Maternal hepatitis B and infant infection among pregnant women living with HIV in South Africa

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Abstract

Introduction: Globally, hepatitis B virus (HBV) infection is the leading cause of liver-related mortality. Newborn vaccination, maternal antiviral therapy and administering hepatitis B immune globulin shortly after birth can greatly reduce the risk of perinatal and infant infection. However, evidence-based policy regarding these interventions in Africa is hampered by gaps in knowledge of HBV epidemiology. We describe maternal chronic hepatitis B (CHB) prevalence and infant infection during the first year of life within a cohort of women living with HIV.

Methods: We recruited and prospectively followed pregnant women living with HIV and their infants from prenatal clinics in an urban area of South Africa. Hepatitis B surface antigen, anti-hepatitis B surface antibodies and HBV DNA were assessed in all women. Hepatitis B testing was also performed at 6 and 52 weeks for all infants born to mothers with either positive surface antigen or detectable HBV DNA.

Results: We enrolled 189 women with a median age of 29 years and median CD4 count of 348 cells/mm³. Fourteen had a positive surface antigen (7.4%), of which six were positive for “e” antigen. An additional three had detectable HBV DNA without positive surface antigen. One infant developed CHB and three others had evidence of transmission based on positive HBV DNA assays. HBV vaccinations were delivered at six weeks of life to all infants.

Conclusions: Our findings highlight the risk of peripartum HBV transmission in this setting. Approaches to reducing this transmission should be considered.

Keywords: HIV; HBV; peripartum; transmission; vaccination; Africa; occult HBV.
All participants received prenatal, peripartum and postnatal care through the public-sector health system. Study-specific laboratory testing included HIV and hepatitis B specific assays, including hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs), and quantitative HBV DNA for all participants. Women and infants positive for HBsAg had testing for hepatitis B e antigen (HBeAg). Children born to women positive for HBsAg or with detectable HBV DNA had HBV specific testing at 6 and 52 weeks. Infants with a positive HBsAg test at six weeks had testing of stored whole blood from the third day of life for HBsAg and HBV DNA.

We used a single positive HBsAg result as a surrogate for CHB based on the assumption that the women participating in this study were probably infected earlier in life and acute HBV infection was not the cause of the positive assay. The formal definition of chronic HBV is two consecutive positive HBsAg tests six or more months apart. We defined occult hepatitis B as detectable HBV DNA among women without a positive HBsAg, consistent with other publications [14]. Perinatal transmission was defined by a third day of life sample positive for HBV DNA and negative for HBsAg. HBsAg and HBeAg testing was performed using the Abbott ARCHITECT system (Abbott Laboratories, Abbott Park, Illinois, USA) and quantitative HBV DNA was assayed using the COBAS Ampliprep/COBAS TaqMan HBV Test with a lower limit of detection of 20 IU/mL (Roche Molecular Diagnostics, Basel, Switzerland). All laboratory testing occurred at an accredited commercial research laboratory. Written informed consent was obtained from all adult participants prior to study procedures. Approvals of the study and consent process were received from the Johns Hopkins University and the University of the Witwatersrand.

We compared proportions or medians in the cohort using non-parametric measures, due to a small number of women with CHB, using either the chi-square test or Wilcoxon rank sum test. We calculated exact 95% confidence intervals around our estimate of CHB prevalence using the binomial method. STATA version 13 (Stata Corporation, College Park, Texas, USA) was used for all analyses.

**Results**

We recruited 189 pregnant women living with HIV with a median age of 29 years (interquartile range [IQR]: 26 to 31) and median enrolment CD4 count of 348 cells/mm³ (IQR: 232–471; Table 1). Prior to presenting in labour, the following prevention of mother-to-child-transmission of HIV approaches were used: 44 (23%) received zidovudine monotherapy, 20 (10%) received stavudine or zidovudine-based antiretroviral therapy, and 120 (63%) received tenofovir disoproxil-based ART.

