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Short Communication

Safety of coitally administered tenofovir 1% gel, a vaginal microbicide, in chronic hepatitis B virus carriers: Results from the CAPRISA 004 trial

Cheryl Baxter [a,*], Nonhlanhla Yende-Zuma [a], Phindile Tshabalala [a], Quarraisha Abdool Karim [a,b], Salim S. Abdool Karim [a,b]

[a] Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa
[b] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

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ABSTRACT

Tenofovir disoproxil fumarate, a licensed oral treatment for both HIV and Hepatitis B virus (HBV) infections, has been associated with severe rebound hepatic flares when treatment is interrupted. A gel formulation of tenofovir is currently being assessed as a microbicide against HIV. If licensed, it is possible that tenofovir gel could be used either intentionally or unintentionally by HBV carriers. The purpose of this study was to establish the safety of tenofovir gel use in this patient group participating in the CAPRISA 004 tenofovir gel trial. HBV infection status was assessed at enrolment and study exit. Liver function testing was performed at enrolment, study months 3, 12, 24, study exit, and 2 months after exiting the study. At enrolment, 34 women were identified as being HBV carriers and 22 women acquired HBV infections during follow-up; 14 and 8 in the tenofovir and placebo gel arms, respectively ($p = 0.21$). Intermittent tenofovir gel use did not cause an increase in hepatic flares or impact on viral load suppression in women with HBV infection. There were 2 hepatic flares in each gel arm during follow-up and none 2 months after cessation of gel at study exit. The mean HBV DNA levels were similar at enrolment and exit in both study arms. Tenofovir gel, when used intermittently, was safe to use in women with HBV infection.

Tenofovir 1% gel, a vaginal microbicide, has been shown to reduce HIV acquisition by 39% when used intermittently before and after sex (Abdool Karim et al., 2010). Research is underway to obtain the additional data for licensure as tenofovir 1% gel has the potential to alter the HIV epidemic trajectory, particularly in sub-Saharan Africa (Williams et al., 2011).

Tenofovir disoproxil fumarate (the oral formulation of tenofovir), is already licensed for the treatment of both HIV and HBV. However, one of the potential side effects of using tenofovir in individuals with HBV infection is a relapse of hepatitis symptoms ("flares") when the drug is withdrawn (Lim et al., 2002; Nuesch et al., 2008; Puoti et al., 2006). Even though it is not known whether the hepatic flares associated with the use of oral tenofovir also apply to the gel formulation, HBV carriers are often excluded from antiretroviral-based microbicide trials.

In order for tenofovir 1% gel to have an appreciable impact on HBV viremia, it would need to be absorbed systemically. Pharmacokinetic studies have shown that intravaginally administered tenofovir 1% gel is systemically absorbed. However, topical application leads to substantially lower drug concentrations in plasma than that achieved following oral administration of tenofovir (Hendrix et al., 2013; Kashuba, 2008; Schwartz et al., 2011) and may therefore have limited impact on HBV viremia.

However, given that tenofovir 1% gel could be used either intentionally or inadvertently by chronic hepatitis B infected individuals at risk of acquiring HIV infection, it is important to establish whether it was safe to use the gel formulation of tenofovir in women who are infected with HBV, which has not been established in any clinical trial.

The potential risks of intermittent use of tenofovir 1% gel were assessed in a sub-group of women who were already infected with hepatitis B or acquired infection during the CAPRISA 004 trial. Details of the CAPRISA 004 tenofovir gel trial procedures have been described in detail previously (Abdool Karim et al., 2010). In brief, enrolled women were randomly assigned in equal proportions to receive one of two identically looking study gels: tenofovir 1% gel or placebo gel. Women were requested use the gel in relation to coitus; to insert one dose of gel within 12 h before sex and a second dose of gel as soon as possible within 12 h after sex and no more than two doses of gel in a 24-h period. Gel adherence was assessed each month by counts of returned empty applicators. Participants had a rapid HIV test each month.

