolerant patients who are often not treated despite increasing evidence of potential liver damage (3). Also, the Zambian Ministry of Health recommends long-term HBV therapy for any HBsAg-positive individual referred for HIV PrEP due to high perceived HIV risk. Patient 5 had suboptimal medication adherence, the major barrier to PrEP effectiveness (4), and the presence of the M184V mutation could be explained by selection pressure of HBV therapy. As HBV therapy does not select for TAMs, this patient probably acquired an HIV infection with pre-existing mutations. On the basis of these cases we recommend that HBV programs in settings with high HIV incidence ensure strong access to HIV testing. The potential public health benefits of HBV therapy in moderate/high prevalence settings should be investigated.

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FOOTNOTE PAGE

Corresponding author contact information:

Dr. Michael J. Vinikoor, Department of Medicine, University of Alabama at Birmingham, Centre for Infectious Disease Research in Zambia, Plot # 34620 Off Alick Nkhata Road, Mass Media, P.O. Box 34681 Lusaka, Zambia 10101; Phone: +260 211242257, Email: mjv3@uab.edu

List of abbreviations:

HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization
HBeAg	Hepatitis B e antigen
ALT	Alanine aminotransferase
PrEP	Pre-exposure prophylaxis
TAM	Thymidine analog mutation

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Table 1. Demographic and clinical characteristics of HBV monoinfected Zambian adults who became HIV-antibody positive during follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	28 years	30 years	23 years	38 years	45 years
Sex	male	male	male	male	male
Enrollment HBV DNA, U/L	23,017	53	85	232	170,000,000
Enrollment HBeAg status	non-reactive	non-reactive	reactive	missing	reactive
Enrollment ALT level, U/L	79	33	26	26	110
HBV disease stage	immune active	inactive carrier	inactive carrier	inactive carrier	immune active
Initiation of HBV therapy*	yes	no	no	no	yes
Time from enrollment to start of HBV therapy	5 months	N/A	N/A	N/A	2 months
Reduced medication adherence (per pharmacy records)	no	N/A	N/A	N/A	no
Time from enrollment to HIV-positivity	18 months	8 months	8 months	4 months	44 months
HBV DNA at HIV diagnosis, IU/ml	<20	missing	missing	missing	3,417
HIV RNA at HIV diagnosis, copies/ml	<20	missing	missing	missing	4,523

*HBV therapy was prescribed when patients met World Health Organization criteria and consisted of fixed dose combination tenofovir disoproxil fumarate and lamivudine. Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; N/A, not applicable