**Table 1. Maternal characteristics overall and by HBsAg status**

|                        | Total cohort | HBsAg-negative | HBsAg-positive |
|------------------------|-------------|----------------|---------------|
| **Pregnant women, number** | 189         | 175            | 14            |
| **Age, years**         | 29 (26, 31) | 29 (26, 31)    | 32 (30, 34)   |
| **CD4 count at enrolment, cell/mm³** | 348 (232, 471) | 342 (232, 471) | 364 (126, 459) |
| **HIV RNA closest to delivery, log₁₀ c/mL** | 2.1 (1.3, 3.4) | 2.0 (1.3, 3.4) | 2.7 (1.7, 3.4) |
| **HIV RNA <400 c/mL**   | 108 (58)    | 97 (55)        | 11 (78)       |
| **Yes**                | 81 (42)     | 78 (44)        | 3 (21)        |
| **Antiretroviral therapy** |            |                |               |
| Single dose NVP only   | 5 (3)       | 3 (2)          | 2 (14)        |
| AZT monotherapy + s d NVP | 44 (23)   | 41 (23)        | 3 (21)        |
| D4T or AZT based ART    | 20 (10)     | 20 (11)        | 0             |
| TDF-based ART          | 120 (63)    | 111 (63)       | 9 (64)        |
| **HBeAg**              |             |                |               |
| Negative               | 8 (57)      |                |               |
| Positive               | 6 (43)      |                |               |
| **Detectable HBV DNA**  |             |                |               |
| No                     | 165 (94)    | 5 (36)         |               |
| Yes                    | 3 (2)       | 9 (64)         |               |
| Missing                | 7 (4)       | 0              |               |
| **HBV DNA, log₁₀ IU/mL (among those with detectable HBV DNA)** | 1.7 (1.7, 2.2) | 3.2 (2.3, 4.4) |               |
| **Anti-HBs antibody**  |             |                |               |
| Negative               | 128 (74)    |                |               |
| Positive               | 47 (26)     |                |               |

*Also including lamivudine and efavirenz, nevirapine, or lopinavir/ritonavir. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen, NVP, nevirapine, AZT, zidovudine; D4T, stavudine; TDF, tenofovir disoproxil.
therapy (ART), 120 (63%) received tenofovir-based ART, and 5 (3%) were not recorded as having received any form of prevention-of-mother-to-child-transmission prior to presenting in labour. All women receiving zidovudine monotherapy or not receiving any form of prevention-of-mother-to-child-transmission received maternal single-dose nevirapine during labour. All infants received nevirapine prophylaxis postpartum. CHB was diagnosed in 14 women (7.4%; 95% CI: 4.3, 12). Of these women, 6/14 (43%) were positive for HBsAg and 9/14 (64%) had detectable HBV DNA. Three women with negative HBsAg assays also had detectable HBV DNA. Of the women negative for HBsAg, 47 (26%) had detectable anti-HBs antibodies resulting from either resolved HBV infection or immunization.

Postnatal data were available for 11 infants born to women with CHB and 3 born to women without CHB but with detectable HBV DNA. Three infants born to mothers with CHB were not tested because of the mothers moving away (two) or maternal death (one). Of these 14 infants tested for hepatitis B, 1 had CHB following peripartum infection. The infected infant had third day blood positive for HBV DNA at log10 2.7 IU/ml but negative for HBsAg; at six weeks HBV DNA was log10 6.8 IU/mL and HBsAg was positive. HBsAg remained positive and HBeAg was positive at 12 months at which time HBV DNA was not assayed. Three other infants appeared to have been infected based on detectable HBV DNA at either week 6 (one) or at 12 months (two) of life but we did not detect HBsAg in these infants (Table 2). The infant with peripartum CHB was born to a mother who received stavudine, lamivudine, and efavirenz whereas one received zidovudine mono-therapy. All HBV exposed and unexposed infants received the initial dose of HBV vaccine when they were six weeks old; seven of the twelve mothers with CHB or occult HBV received tenofovir containing ART. None of the 14 infants were HIV-infected by 12 months post-partum.

