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Anti-infectives' Penetration in Upper and Lower Female Genital Tissues

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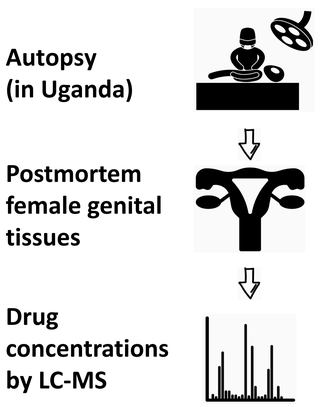
BACKGROUND

- Research question: **Do anti-infectives have optimal exposure at a major transmission site, female genital tract?**

The female genital tract is a major route for HIV transmission and a potential viral reservoir. While drug exposure in lower female genital tract (eg. cervix, vagina) has been described, little data exist on upper genital tissues (e.g., ovary, uterus). We sought to explore tissue penetration of two antiretroviral drug **tenofovir, lamivudine** and an anti-fungal **fluconazole**, in **ovarian, uterine, cervical and vaginal tissues** using **post-mortem** specimens.

METHODS

1. With next-of-kin consent, autopsies were performed within 24hr of death of participants with HIV in Uganda. Most of the participants were on TDF/3TC/EFV regimen (44.4%). Postmortem tissue samples were snap frozen and stored at -80°C until analysis.
2. Concentration of tenofovir, lamivudine and fluconazole were determined using high-performance liquid chromatography- tandem mass spectrometry (LC-MS/MS) in plasma, **ovarian, uterine, cervical and vaginal tissues**.
3. Tissue-to-plasma concentration ratios were calculated as measurement of penetration.

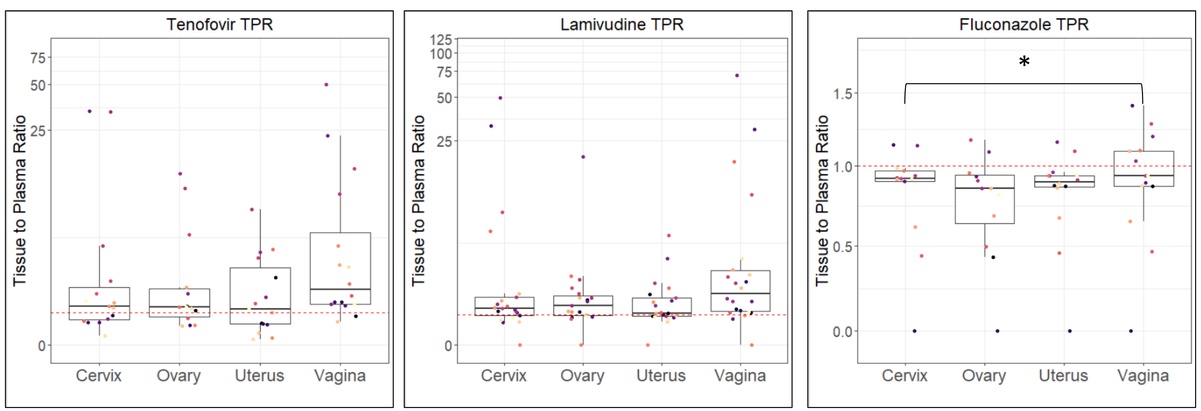


Tenofovir, lamivudine, and fluconazole exposure is consistently **highest in vaginal** tissue compared to rest of ***female genital tract***.

RESULTS

1. Tenofovir, lamivudine and fluconazole had higher penetration in vaginal tissue compared to cervical, uterine and ovarian tissue.
2. For all 3 drugs, the penetration is highly variable between individuals.
3. Tenofovir and lamivudine had better penetration than fluconazole.
4. The tissue-to-plasma ratios were not significantly correlated with postmortem interval.

➢ **Most tissue-to-plasma ratios (TPRs) of tenofovir and lamivudine were > 1 (first two graphs) while most fluconazole TPRs were < 1 (third graph) in all 4 FGT compartments. Different color indicates different participant. Red dashed line is TPR = 1.**

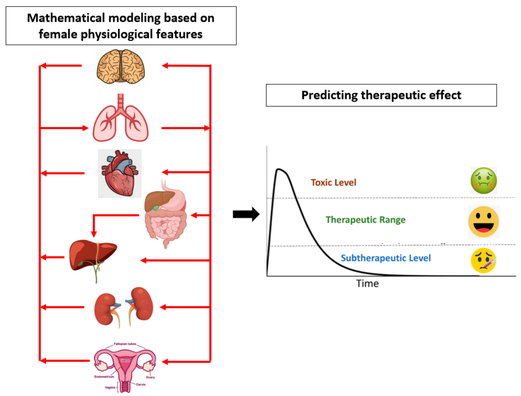


CONCLUSIONS

- The current study measured concentrations and determined penetration ratios of tenofovir, lamivudine and fluconazole in postmortem ovarian, uterine, cervical and vaginal tissues from a population of Uganda women who lived with HIV while alive.
- At steady state, tenofovir and lamivudine had optimal penetration to the solid tissue compartment, the female genital tract. While fluconazole had less penetration, if the penetration ratio is dose-independent, the current fluconazole exposure is still optimal for treatment of vaginal candidiasis when the dose is much lower.
- Postmortem analysis provides a unique opportunity to evaluate ARV exposure in submucosal tissues.

FUTURE DIRECTIONS AND ONGOING WORK

- Exploring postmortem redistribution of ARVs in animal model.
- Development of physiologically-based pharmacokinetic models for prediction of exposure of ARVs at female genital tract.



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