A PENILE MODEL IN RHESUS MACAQUES

TO ASSESS PHARMACOKINETICS AND CHARACTERIZATION OF HIV TARGET CELLS WITHIN ANATOMICAL COMPARTMENTS OF PENILE TISSUE

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Penile transmission

- **Penile transmission accounts for nearly half of all HIV infections globally[1]**
- **The mechanisms of HIV penile acquisition are poorly understood**
  - Inner foreskin, and urethra are likely entry points for HIV
  - Condoms and medical male circumcision practices can effectively reduce HIV infection in men
- **Oral Truvada (TDF/FTC) protected heterosexual men in Partners PrEP and TDF-2 (80-84% efficacy)[2-3]**
- **Preclinical animal models of penile transmission are needed**
  - Investigate mechanisms of penile transmission
  - Identify sanctuary HIV target sites in penile tissue
  - Inform on biomedical penile prevention interventions

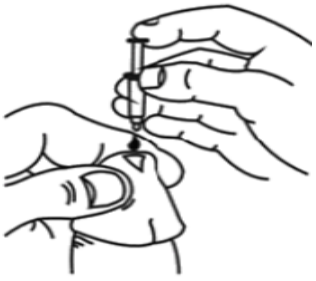
1-Boily, Lancet Infect Dis. 2009.
2-Baeten et al., N Engl J Med 2012
3-Thigpen M (2012)

Rhesus macaque model of penile SHIV transmission

- **Similar approach to rectal and vaginal SHIV transmission models**
  - Repeated low-dose SHIV challenges
- **Dual compartment exposures**
  - Urethra
  - Prepuce pouch

No-contact inoculation

Urethra



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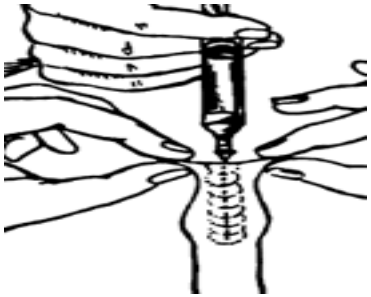
Foreskin



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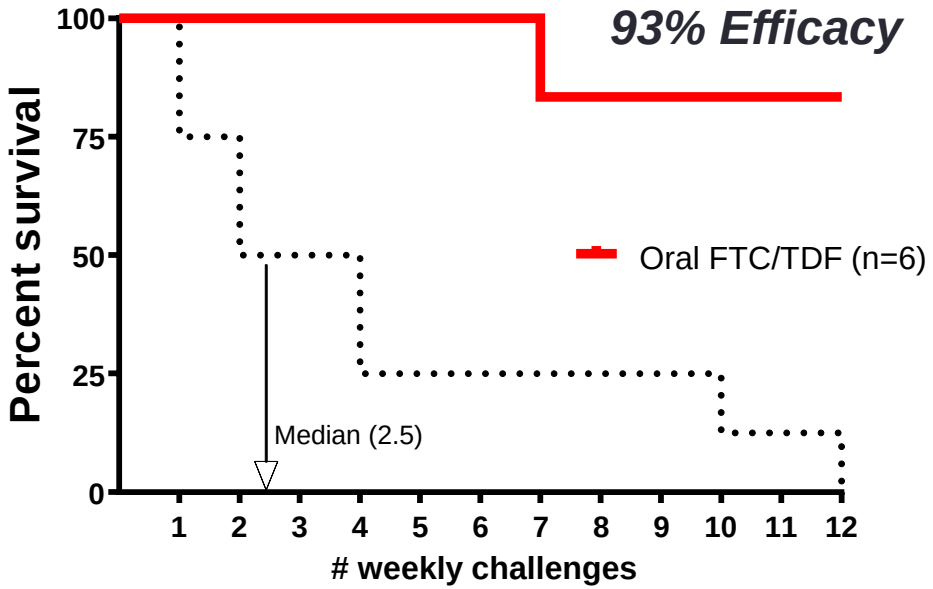