Conclusions
In our study, we observed four vertically-infected infant HBV infections from fourteen CHB-infected pregnant women living with HIV—one infant with CHB and three with detectable HBV DNA without HBsAg. Unfortunately, because HBV vaccination at birth and HBV immune globulin are not routinely used in the public sector in South Africa, none of these infants received either intervention [6,15]. In addition, the mother of the infant who developed CHB did not receive tenofovir, an agent associated with HBV control [16]. She was receiving lamivudine, another agent with HBV activity, but her high HBV DNA level suggests that she had lamivudine resistant HBV, although we did not confirm this through molecular testing.

One infant developing CHB is insufficient to estimate incidence or draw broad conclusions on the risk of peripartum HBV infection. However 28% of infants born to mothers with CHB or occult HBV having some evidence of hepatitis B infection by the 12th month of life seems high and suggests that increased attention is warranted regarding peripartum and infant HBV transmission. An even higher incidence of

Table 2. Maternal and infant test results for the 14 mothers-infant pairs with a positive maternal HBsAg test or detectable HBV DNA

| Participant number | HBsAg/ HBeAg | HBV DNA* (log10 IU/mL) | HIV RNA* (c/mL) | HBV active ART agents | Duration on ART, monthsb | Infant HBsAg | HBV DNA, log10 IU/mL |
|--------------------|--------------|------------------------|----------------|-----------------------|------------------------|-------------|---------------------|
| 1                  | +/ +         | 7.3                    | <20            | 3TC                   | 60                     | Yes         | 6.8                 |
| 2                  | +/ +         | 2.6                    | 7435           | TDF, 3TC              | 3                      | No          | 0                   |
| 3                  | +/ +         | 3.8                    | 605            | TDF, 3TC              | 1                      | No          | 1.9                 |
| 4                  | +/ +         | 4.9                    | 365,673        | TDF, 3TC              | 1                      | No          | 0                   |
| 5                  | +/ +         | 0                      | <20            | TDF, 3TC              | 3                      | No          | 0                   |
| 6                  | +/ +         | 2.0                    | 939            | TDF, 3TC              | 0.5                    | No          | 3.5                 |
| 7                  | +/ –         | 4.0                    | 240            | TDF, 3TC              | 3                      | No          | 0                   |
| 8                  | +/ –         | 2.1                    | 2660           | TDF, 3TC              | 3                      | No          | 0                   |
| 9                  | +/ –         | 0                      | 535            | None                  | 2                      | No          | 0                   |
| 10                 | +/ –         | 0                      | <20            | TDF, 3TC              | 4                      | No          | 0                   |
| 11                 | +/ –         | 0                      | 87             | TDF, 3TC              | 3                      | No          | 0                   |
| 12                 | –/ –         | 2.2                    | <20            | TDF, 3TC              | 22                     | No          | 0                   |
| 13                 | –/ –         | 1.7                    | 9250           | None                  | 0                      | No          | 0                   |
| 14                 | –/ –         | 1.7                    | <20            | TDF, 3TC              | 4                      | No          | 3.4                 |

*Prepartum result closest to delivery; b Prepartum ART duration. HBV, hepatitis B virus; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; TDF, tenofovir; 3TC, lamivudine.
perinatal transmission may have occurred had three-quarters of the women with CHB or occult HBV not received TDF-based ART [17].

Providing a first dose of HBV vaccine at birth (as is done for BCG and oral polio vaccine in South Africa and for hepatitis B in some Asian countries) may be an important step to reduce mother-to-child HBV transmission [7]. Future consideration of newborn vaccination needs to also be informed by cost. Although the protective effect of HBV vaccination among HIV exposed newborns is undefined, data on immunogenicity in HIV-exposed infants suggest an effective response [18,19].