* Corresponding author. Address: CAPRISA, 2nd floor, K-RITH Tower Building, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Private Bag X7, Congella 4013, South Africa. Tel.: +27 31 260 4559; fax: +27 31 260 4549.
E-mail addresses: baxterc1@ukzn.ac.za (C. Baxter), yende@ukzn.ac.za (N. Yende-Zuma), tshabalala@ukzn.ac.za (P. Tshabalala), abdoolq2@ukzn.ac.za (Q. Abdool Karim), karims1@ukzn.ac.za (S.S. Abdool Karim).

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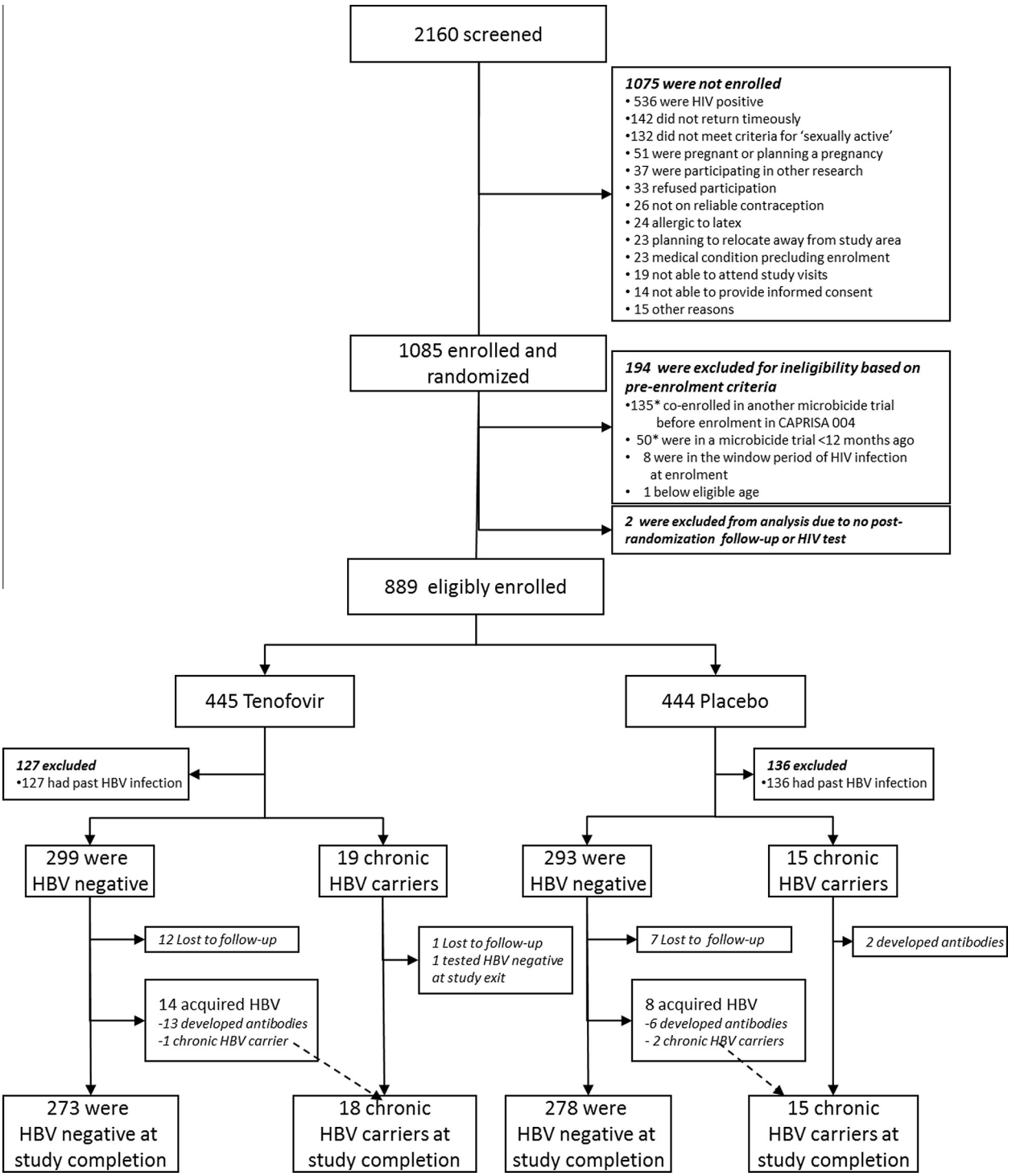

