EFFECT OF ANTIMICROBIALS ON PENILE BACTERIAL DENSITY AND FORESKIN INFLAMMATION

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BACKGROUND

Penile microbiome, particularly abundance of specific anaerobes, has been associated with HIV acquisition, potentially through impacting foreskin immune response. Little is known regarding the impact of antimicrobials on penile microbiome or foreskin immunology.

METHODS

We conducted a randomized trial with 125 HIV-negative uncircumcised men in Rakai, Uganda. Participants were randomized into five study arms (n= 25); control arm underwent immediate circumcision, while intervention arms deferred circumcision for 4 weeks and received either: 1) oral tinidazole for 2 days, 2) topical metronidazole, 3) topical clindamycin or 4) hydrogen peroxide. We collected sub-preputial swabs at baseline and at weeks 1 and 4 to examine the impact of treatment on total penile bacterial density and on sub-preputial IL-8 and soluble E-cadherin (sE-Cadherin) as indicators of inflammation and impaired epithelial integrity, respectively.

RESULTS

Total penile bacterial density was similar across all study arms at baseline. At week 1, significant decreases in total penile bacterial load was seen in all study arms except the tinidazole arm, with the largest decrease seen in topical clindamycin group (**Fig 1**). By week 4, total penile bacterial density remain significantly decreased in topical clindamycin and hydrogen peroxide arms (**Fig 1**). Even though bacterial density did not correlate with IL-8 or sE-Cadherin at baseline, at week 1, bacterial density correlated significantly and positively to IL-8 with metronidazole and to both IL-8 and soluble E-cadherin with hydrogen peroxide (**Table 1**). At week 4, only clindamycin arm showed positive correlations between bacterial density to both immune outcomes (**Table 1**). Over the course of treatment, clindamycin and metronidazole enhanced the association between penile bacterial density to inflammation and decreased epithelial integrity.

Topical antimicrobials significantly reduce penile bacterial density and showed antimicrobial-specific impact on foreskin immunology.

Oral tinidazole did not have a significant effect on penile bacterial density nor foreskin immunology.

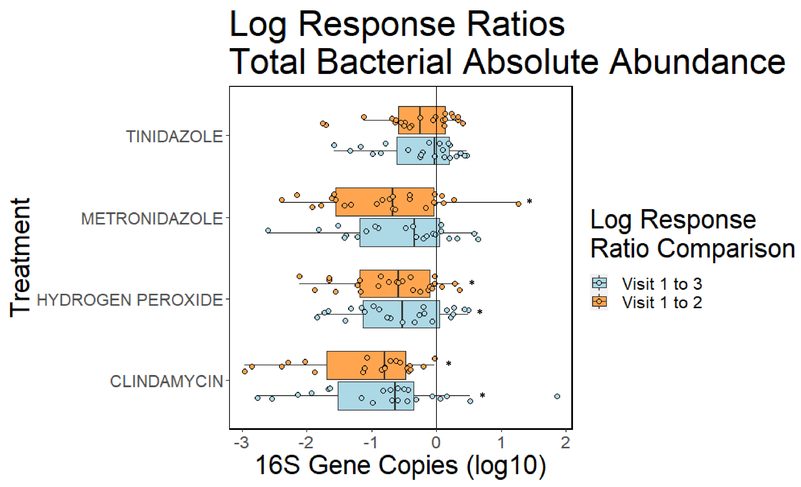

Figure 1. Log Response Ratios across treatment arms Visit 1 to 2 and Visit 1 to 3.
Visit 1 to 2: Clindamycin median log response ratio – (MLRR= -0.79 IQR= -1.69, -0.48). Tinidazole (MLRR= -0.26 IQR= -0.59, 0.13) metronidazole (MLLR= -0.68 IQR= -1.56, -0.04) and hydrogen peroxide (MLLR= -0.59 IQR= -1.19, -0.10).
Visit 1 to 3: Clindamycin median log response ratio - MLRR= -0.64 IQR= -1.52, -0.35). Tinidazole (MLRR= -0.03 IQR= -0.61, 0.20) metronidazole (MLLR= -0.34 IQR= -1.19, 0.05) and hydrogen peroxide (MLLR= -0.53 IQR= -1.14, 0.04)
Decreases in total bacterial abundance for all treatments except for Tinidazole were significant (P-values < 0.05) between visit 1 & 2. Total bacterial load continued to significantly decrease between visit 1 & 3 for Clindamycin and Hydrogen Peroxide. Total bacterial abundance experienced a similar trend of rebound between visit 2 and 3 for all treatments.

Study Arm	IL-8 Enrollment	IL-8 Week 1	IL-8 Week 4	E-cadherin Enrollment	E-cadherin Week 1	E-cadherin Week 4
Clindamycin	0.22	0.40	**0.47***	0.00	-0.08	**0.65***
Metronidazole	0.14	**0.44***	0.43	0.04	0.39	0.43
Hydrogen Peroxide	-0.25	**0.40***	0.14	0.04	**0.60***	-0.04
Tinidazole	-0.02	-0.19	-0.02	0.08	-0.08	0.37

Table 1. Spearmen Correlation between bacterial density, IL-8, and sE-cadherin.
*P-value < 0.05.

CONCLUSIONS

- Topical antimicrobials significantly decreased total penile bacterial density, which also decreased levels of sub-preputial sE-cadherin, suggesting improved foreskin epithelial integrity with decreasing penile bacterial density.
- Individuals receiving topical clindamycin showed largest decrease in total penile bacterial density, and the strongest correlations between penile bacterial density and foreskin immune responses.
- It will be important to characterize change in penile microbiome to better understand the impact of oral and topical antimicrobial on specific penile bacteria and how changes in these bacteria correlate with foreskin immunology.
- This is the first study that looked at the impact of oral and topical antimicrobial on penile bacterial density and its association with foreskin immunology, including IL-8, which was previously associated with increased risk for HIV acquisition.

ADDITIONAL KEY INFORMATION

We would like to thank the Canadian Institutes of Health Research and the NIH Fogarty International Center for funding this work. Research reported in this poster was supported by NIDDK of the National Institutes of Health under award 1R01DK131936-01. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.