Our finding of 7.4% of women with CHB is consistent with prior studies from the region [20,21]. Our proportion of 43% with “e” antigenemia is also consistent with other reports from HIV-coinfected populations in the region in which 38 to 53% of HbsAg positive participants were also positive for HBeAg [20–23]. Our finding of only 2% of women with occult hepatitis B (as defined by detectable HBV DNA with a negative HbsAg) is lower than reported from some studies that had sicker participants with lower CD4 counts [24,25]. The higher median CD4 count in our cohort and a higher fraction of participants receiving ART likely accounts for the low proportion of occult HBV as occult HBV appears to be partly a phenomenon of low CD4 count and lack of ART [26–28].

The strength of our study is that it is based on a prospective cohort recruited from routine prenatal care clinics with follow-up through the first year of an infant’s life. However, there are several limitations. One is that we were missing data on infant HBV status for three infants born to women with CHB because the mothers moved locations or died. Another important limitation is the small number of mothers with CHB and the single HBV infected infant. Our results provide insight, but not sufficient data to draw broad conclusions, regarding HBV transmission epidemiology.

Additional data would be useful to describe the current transmission epidemiology in southern Africa—perinatal, infant, and adult. To that end, additional mother-infant pair surveys would be valuable among mothers living with HIV and mothers not living with HIV. However, we believe that treatment of all women living with HIV with effective antiretrovirals during pregnancy, such as tenofovir, and instituting newborn HBV vaccination may be reasonable practice modifications while awaiting additional research findings.

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References
1. Dienstag JL. Hepatitis B virus infection. N Engl J Med. 2008;359(14): 1486–500.
2. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. Lancet Infect Dis. 2007;7(6):402–9.
3. Schoub BD, Matai U, Singh B, Blackburn NK, Levin JB. Universal immunization of infants with low doses of a low-cost plasma-derived hepatitis B vaccine in South Africa. Bull WHO. 2002;80:277–81.
4. Hino K, Katoh Y, Vardas E, Sim J, Okiro E, Carman WF. The effect of introduction of universal childhood hepatitis B immunization in South Africa on the prevalence of serologically negative hepatitis B virus infection and the selection of immune escape variants. Vaccine. 2001;19(28–29):3912–9.
5. Su WJ, Liu CC, Liu DP, Chen SF, Huang JJ, Chan TC, et al. Effect of age on the incidence of acute hepatitis B after 25 years of a universal newborn hepatitis B immunization program in Taiwan. J Infect Dis. 2012;205(5):757–62.
6. Li F, Wang Q, Zhang L, Su H, Zhang J, Wang T, et al. The risk factors of transmission after the implementation of the routine immunization among children exposed to HBV infected mothers in a developing area in northwest China. Vaccine. 2012;30(49):7118–22.
7. Cui FQ, Wang XJ, Cao L, Liang XF, Li Y, Hu YS, et al. Progress in hepatitis B prevention through universal infant vaccination – China, 1997–2006. MMWR Morb Mortal Wkly Rep. 2007;56(18):441–5.
8. Vardas E, Mathai M, Blauw D, McAneney J, Coppen A, Sim J. Preimmunization epidemiology of hepatitis B virus infection in South African children. J Med Virol. 1999;58(2):111–5.
9. Abdool Karim SS, Thegapal R, Coovadia HM. Household clustering and intra-household transmission patterns of hepatitis B virus infection in South Africa. Int J Epidemiol. 1991;20(2):495–503.
10. Prozesky OW, Szmuness W, Stevens CE, Kew MC, Harley EJ, Hoyland JA, et al. Baseline epidemiological studies for a hepatitis B vaccine trial in Kangwane. S Afr Med J. 1983;64(23):891–3.
11. Tsebe KV, Burnett RJ, Hlungwani NP, Sibara MM, Venter PA, Mphahlele MJ. The first five years of universal hepatitis B vaccination in South Africa: evidence for elimination of HbsAg carriage in under 5-year-olds. Vaccine. 2001;19(28–29):3919–26.
12. Guidozzi F, Schoub BD, Johnson S, Song E. Should pregnant urban south African women be screened for hepatitis B? S Afr Med J. 1993;83(2):103–5.
13. Roegger P, Diouf A, Sankale JL, Boye C, Mboup S, Diadhio F, et al. Perinatal transmission of hepatitis B virus in Senegal, West Africa. Viral Immunol. 1993;6(1):65–73.
14. Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis. 2002;2(8):479–86.
15. Beasley RP, Hwang LV, Lin CC, Stevens CE, Wang KY, Sun TS, et al. Hepatitis B immune globulin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. Initial report of a randomised double-blind placebo-controlled trial. Lancet. 1981;2(8243):388–93.
16. Pan CO, Mi Li, Bunchornvatavul C, Kandou J, Huang WM, Singhvi G, et al. Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series. Dig Dis Sci. 2012;57(9):2423–9.
17. Han GR, Cao MK, Zhao W, Jiang HY, Wang CM, Bai SF, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55(6):1215–21.
18. Reike BA, Naidoo S, Ruck CE, Slogrove AL, de Beer C, la Grange H, et al. Antibody responses to vaccination among South African HIV-exposed and unexposed uninfected infants during the first 2 years of life. Clin Vaccine Immunol. 2013;20(1):33–8.
19. Jones CE, Naidoo S, de BC, Esser M, Kampmann B, Hesseling AC. Maternal HIV infection and antibody responses against vaccine-preventable diseases in uninfected infants. JAMA. 2011;305(6):576–84.

