Response to a replication study of
Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: a Randomized Controlled Trial
by

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Introduction

First, we would like to thank Drs. Djimeu, Korte and Calvo (DK&C) for undertaking the replication of our analyses of the data from the randomized controlled trial (RCT) of male circumcision (MC) in Kisumu, Kenya, which we published in the Lancet in 2007 (Bailey et al., 2007). We recognize the large amount of work and thought that went into their re-investigation. We are gratified that the results of their replication conform with our findings. Both their "pure" replication, using the same methods as we, and their extended analyses applying econometric methods, arrive at essentially the same results as our analysis, with very small differences. It should be noted that we did not provide any assistance to DK&C during their work with the exception of a few insights to steer them to the approximate data used for the DSMB report that unblinded the trial and resulted in the publication of the results. Their analyses with ours serve as essentially a triangulation of results that not just confirms, but strengthens the conclusion that MC is approximately 60% protective against HIV acquisition among men in Kisumu and that circumcision can be provided safely with little if any risk compensation. Further, DK&C are to be commended for going beyond the results that we published to perform various sensitivity analyses that further strengthen the main conclusions to be drawn from this RCT.

Data Used by DK&C and Data Used for the Original Lancet Paper

There are small differences between selected results from the DK&C analysis and ours. This is in part due to differences in the public access database (available at https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=Male%20circumcision) used by DK&C versus the database used for the Lancet publication. The public access database used by DK&C includes data that were collected far beyond the period when the data were locked for the DSMB report that ultimately resulted in the trial being halted and our publication of the trial results. When we created the public access database, it was not with the intention of making the

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Lancet results replicable, but rather to make a more extensive database widely available to other investigators to explore questions that we had not addressed.

The database was locked for the DSMB report on October 31, 2006 with participants at various time points in their follow-up to 24 months. Follow-up continued within the context of the trial until the DSMB met in December 2006. Participants were then informed of the trial results and uncircumcised participants were offered circumcision. Although the trial was stopped and the participants unblinded, participants continued to be followed and data collected through September 30, 2010. To fully replicate the trial results would require access to records available at the time of the data lock of October 31, 2006. This could be approximated with the public access database but would not account for visits conducted but forms not yet entered by that date.

To further complicate matters, public access data must be anonymized. To this end, three randomized subjects were excluded because they were outside of the age range for the trial making them easy to identify by age. Furthermore, a random number (-5 to +5) was assigned to each participant and this random number was used to perturb all dates (including visit dates) associated with the participant. Finally text fields and administrative data were eliminated and categories of variables were collapsed when a category had too few responses.

Finally, there were a few updates to the data in the October 31, 2006 data lock that were integrated in the public access database. Specifically, there was confirmatory HIV testing for early seroconverters which resulted in a few changes to seroconversion status and timing. The updated HIV results with these changes were later presented at the International AIDS Society meetings in Mexico City in 2008. Also, the baseline HSV-2 antibody test results were not complete at the time of the October 31, 2006 data lock. The final HSV-2 data were reported by Mehta, et al (2012). The baseline HSV-2 results reported by DK&C match closely with baseline HSV-2 data in the 2012 publication. In brief, the differences between the public access database and the December, 2006 database are few, but could account for some of the small differences between our published results and those published in the replication by DK&C.

Risk Compensation

Our analysis of the trial behavioral data was based on a comprehensive GEE model that accounted for the longitudinal aspects of the data. DK&C replicate our results and then apply econometric methods in their re-investigation of the behavioral data. Their results do not differ substantially from ours.[2] We found a reduction in risk behaviors of both circumcised and

[2] In the DK&C report, it is stated that we used Fisher exact tests and □2 tests to study behavioral outcomes. However, our analyses of the behavioral data were based strictly on generalized estimating equations (GEE) models, which accounted for baseline differences and made full use of the incomplete longitudinal stream of data available at the time of our analysis. The approach is described in the methods section of the Lancet paper and acknowledged at one point by DK&C, but subsequently ignored. DK&C also used GEE, but they had more participants included in the analysis at later visits. This could be the result of their inclusion of all data through 24 months on participants rather than

uncircumcised participants from baseline through 24 months of follow-up. There were no significant differences between circumcised and uncircumcised men in regard to changes in the measured sexual behaviors, except with respect to reporting two or more sexual partners in the previous 6 months. Circumcised men exhibited somewhat riskier behavior on all five variables at 24 months (24M) post-enrollment; however, the differences are small, the largest being a 5 percentage point difference (51% versus 46%) in the proportion of men practicing unprotected sex with any partner in the last 6 months. In our original publication, we interpreted the reduction in risk behaviors by both study groups as absence of risk compensation, defined as increases in risky behaviors sparked by decreases in perceived risk (Cassell et al., 2006). DK&C have a different interpretation of our results and of theirs. Because there are statistically significant differences in two of the behavioral measures by 24M (consistent condom use in circumcised men less than in controls and more circumcised than uncircumcised men practicing unprotected sex in the previous six months), DK&C feel that this represents a substantive difference between the two arms and thus a relative increase in risky behaviors on the part of the circumcised men. The difference between our and their analysis is in interpretation, not in substance.

