MZC Gel Inhibits *ex vivo* HIV-1 and HSV-2 Infection in Human Cervical Mucosa

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BACKGROUND

- HSV-2 increases the risk of HIV-1 acquisition.
- Microbicides that protect women against HIV and HSV-2 would make a major contribution to public health globally.
- The Population Council's leading microbicide gel (MZC) containing 50μM MIV-150 (M), 14mM Zinc acetate dihydrate and Carrageenan (CG) protect macaques against single high dose SHIV-RT challenge vaginally for up to 8h and rectally for 1h (1, 2)
- MZC significantly reduces HSV-2 and HPV infection in murine models (2)
- MZC reduces vaginal HSV-2 infection after single (3) or repeated HSV-2 challenge, and significantly reduces HSV-2 shedding in macaques (4).
- This study aimed to test activity of MZC against HIV only and HIV-1/HSV-2 co-infection in human cervical mucosa.

RESULTS

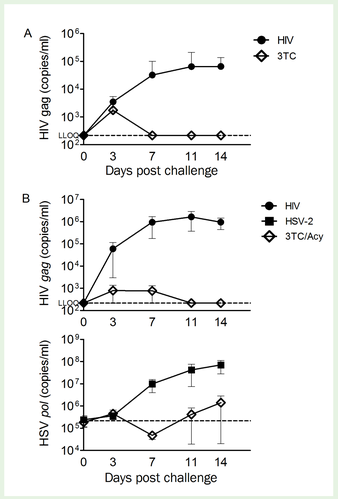

Figure 1- Single HIV-1_{BaL} challenge and HIV-1_{BaL}/HSV-2 co-challenge result in reproducible tissue infection with both viruses.
Ectocervical explants were challenged with 500 $TCID_{50}$ HIV-1_{BaL} (A) or co-challenged with 500 $TCID_{50}$ HIV-1_{BaL} and 10^6 pfu HSV-2 (B) per explant (vs. 3TC or 3TC/Acyclovir controls) for ~18h. After washout, tissues were cultured for 14d. A) Shown are (Mean±SEM, 9 experiments) HIV *gag* copy numbers in the single challenge model. The LLOQ for HIV *gag* qRT-PCR is indicated (dotted line). B) Shown are (Mean±SEM, 5 experiments) HIV-1_{BaL} and HSV-2 copy numbers in the co-challenge model. The LLOQ for HIV *gag* qRT-PCR and input HSV-2 *pol* copy numbers (Mean; post washout after challenge) are indicated (dotted line).

RESULTS

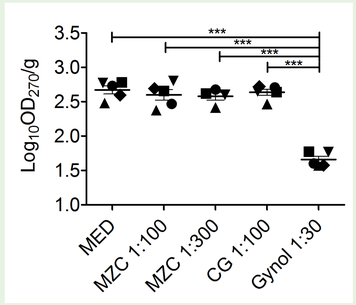

Figure 2- Diluted MZC does not decrease tissue viability.
Viability of ectocervical tissue after immersion in medium containing diluted gels for ~18h was tested by MTT assay (OD_{570} of the formazan product were measured in triplicate and normalized by the dry weight of the explants). Each symbol indicates an individual donor and the Mean±SEM of the Log_{10} OD_{570}/g of tissue for each condition is shown. Log-normal generalized linear mixed models were used for statistical analysis. Significant p-values of <0.001 (***) are indicated.

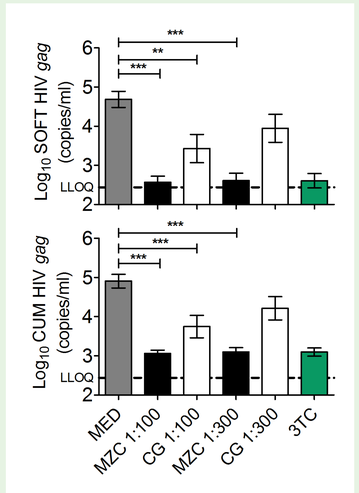

Figure 3- MZC significantly inhibits HIV-1_{BaL} infection in the single challenge model.
Ectocervical explants were challenged with 500 $TCID_{50}$ HIV-1_{BaL} in the presence of diluted MZC (vs. untreated control (MED), CG and 3TC controls). Tissues were cultured as in Fig. 1. Shown are log_{10}-transformed SOFT endpoint and CUM endpoint analyses (d3-14 of culture; Mean±SEM, 9 experiments) (5). The LLOQ for HIV *gag* qRT-PCR is indicated (dotted lines). Log-normal generalized linear mixed models were used for statistical analysis. Significant p-values of <0.01 (**), <0.001 (***) are indicated.

RESULTS

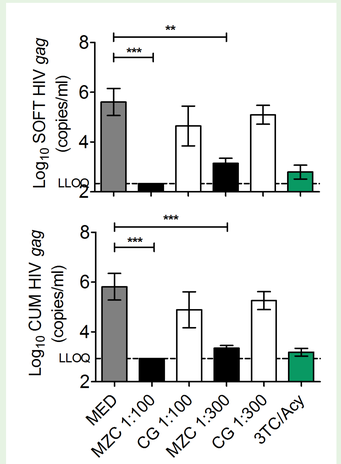

Figure 4- MZC significantly inhibits HIV-1_{BaL} infection in the co-challenge model.
Ectocervical explants were co-challenged with 500 $TCID_{50}$ HIV-1_{BaL} and 10^6 PFU HSV-2 per explant in the presence of diluted MZC. Shown are log_{10}-transformed SOFT and CUM analyses as described in Fig.3. Shown are Mean±SEM (5 experiments). The LLOQ for HIV *gag* qRT-PCR is indicated (dotted lines). Log-normal generalized linear mixed models were used for statistical analysis. Significant p-values of <0.01 (**), <0.001 (***) are indicated.

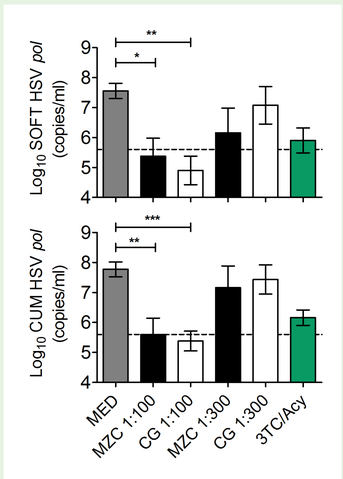

Figure 5- MZC and CG gels inhibit HSV-2 in the co-challenge model.
Log_{10}-transformed SOFT and CUM analyses of the HSV-2 infection in the experiments described in Fig. 5 are shown (Mean±SEM, 5 donors). The input virus after washout is indicated (dotted lines). Log-normal generalized linear mixed models were used for statistical analysis. Significant p-values of <0.05 (*), <0.01 (**), <0.001 (***) are indicated.

CONCLUSION

- MZC is active against HIV-1_{BaL} infection in human ectocervical mucosa in the single challenge model as well as under stringent conditions of co-challenge with HSV-2.
- The gel provides CG-mediated activity against high dose HSV-2 challenge.
- These results highlight the promise for further development of MZC as a microbicide and support ongoing Phase 1 clinical evaluation of vaginal MZC gel.

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FOR MORE INFORMATION

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