Fig. 1. Screening, enrolment, randomization and follow-up of the study participants in relation to Hepatitis B infection status in the CAPRISA 004 tenofovir gel trial. * Note: co-enrolments only occurred at the urban site.

Hepatitis B status was established using routine Hepatitis B virus serology (Abbott Architect C8200, Abbott Laboratories, Detroit, MI) testing conducted at the enrolment and exit visits and included Hepatitis B surface antigen (HBsAg), antibodies to HBsAg (anti-HBs), antibodies to HBcAg (anti-HBc), IgM anti-HBc, and "e" antigen (HBeAg). HBV DNA levels (COBAS TaqMan HBV test, Roche, Branchburg, NJ) were established retrospectively on stored samples. Hepatic flares, defined as alanine transaminase (ALT) $5 \times$ the upper limit of normal (ULN), were assessed by liver function tests performed at enrolment, during the trial when clinically indicated, and at study months 3, 12 and 24, and at study exit.

The statistical analysis included the Fisher's exact test, Wilcoxon two-sample test and Wilcoxon signed rank test for paired samples. The log rank test was used to compare the incidence of HBV between the two treatment arms.

This sub-study was approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BE025/010).

Table 1
Impact of tenofovir gel on liver-related adverse events (all grades) in women in the CAPRISA 004 tenofovir gel trial.

Liver-related adverse events in	All women		Chronic HBV carriers		Incident HBV infected who recovered	
	Tenofovir $N = 445$	Placebo $N = 444$	Tenofovir $N = 20$	Placebo $N = 17$	Tenofovir $N = 13$	Placebo $N = 6$
Elevated liver enzymes[a]						
Alanine transaminase (ALT)	10	9	1	3	1	0
Aspartate aminotransferase (AST)	3	5	0	2	0	0
Bilirubin	3	3	0	0	0	0
Gamma-glutamyltransferase (GGT)	5	6	0	1	1	0
Hepatic and hepatobiliary disorders						
Cholestasis	1	2	0	0	0	0
Jaundice	0	1	0	0	0	0

[a] Any abnormality, regardless of severity.

Of the 889 eligible women enrolled in the CAPRISA 004 trial (Fig. 1), HBsAg was detected at enrolment in 34 (3.8%) women (chronic HBV carriers), combined anti-HBc and anti-HBs, indicating established immunity from prior infection, in 230 (25.9%), anti-HBc only in 17 (1.9%), and anti-HBs only, indicating established immunity from vaccination, in 16 (1.8%). HBeAg, a marker of active viral replication, was detected in only 9% (3/34) of all HBsAg positive women. The remaining 592 (66.6%) women had no markers of HBV exposure (Fig. 1).

By comparing HBV status at study exit with that at study entry, it was retrospectively established that 22 women acquired HBV infection during the 878.7 women-years (mean = 18 months) of follow-up: 14 and 8 in the tenofovir and placebo gel arms, respectively. The HBV incidence rate in the tenofovir 1% gel arm was 3.2 per 100 women-years (wy) (95% CI: 1.7, 5.3) compared to 1.8 per 100 wy (95% CI: 0.8, 3.6) in the placebo gel arm (IRR = 1.8; 95% CI: 0.7, 4.8; $p = 0.21$). By study exit, 19 of these 22 women (86.4%) with newly acquired HBV infection during trial follow-up had developed antibodies and 13.6% (3/22) were still chronic HBV carriers (Fig. 1). Therefore, a total of 37 women were identified as being persistently HBsAg positive during the trial; 34 at enrolment and a further 3 by study exit.

