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Uptake of Male Circumcision in an HIV Vaccine Efficacy Trial

Guy de Bruyn, MBBCh, MPH[1], **Neil A. Martinson, MBBCh, MPH**[1,2], **Busisiwe D. Nkala, RN**[1], **Nkeko Tshabangu, RN**[1], **George Shilaluka, MBBCh**[1], **James Kublin, MD**[3], **Lawrence Corey, MD**[3], and **Glenda E. Gray, MBBCh, FCP(SA)**[1]

1 *Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa*

2 *Department of Medicine, Johns Hopkins University, Baltimore, MD*

3 *Fred Hutchinson Cancer Research Center, Seattle, WA*

To the Editor

Ethical guidelines require clinical investigators to provide or facilitate access to an optimal standard of care for the target condition. UNAIDS guidance on ethical considerations in biomedical HIV prevention trials proposes that “new HIV-risk-reduction methods should be added….as they are scientifically validated…” [1]. In the case of HIV prevention studies, circumcision represents a recently validated method, with the results of three randomized trials showing strong, but partial, benefit in African locations where heterosexual acquisition in the primary mode of transmission [2–4]. The challenge to investigators dealing with men in HIV prevention trials is how to meet their responsibilities by incorporating these new data in providing optimized HIV prevention. In Soweto, we had previously noted that public sector access to adult male circumcision was limited [5], with approximately 360 procedures being done per year, in an area with a male birth cohort of approximately 15,000 live male births per annum. Moreover, no public sector or donor funded program or other efforts to expand circumcision capacity have been implemented since the results of the trials became known. Procedures in the adult male circumcision trial conducted in Orange Farm [4], adjacent to Soweto, were performed by private practitioners in their consulting rooms. Thus, in preparation for HVTN 503 (“Phambili”), an efficacy trial of the Merck Adenovirus Serotype 5 HIV-1 Gag/Pol/Nef vaccine, we developed a pilot program to provide male circumcision to study participants who requested the procedure. We present data emanating from the circumcision program in this trial through the end of enrolment and vaccination in September 2007, the time in which the trial was prematurely ended because of the lack of efficacy of the vaccine in the comparison STEP trial.

HVTN 503 was a multisite, phase IIb randomized controlled trial of the Merck Adenovirus Serotype 5 HIV-1 Gag/Pol/Nef vaccine among HIV-uninfected adults in South Africa [clinicaltrials.gov identifier: NCT00413725]. Key eligibility criteria included: age 18–35 years; sexually active in the six months prior to enrolment; alanine transaminase less than 2.6 times the upper limit of the normal range. The first enrolment in the trial occurred in January 2007, at the Soweto site. In September 2007, further enrolment into the study was halted and vaccinations were discontinued when the data and safety monitoring board for a parallel trial (HVTN 502, or “STEP” trial) of the same product found on a review of interim data that the vaccine had neither prevented infection nor did it appear to modify the course of post-infection viremia [6].

We analyzed data for the male participants who enrolled in HVTN503 at the Soweto site between opening of the trial and August 31, 2007. We included follow up time to 21 September, 2007, which is when participants began to be informed of the results of Merck 023/HVTN 502 and the halting of enrolment and vaccinations in HVTN 503. We hypothesized that motivations

for requesting circumcision may have been influenced by trial developments when participants were informed of the interim data. Thus, we restricted this analysis to procedures prior to the suspension of enrolment. We defined circumcision status as uncircumcised throughout the trial (UC), previously circumcised at baseline, prior to study entry (PC), or uncircumcised at baseline, but circumcised during follow up (CFU). We compared participants' baseline demographics, motivations for joining the trial, and sexual risk factors for HIV acquisition among the circumcision groups. The sexual risk assessment was ascertained at the screening visit and motivations for joining the trial at the enrolment visit. Both assessments were undertaken using an interviewer-administered questionnaire given to all participants. Circumcision status was determined for all participants, either through self-report (13%) or clinician observation (86%). Standard methods for time-to-event data were used. Categorical variables were compared using Chi-square tests or Fisher's exact test as appropriate. Continuous variables were compared using ANOVA or Kruskal-Wallis tests, as appropriate.