It would be misleading to take from DK&C's analysis that there was risk compensation or that, if there was, it was substantial enough to influence the strong protective effect of MC against HIV acquisition. Both we and DK&C, using very different techniques, showed that, after controlling for any differences between study groups, the protective effect of MC was unchanged. In our Lancet paper we did caution readers to be aware that the differences between the circumcised and uncircumcised men were manifest primarily at M24, suggesting that risk compensation could occur over time if men became comfortable with their circumcision status and complacent about curtailing their risky behaviors. We also cautioned that once the results of all three clinical trials became widely publicized and MC was promoted for HIV prevention, men could feel well protected and increase their risky behaviors. However, there is actually no evidence of men increasing their risk behaviors after circumcision in the context of either the clinical trials or the subsequent scale-up of MC for HIV prevention (Auvert et al. 2007; Gray et al. 2007)). During extended follow-up of our Kisumu trial participants, the protective effect of MC was sustained over 72 months (hazard ratio 0.38 [95% CI: 0.26-0.55) (Mehta et al. 2013]. This indicates that risk compensation, if any indeed did occur, did not mitigate the protection conferred by this one time surgical procedure.

A subsequent comprehensive longitudinal study was specifically designed to observe behavioral change in men from before through 24 months after circumcision in the context of programmatic scale-up of MC interventions. The behaviors of 1,588 newly circumcised men and 1,598 age-matched uncircumcised controls were assessed at baseline, 6, 12, 18 and 24 months of follow-up. Despite a precipitous decline in perception of high HIV risk among circumcised men (30-14% vs. 24-21% in controls) and increased sexual activity among the youngest participants (18-24 years) in both groups, all specific risk behaviors decreased over time similarly in both groups. For example, the proportion of men reporting condom use at last sex increased for both groups,

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exclusion of visits that had not occurred by October 31, 2006. This is just conjecture, as the exact details are not known to us.

with much greater increase among circumcised men (30 vs. 6 %). The authors found no evidence of risk compensation in men following circumcision and concluded that "concerns about risk compensation should not impede the widespread scale-up of VMMC initiatives." (Westercamp et al. 2014). We agree.

Another recent analysis reinforces the conclusion that risk compensation is not occurring in the context of programmatic scale up of MC. Galbraith and colleagues (Galbraith et al. 2014), using data from the 2012 Kenya AIDS Indicator Survey found that HIV-uninfected uncircumcised men were more likely to not use a condom consistently than uninfected recently circumcised men (81.9% vs 50.5%). Moreover, a greater proportion of uncircumcised men reported four or more lifetime sex partners compared to circumcised men (74.3% vs 42.0%). Rather than increasing risky sexual behaviors, circumcised men in Kenya appear to be reducing behaviors that could expose them to HIV acquisition.

Additional Analyses by DK&C

DK&C use a range of analytic approaches including ordinary least squares (OLS), fixed effects estimation (FE) and instrumental variables (IV) to extend our analyses to several very useful and informative sensitivity analyses. Using these techniques in an attempt to control for both measured and unmeasured variables which might affect HIV acquisition in addition to circumcision, they conclude “that the protective effect is independent from unobserved individual characteristics.” They also show that the impact of male circumcision on HIV acquisition is not moderated by the level of men's risky sexual behaviors at the baseline. As they propose, this is a strong indicator that the protective effect of MC has high external validity - that the protective effect is likely to be similar in contexts where men engage in high risk or low risk sexual behaviors. Although DK&C do not mention it, this finding again suggests that sexual risk compensation, even if it did occur in a given setting, would be unlikely to impact the reduction in risk of HIV by circumcision. Further, this is consistent with our finding, confirmed by DK&C, that the effect of MC is not different by age group, despite frequency of sexual activity being different by age group. DK&C further examine the possibility that bias resulting from missing data could explain the observed association between lack of circumcision and HIV incidence and find it extremely implausible.

Conclusion

In sum, the extended analyses by DK&C using techniques different from conventional epidemiological methods, reinforce, indeed in most cases strengthen, the results that we published in the Lancet.

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