Gel was used on average 5.9 (median: 5.7) and 5.9 (median: 5.2) times per month in women in the tenofovir 1% and placebo gel groups, respectively. In the 37 chronic HBV carriers, tenofovir 1% gel was used on average 5.5 (median: 4.3) times per month.

Overall, the number of liver-related adverse events in women in the tenofovir 1% gel and the placebo gel groups was similar, regardless of HBV status (Table 1). In women with chronic HBV infection, there were two cases of hepatic flares in each study arm and none of the chronic HBV carriers were temporarily discontinued from using product for liver-related adverse events. Among women who remained HBV uninfected throughout the study ($n = 551$), there were three hepatic flares in each study arm ($p = 0.51$). Tenofovir gel did not impact on HBV DNA in chronic HBV carriers (see Supplementary Appendix).

There was no increase in the number of HBV-associated hepatic flares in women using tenofovir 1% gel. These results extend the current safety profile of tenofovir 1% gel. Previous data from the CAPRISA 004 trial showed that intermittent tenofovir 1% gel caused no significant renal, hematological, genital or bone effects (Sokal et al., 2013). As future policy and programs are being developed (WHO/UNAIDS, 2010), this reassuring result indicates that women who have chronic HBV infection need not be excluded from roll-out programs. The low level of liver-related adverse events and hepatic flares observed in this study are most likely explained by the low systemic levels of tenofovir following gel administration. One pharmacokinetic study has shown that tenofovir concentrations in the blood reach 4 ng/mL while cervicovaginal concentrations of up to 1.9×10^6 ng/mL are achieved following a single intravaginal dose of tenofovir (Schwartz et al., 2011).

Recent analyses from antiretroviral treatment programs have shown that oral lamivudine- or tenofovir-containing regimens may prevent new HBV infections (Gatanaga et al., 2013; Heuft et al., 2013). A similar prophylactic effect of tenofovir 1% gel on HBV infection was not observed in this study, possibly due to the too low levels of systemic absorption following gel administration. The coitally-linked intermittent dosing regimen would have also contributed to lower levels of systemic absorption compared to daily or more frequent dosing strategies. The extent to which a daily dosing regimen or oral pre-exposure prophylaxis could have on HBV viremia is not known. More data is needed from larger cohorts that include alternate dosing strategies and formulations.

The moderate sample size limits statistical inference and the generalizability of the results and also our ability to draw any conclusions on the ability of tenofovir gel to prevent HBV. Even with a larger sample size, it is unlikely that the gel formulation will prevent new HBV infections due to the lower levels of systemic absorption achieved. It was also not possible to extrapolate the findings from this study using tenofovir gel to other HIV prevention studies investigating oral tenofovir for HIV prevention. Hepatic flares should continue to be closely monitored in HBV-infected individuals in those studies.

In conclusion, no safety concerns were identified from intermittent use of tenofovir 1% gel by women who were chronic HBV carriers or who developed acute HBV infection while using tenofovir 1% gel as prophylaxis against HIV.

1. Conflict of interest

Quarraisha Abdool Karim was the Co-Principal investigator of the HPTN Prevention Leadership Group (NIH/NIAID U01AI068619). Salim S Abdool Karim was the Protocol Chair of the HPTN 035 trial which was supported by the National Institutes of Health (Grant # U01AI46749 and U01AI068633). Salim Abdool Karim and Quarraisha Abdool Karim are co-inventors of two pending patents (61/354.050 and 61/357,892) of tenofovir gel against HSV-1 and HSV-2 with scientists from Gilead Sciences. Gilead Sciences did not have any role in the experiments or analyses presented here. The other authors have no financial conflicts of interest.

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This sub-study was conceptualized and designed by SSAK, QAK and CB. The data was gathered, analyzed and interpreted by CB, SSAK, PT, and NY. SSAK, CB, and NY had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. CB took responsibility for writing the paper and all co-authors contributed to critical revisions of the paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.antiviral.2013.06.019.

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