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Author’s contributions
Study design and implementation: CJH, FM, JDH, SL, NAM, REC. Data analysis: CJH, SC. Drafting manuscript and final approval: CJH, FM, SC, JDH, SL, NAM, REC. All authors have read and approved the final version.

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http://www.jiasociety.org/index.php/jias/article/view/18871 | http://dx.doi.org/10.7448/IAS.17.1.18871
20. Firnhaber C, Reyneke A, Schulze D, Malope B, Maskew M, MacPhail P, et al. The prevalence of hepatitis B co-infection in a South African urban government HIV clinic. S Afr Med J. 2008;98(7):541–4.
21. Hoffmann CJ, Dayal D, Cheyip M, McIntyre JA, Gray GE, Conway S, et al. Prevalence and associations with hepatitis B and hepatitis C infection among HIV-infected adults in South Africa. Int J STD AIDS. 2012;23(10):e10–3.
22. Andersson MI, Maponga TG, Ijaz S, Theron G, Preiser W, Tedder RS. High HBV viral loads in HIV-infected pregnant women at a tertiary hospital, South Africa. J Acquir Immune Defic Syndr. 2012;60(4):e111–2.
23. Chasela CS, Kourtis AP, Wall P, Drobeniuc J, King CC, Thai H, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. J Hepatol. 2014;60(3):508–14.
24. Mphahlele MJ, Lukwareni A, Burnett RJ, Moropeng LM, Ngobeni JM. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. J Clin Virol. 2006;35(1):14–20.
25. Firnhaber C, Viana R, Reyneke A, Schulze D, Malope B, Maskew M, et al. Occult hepatitis B virus infection in patients with isolated core antibody and HIV co-infection in an urban clinic in Johannesburg, South Africa. Int J Infect Dis. 2009;13(4):488–92.
26. Cohen Stuart JW, Velema M, Schuurman R, Boucher CA, Hoepelman AI. Occult hepatitis B in persons infected with HIV is associated with low CD4 counts and resolves during antiretroviral therapy. J Med Virol. 2009;81(3):441–5.
27. Barth RE, Huijgen Q, Tempelman HA, Mudrikova T, Wensing AM, Hoepelman AI. Presence of occult HBV, but near absence of active HBV and HCV infections in people infected with HIV in rural South Africa. J Med Virol. 2011;83(6):929–34.
28. Khamduang W, Ngo-Giang-Huong N, Gaudy-Graffin C, Jourdain G, Suwankornsakul W, Jarupanich T, et al. Prevalence, risk factors, and impact of isolated antibody to hepatitis B core antigen and occult hepatitis B virus infection in HIV-1-infected pregnant women. Clin Infect Dis. 2013;56(12):1704–12.