Post-use ring weight, residual drug content and drug depletion zone thickness as objective measures of vaginal ring adherence

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Adherence and Acceptability of Rectal Microbicides: A Synthesis Review

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Background: Rectal microbicides (RM) will require high product acceptability and adherence to be efficacious. Given the diverse approaches to measure RM acceptability and adherence, we used a synthesis review to characterize how researchers have ascertained RM acceptability and adherence in clinical trials.

Methods: We searched multiple digital libraries for RM studies published from January 2000 to August 2017. Following abstract extraction and review, we included 23 articles in our review. These articles were organized based on whether the main outcomes measured microbicide acceptability (n=12), adherence (n=2), or both (n=9). Raters were randomly assigned into pairs, and asked to review the RM studies to ensure congruent interpretation of findings. Study acceptability and adherence results were standardized and pooled to test for systematic differences by assessment and product type.

Results: Publications stemmed from 15 distinct RM studies. Acceptability measures included point-scale responses (N=12/15), category selection (N=1/15) and interviews (N=6/15). Acceptability responses were generally favorable across data collection methods used in the trials. Participants rated responses of microbicides after using a product with an active ingredient (N=7/15), placebo only (N=2/15) or a hypothetical scenario (N=6/15). In a meta-analytic estimate of acceptability differences across product types, we found a small and negligible mean effect (-0.083, 95% CI: ±0.0009). Adherence was measured using product count (N=4/15), events-monitoring system (N=1/15), IVRS (N=2/15), and pharmacokinetic plasma assays (N=1/15). All articles reported favorable RM adherence. Given limited data on adherence, a meta-analytic estimate could not be computed.

Conclusions: RM acceptability and adherence were favorable across trials. To ensure robust and reliable comparisons across trials, future research should consider the use of harmonized acceptability measures and improve the specificity of product adherence reported in publications.

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Post-use Ring Weight, Residual Drug Content and Drug Depletion Zone Thickness as Objective Measures of Vaginal Ring Adherence

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Background: A challenge in the development of microbicide-releasing vaginal rings is the accurate and reliable measurement of adherence during clinical testing. To move away from self-reported measures of adherence, there is considerable interest in the development and testing of more objective, quantitative measures. Here, we assessed post-use ring weight, residual drug content and drug depletion zone thickness as potential measures of adherence to a highly-loaded progesterone-releasing ring.

Methods: Matrix-type silicone elastomer vaginal rings containing progesterone (n=89) were used by breastfeeding women across three sites in Africa to extend the contraceptive effectiveness of lactational amenorrhea. Used rings were assessed for ring weight, residual progesterone content (via solvent extraction and HPLC-UV analysis), and drug depletion zone thickness (using digital microscopy) as potential measures of user adherence.

Results: Unused control rings (n=6) had a mean progesterone content of 2058 ± 21 mg (99.2 ± 1.0 %; relative to 2074 mg nominal loading) and mean ring weight of 9.37 ± 0.02 g. Mean residual progesterone content and post-use ring weight for clinical rings were 1212 ± 220 mg and 8.60 ± 0.22 g, respectively. Wide variations in residual progesterone content (range 45.5-99.2 % of controls) and ring weight (range 88.0-99.9%) of used rings were attributed to differences in extent of ring use. Linear correlations were observed between residual progesterone content and post-use ring weight (r2=0.7331), and thickness of the drug depletion zone with post-use ring weight (r2=0.9757) and residual drug content (r2=0.9743).

Conclusions: For vaginal rings with a high drug load like the matrix-type progesterone ring, where a relatively large fraction of the initial drug loading is released during use, post-use ring weight, residual drug content and depletion zone thickness may offer accurate methods for monitoring user adherence. Ring weight measurement offers a particularly simple and inexpensive method.