NATIONAL CENTER FOR HIV, VIRAL HEPATITIS, STD, AND TB PREVENTION

TAF/EVG DUAL COMPARTMENT INSERT EFFICACY AGAINST RECTAL SHIV TRANSMISSION IN MACAQUES

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Natalia Makarova[1], Tyana Singletary[1], M. Melissa Peet[2], Vivek Agrahari[2], James Mitchell[1], Angela Holder[1], Chuong Dinh[1], Maria Mendoza[1], Yi Pan[1], Walid Heneine[1], Gerardo Garcia-Lerma[1], Meredith Clark[2], James Smith[1], Gustavo Doncel[2]

[1]CDC, Atlanta, GA, USA, [2]CONRAD, Eastern Virginia Medical School, Norfolk, VA, USA,

BACKGROUND

Topical on-demand HIV prevention modalities are a desirable alternative to daily oral or long-acting injectable PrEP. CONRAD has developed inserts containing tenofovir alafenamide (TAF) and elvitegravir (EVG) for on-demand vaginal or rectal pericoital use, which are currently in early clinical testing. TAF/EVG inserts provided high protection as PrEP or PEP in pigtailed macaques exposed vaginally to simian HIV (SHIV). We recently reported on the pharmacokinetics of the same inserts when applied rectally. Here, we assessed the efficacy of 1 or 2 inserts against rectal SHIV transmission in a repeat low-dose SHIV challenge model in pigtailed macaques.

METHODS

Macaques were challenged rectally with low-dose SHIV162p3 4h after application of 1 or 2 TAF/EVG (20 mg/16 mg) inserts (n=6 per group). Single inserts and virus inoculums were placed at 4 cm from the anal sphincter. For 2 inserts, the second insert was placed 8 cm deep. Animals were challenged once weekly with SHIV162P3 for up to 10 weeks. Efficacy was estimated for 1 or 2 TAF/EVG inserts. Time to infection was compared to 6 placebo animals using the log rank test. Drug concentrations (EVG and TFV-DP) in rectal tissues were measured 4h after insert application by ~~HP~~LC-MS/MS.

RESULTS

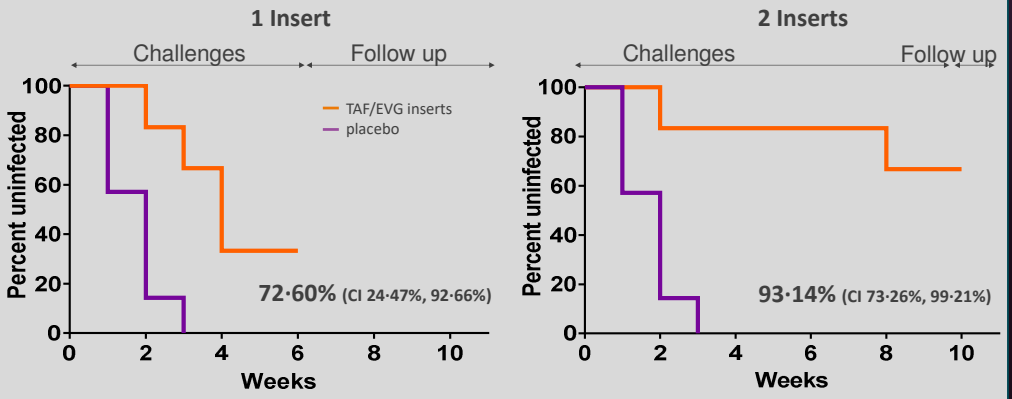
Median rectal tissue EVG and TFV-DP levels with 1 insert at 4h were 8128 ng/mg (range=BLQ–515,053) and 2187 fmol/mg (range=411–2500), respectively. With 2 inserts, EVG and TFV-DP were approximately one log higher compared with 1 insert (EVG 73,708 ng/mg; range BLQ–271,316 and TFV-DP 66,553 fmol/mg; range 2801–540,823). The single TAF/EVG insert arm was terminated after 6 exposures given the high rate of infection (4/6 infected at exposures 2, 3, 4, and 4). However, the time to infection was significantly delayed when compared to the placebo controls (p=0.0046). Calculated efficacy was 72.6% (95% exact CI =24.5%, 92.7%). With 2 inserts and 10 virus challenges, 2/6 animals became infected at exposures 2 and 8 resulting in 93.1% (95% CI=73.2%, 99.2%) efficacy (p=0.0022).

CONCLUSIONS

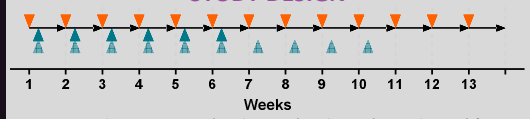
Despite similar tissue drug levels after vaginal and rectal application, a single TAF/EVG insert only achieved moderate protection after rectal challenge. Adding a second insert increased drug distribution through rectal tissues and boosted efficacy to 93%. Collectively, these data document pharmacodynamic differences between rectal and vaginal mucosa, informing insert dose selection in both compartments for advanced clinical development.

- A single TAF/EVG (20mg/16mg) rectal insert achieved only partial protection (~72%) from repeated SHIV exposures in macaques at a dose that was highly efficacious when used for vaginal PrEP
- Adding a second insert increased drug distribution in rectal tissues and resulted in increased efficacy (>90%)
- These studies highlight differences in achieving protection with vaginal vs rectal dosing
- Results inform clinical dosing and support advanced development of TAF/EVG inserts for on-demand prevention of HIV

RECTAL EFFICACY OF TAF/EVG INSERTS ADMINISTERED 4h BEFORE SHIV EXPOSURE

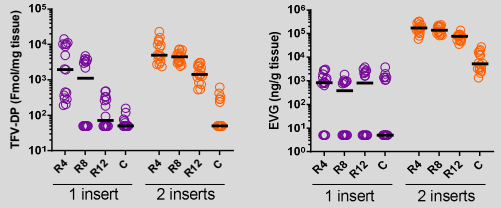


STUDY DESIGN



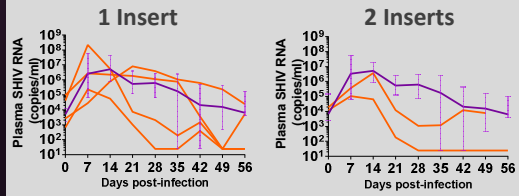
- Inserts application at 4 cm (single insert) and 8 cm (second insert) from anal sphincter
- 1 insert arm virus challenges
- 2 inserts arm virus challenges

RECTAL DRUG DISTRIBUTION 4h AFTER TAF/EVG INSERTS



Rectal biopsies were collected 4 cm (R4), 8 cm (R8), 12 cm (R12), and 25 cm (C) from the anal sphincter.

PLASMA VIRAL LOAD



CONTACT INFO

Natalia Makarova
wcn5@cdc.gov

www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.