Topical Doxycycline Inserts Show High Efficacy Against Vaginal Chlamydia Acquisition in Macaques

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BACKGROUND

- We tested the hypothesis that topical delivery of doxycycline via a fast-dissolving insert could protect against vaginal acquisition of *C. trachomatis* infection in pigtail macaques when used as post-exposure prophylaxis.

Bacterial STIs are on the rise globally. Fast-dissolving dual-compartment (vaginal/rectal) inserts containing doxycycline (DOX) provide an alternate approach to STI prevention that can maximize local DOX concentrations while minimizing systemic distribution. Here, we performed preclinical studies to evaluate the pharmacokinetics (PK) and protective efficacy following vaginal administration of CONRAD-developed inserts containing DOX against vaginal *C. trachomatis* (CT) infection in pigtail macaques.

METHODS

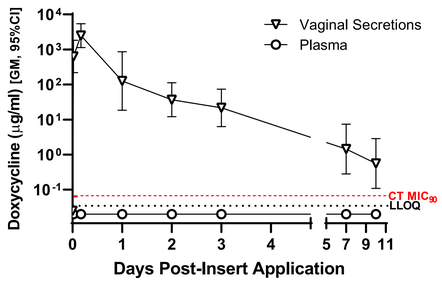
- Inserts were manufactured using a simple, easy-to-scale direct compression process containing 10 or 50mg DOX.
- DOX PK was determined via HPLC-tandem mass spectrometry analysis of vaginal swabs and plasma samples collected from macaques following vaginal administration of a 10mg DOX insert.
- A physiologically-relevant challenge dose of 10^4 inclusion forming units (IFU) was identified for CT (serovar E) following a vaginal dose titration (10^6-500 IFU).
- For efficacy studies, macaques were administered either a single vaginal insert containing DOX (50mg or 10mg) or no insert (Controls), at 4 hours (h) following vaginal challenge with 10^4 IFU CT. Animals were followed weekly, for 9 weeks, to monitor CT infection by testing vaginal swabs for the presence of CT rRNA via the Aptima Combo 2 target amplification assay. Macaques were considered to have an established CT infection if they exhibited Aptima positivity for 4 or more weeks following CT challenge.

CT-Positive
CT-Negative

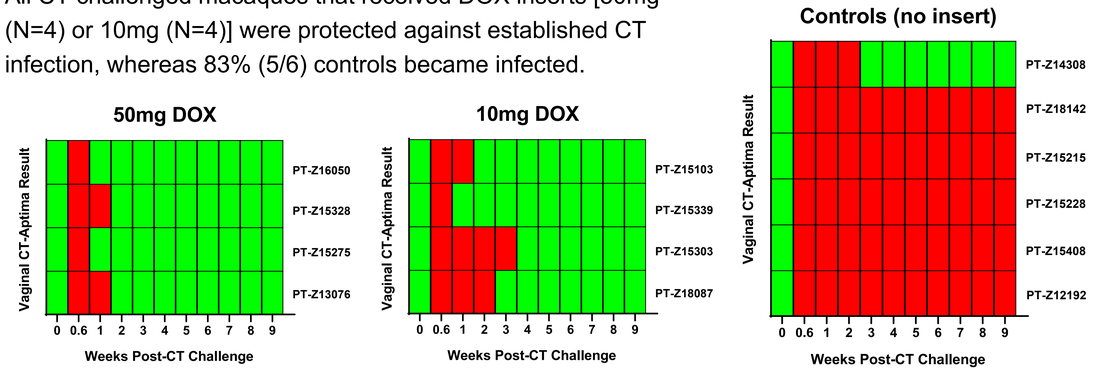
Fast-dissolving inserts that deliver doxycycline topically protected macaques against vaginal chlamydia infection when administered as post-exposure prophylaxis.

RESULTS

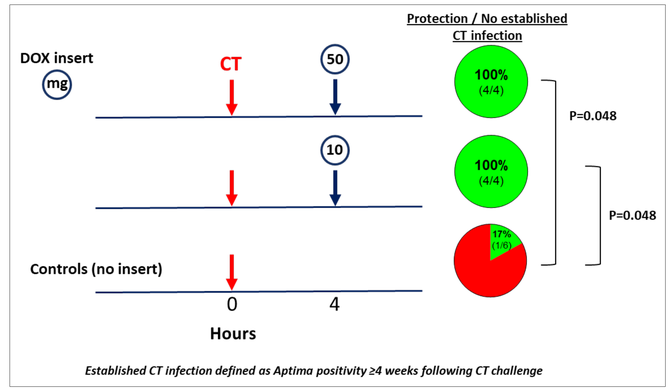
1. Vaginal administration of a single 10mg DOX insert conferred DOX concentrations in vaginal swab eluates that exceeded the MIC_{90} of DOX against CT (0.064µg/ml) for ≥10 days, with undetectable systemic DOX exposure.



2. All CT-challenged macaques that received DOX inserts [50mg (N=4) or 10mg (N=4)] were protected against established CT infection, whereas 83% (5/6) controls became infected.



SUMMARY



CONCLUSIONS

- Vaginal delivery of DOX by inserts containing 10mg or 50mg DOX protected macaques against CT infection when administered 4h after CT challenge.
- Data provide the first evidence of a novel topical DOX modality for CT prevention.
- PK data demonstrated lack of systemic DOX distribution and highlight the role of sustained vaginal DOX in protection against CT

Findings inform the clinical development of DOX inserts for on-demand CT prevention and support DOX coformulation into tenofovir alafenamide and elvitegravir-containing inserts, which are currently in clinical development for HIV prevention.

ACKNOWLEDGEMENTS

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention