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I have the pleasure of co-authoring this presentation with Drs. Gita Ramjee, Joanne Mantell and Landon Myer. Because of the crucial importance of today's meeting to the future of microbicide development, we want to bring to the attention of our colleagues one new set of observations just off the computer, not yet peer-reviewed (although read and approved informally by several colleagues) and not yet submitted for publication. The set of observations we want to share with you concerns qualitative data, based on interviews and focus groups with women who had contributed a major source of data for the N9 study that we all know so well, in which the placebo (Replens) appeared to have done more to protect users than the putative microbicide, N9. The women on the Ramjee-Mantell-Myer study were interviewed some months after the termination of the trial, and after the results had been communicated to them.

For our purposes to-day, this is the relevant message: many women, although they understood that some of them were using a "placebo" and that in any case, the gel under test had not been established as preventive, still they liked using a gel; they felt it was cleansing, and that it probably kept out what was harmful in the semen; and that so good did it feel that they rejected the male condom in favor of the gel: they had of course been strongly and repeatedly counseled against doing just that. But for our purposes to-day, these observations give us the information for the first time that use of the gel (at least among these sex-workers) encouraged them to disregard advice and "emigrate" from use of the male condom.

This is very serious for the whole field. But we're using this information here for just two purposes: one is, once again, to argue against the use of the "condom only" or, as the more recent phrase goes "no gel" arm; the other is for a standard "placebo."

These data demonstrate that emigration from the male condom is not just a hypothetical possibility, but an observed phenomenon that can be expected in future phase 3 trials. This could mean higher levels of condom use in the open arm and different risks of HIV infection.

The idea of adding an open arm evidently emerged with our puzzlement over the results of the N9 trial. Now that we have these post-trial observations, it suggests to us that even if there had been a condoms only arm with that trial, we would still have been puzzled. Because Ladysmith sex workers would have emigrated from the male condom.

We are left to try and measure and adjust statistically for such variations in condom use. The male condom if correctly used, will protect, so that if Replens is indeed inert, the condoms only arm should have given more protection. If, then the condoms only arm had shown the most protection, how would we have distinguished presumed emigration from the possibility that Replens was harmful? No way to do that, save to rely on diaries and reports, from women on gels and condoms, which we could never regard as trustworthy enough for a definitive, multicenter trial like those.

If, on the other hand, Replens had proved superior to condoms only, we would need to establish that, in a future trial, the condoms only group also did not emigrate, or differentially increased their use. . In fact, key to the interpretation of any open arm is the “soft” information we obtain on continuing use of the condom across all groups. All this would become even more complex, given the different range of condom use and expected incidence of infection in each group. We would have to rely on highly sophisticated estimates, based as we all would be aware, on the diaries and reports.