ports. A survey in our laboratory of viruses containing L90M from 78 patient samples demonstrates this point even more clearly (figure 1). The data clearly demonstrate the limitations of genotypic analyses that rely on identification of known mutations, since a significant proportion (40%) of viruses containing the L90M “resistance-associated” mutation remained sensitive to saquinavir. The additional genetic changes that modulate the effects of L90M on protease inhibitor resistance are not known.

Dr. Bakker criticizes our work as anecdotal and likely to fuel the debate over the relative merits of phenotyping versus genotyping. The characterization of drug susceptibility patterns in these 2 patients, who, to our knowledge, were the first previously treatment-naïve patients to experience virus load rebound while undergoing triple combination therapy, is indeed anecdotal. However, strikingly similar results have subsequently been described in larger studies, although not in as much detail on an individual patient basis [6, 7]. The purpose of our study was to carefully characterize the evolution of viral drug susceptibility in a small number of patients treated in an early triple combination drug trial and to generate hypotheses about viral drug resistance for testing in larger clinical trials. The large-scale clinical trials Dr. Bakker calls for are under way, but results are still many months to years away. Until then, detailed but small-scale and anecdotal studies can provide valuable preliminary data to augment our understanding of HIV drug resistance.

Finally, Dr. Bakker correctly points out that the phenotypic assay we developed, as well as other phenotypic assays [8, 9] and most genotypic assays, has a limited ability to detect minor populations of drug-resistant virus. Traditional recombinant virus phenotypic assays that rely on the outgrowth of replication-competent HIV-1 from transfected DNA fragments, such as that cited by Dr. Bakker [10], are especially subject to this limitation, because less fit viruses may be underrepresented in the virus stock used for the susceptibility assay. The assay used in the present study [11] does not involve culture of replication-competent virus and therefore is less subject to this potential bias. Nonetheless, we agree with the statement that phenotypic and genotypic assays are complementary and valuable tools; the concluding statement in our paper reflects this viewpoint.

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References


To Promote Circumcision as a Preventive Measure against Human Immunodeficiency Virus Transmission Is Irresponsible

To the Editor—The prospective study of Kenyan truck drivers by Lavreys et al. [1], which claims a link between possession of a foreskin and susceptibility to infection with human immunodeficiency virus type 1 (HIV-1), is seriously flawed.

Of the 746 men who completed the recruitment procedure, only 95 had intact penises. The circumcised men (no matter how many) are not relevant to the incidence of HIV among the intact men, so the effective sample size for measuring that is only 95. Of those, 11 men contracted HIV-1 in a 20-month period, compared with 32 of the circumcised men in a 21-month period. That is to say, 5 or 6 more intact men contracted HIV-1 than the aggregated rate of 3.34 per hundred per year would predict.

This difference is far too small, outside a laboratory, to draw
any meaningful conclusions. The “law of small numbers” applies. Those 5 or 6 men might have just been unlucky (for example, they might have all patronized the same particularly infectious prostitute). To apply high-powered statistical methods to such a small final subsample with so many unknown variables is to use a sledgehammer to crack a nut. Furthermore, interviewing men at 3-month intervals about their sexual practice exposed the study to unacceptably high levels of faulty memory, even assuming that all subjects tried to tell the whole truth.

Lavreys et al. admit that “because uncircumcised status and ethnicity were so closely correlated, it was not possible to independently assess the effects of circumcision and ethnic origin.” Nor did the authors assess the effects of ethnic origin on other practices that might influence HIV-1 transmission. One such practice is anal sex. Lavreys et al. seem to have assumed that none of the subjects ever had any but vaginal sex and that this is the only means of HIV transmission. An investigation of the truck drivers’ anal sexual (including homosexual) activity and how such activity is affected by ethnicity and religion (both of which affect circumcision status) might cast a completely different light on these results.

Strategies to prevent AIDS are multifaceted and must be implemented in a real world inhabited by fallible humans. For some of the issues involved, see Young [2]. It was irresponsible for Lavreys et al. [1] to “encourage behavioral scientists to conduct acceptability studies...to begin assessing feasibility of circumcision promotion.” Already, and predictably, public media have seized on this recommendation without reference to the many caveats. The average man in the truck will have great trouble understanding that this painful procedure may measurably reduce the rate of transmission of HIV but does not confer significant, let alone complete, protection on him. Given a choice, people prefer to practice unprotected sex and will grasp at any excuse to do so. Promoting circumcision can undo years of safe-sex education and cause HIV rates to skyrocket, whether men are circumcised or not.

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No Protective Effect of Circumcision on Human Immunodeficiency Virus Incidence

To the Editor—Some troubling points arise from a comparison of the JID article by Lavreys et al. [1] and the report on the same study cohort that was published in AIDS [2]. The introduction does not mention important studies that found no protective role for circumcision (and even a tendency in the opposite direction), such as the study by Laumann et al. [3].

There is a 1-man discrepancy in the number of subjects reported in the 2 articles; the JID article reports 746 subjects plus 10 exclusions, whereas the article in AIDS reports a total of 755 subjects. The multivariate analysis in AIDS gives a 2.3 hazard rate ratio (HRR) with borderline significance for the intact (uncircumcised) subjects (P = .05; 95% confidence interval [CI], 1.0–9.0). How did it grow to a more significant HRR of 4.0 (P < .001; 95% CI, 1.9–8.3) in the JID article?

Of the 7 people excluded from the analysis (because of their circumcision status) in the JID article, 6 were partially circumcised. This raises the question of how the authors defined and measured full and partial circumcision. In addition, 1 subject of unknown circumcision status was excluded, raising the question of how a subject’s circumcision status could be unknown. The excluded subjects included 2 seroconverters who should have been analyzed as part of the circumcised group.

In their article in AIDS, the authors wrote, “No sex with men or intravenous drug use was reported.” The reports of no sex with men are unlikely to be accurate, because homosexuality in Kenya—being both an illegal act and a taboo subject—is severely underreported. Nevertheless, homosexuality is fashionable among young men in Kenya, according to the head of the Kenya AIDS Consortium [4], and was also documented among truck drivers [4].

In the JID article, the authors asserted that “no significant correlates of loss to follow-up were identified that were likely to have influenced the results” [1, p. 335]. This statement in the Discussion section of their article contradicts the significant loss to follow-up among drivers and drivers’ assistants (no P value given) mentioned in the Results section. It also contradicts the very significant difference between those who were enrolled in the cohort but were excluded because of lack of any follow-up visit and those who were retained. As stated in AIDS, drivers and drivers’ assistants were more likely to be excluded (32% vs. 20%, P < .0005) than were other occupational groups. If 32% means that 32% of the drivers and their assistants who came for the human immunodeficiency virus (HIV) results did not come to any follow-up visit, then the difference is significant at a level < .0001. A reader may wonder why the significance level was written as P < .0005. According to the multivariate analysis reported in AIDS, the HRR for HIV seroconversion among drivers and drivers’ assistants is 3.9 (P = .002; 95% CI, 1.7–9.0). In the JID article this HRR is 4.9 (P < .001; 95% CI, 2.5–9.5). Drivers and their assistants were therefore more likely to be lost to follow-up during all stages of research and were