Circumcision was discussed as an HIV prevention option and offered to male participants at each study visit. This was in addition to other HIV prevention options made available to participants at the site, including risk reduction counseling, condom provision, symptomatic assessment for sexually transmitted infections and treatment thereof. Participants who requested circumcision were scheduled for elective outpatient surgery at their convenience. The study site contracted with an experienced practitioner (GS) to provide circumcision services to study volunteers. He had performed over 500 outpatient procedures as part of the Orange Farm trial using the forceps-guided method. For Soweto HVTN 503 participants, the procedures were performed under local anesthetic, at the Perinatal HIV Research Unit (PHRU) at the Chris Hani Baragwanath Hospital.

A total of 302 participants were recruited at the Soweto site between January 2007 and enrolment being suspended in September 2007, of whom 158 were men (mean age 22.5 years). Ninety three men remained uncircumcised during study. Forty five men (28.5%) had been circumcised prior to study entry, at a median of 9.4 years prior to enrolment. Twenty men became circumcised during follow up (17.7%). Men who were circumcised after enrolment into the trial were slightly older than men remaining uncircumcised (23.9 vs. 21.8 years, $p = 0.035$).

In the enrolment risk assessment interview, CFU men more frequently reported several behaviors associated with HIV acquisition [Table 1], including having a known HIV-infected partner in the prior six months, recent STD diagnosis, number of sexual partners, and number of binge drinking episodes in the six months before enrolment. In the enrolment interview, there were no differences in self-reported motivations for joining the trial between CFU men and other participants (data not shown). In particular, CFU men did not report higher rates of agreement that they joined the trial because they may receive free medical care or other services than reported by other participants. No serious adverse events were experienced by participants receiving circumcision, although one man required cautery as an outpatient for minor hemorrhage on the first post-operative day.

Owing to the lack of access to readily available male circumcision services, we established a male circumcision service to provide the procedure to men joining an HIV vaccine efficacy trial in Soweto, South Africa. Our experience in providing this additional prevention option to men indicates the potential for impact on future HIV prevention trials. We note that uptake of circumcision was frequent. We have noted that a large proportion of uncircumcised young men enrolled in the trial requested circumcision soon after study entry. Uptake of this magnitude is likely to lead to lower HIV acquisition rates, which has implications for sample size in HIV prevention trials.

Interestingly, men who became circumcised after joining the trial reported lifestyle factors that placed them at higher risk of HIV acquisition than other men entering the trial. We speculate that such individuals may have recognized their own risk for HIV acquisition. If circumcision uptake is differential in a trial according to risk behaviors, as our data suggest, there would be a potentially greater impact on acquisition rates in a trial, which may amplify the impact on study power. We cannot exclude that identification of higher risk behaviors during counseling may have led to more intensive efforts to encourage circumcision among those men. Regardless, our data illustrates the role clinical trials can play in improving HIV prevention services.

Note added: As of September 2008, a total of 38 trial participants have been circumcised (33.6%).

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Table 1

Reported Risk Behaviors For HIV Acquisition, By Circumcision Status

	UC (n = 93)	PC (n = 45)	CFU (n = 20)	*P*-value
Number of female sex partners in last 6 months, mean ± SD	2.3 ± 1.9	2.2 ± 1.5	3.2 ± 2.9	0.14
Proportion reporting a casual partner in the last 6 months	53%	49%	65%	0.48
Proportion reporting known HIV-infected partner	0%	2.2%	15%	0.002
Proportion reporting STD in the last 6 months	3.2%	15.6%	20%	0.005
Proportion reporting sex after alcohol or recreational drugs in last 6 months	45.2%	40%	44.3%	0.72
Number of times drank more than 5 alcoholic drinks in a day in the last 6 months, median [IQR]	3 [0 – 10]	3 [0 – 10]	5.5 [0.5 – 12.5]	0.58

UC denotes uncircumcised throughout the trial; PC denotes circumcised at baseline;

CFU denotes uncircumcised at baseline, but circumcised during follow up; IQR, interquartile range; SD, standard deviation