Model validated with human-equivalent dosing w/ oral FTC/TDF (Dobard, CROI 2018)

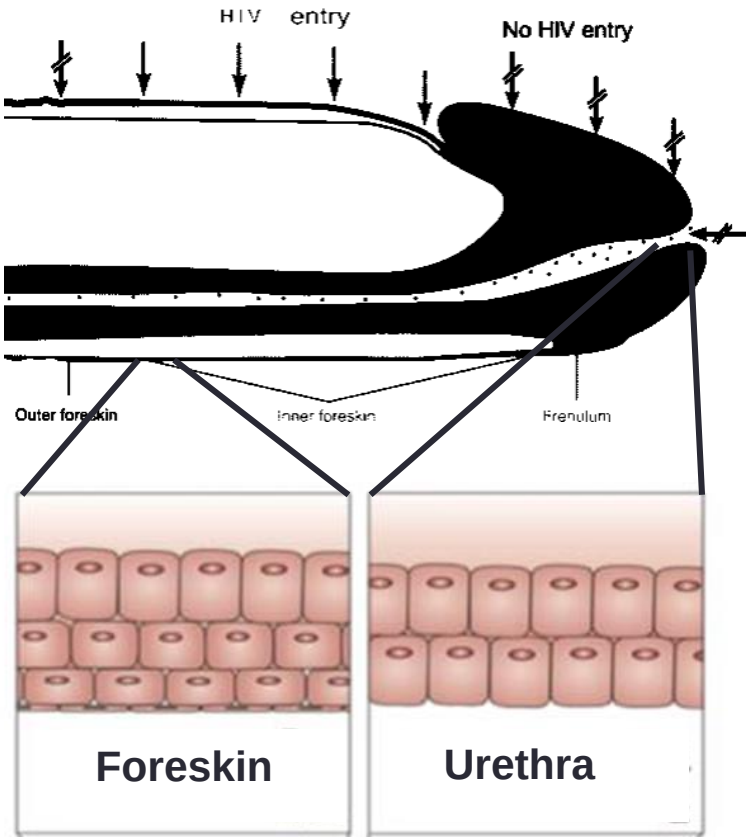
Garber D, PLoS ONE (2018)

Objectives

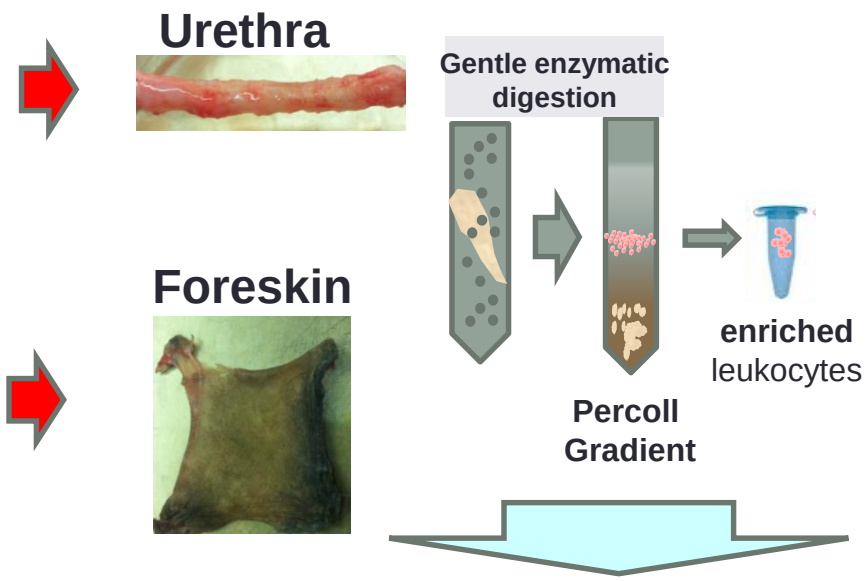
- Comprehensive immune characterization of HIV target cells in foreskin and urethra tissue

- Pharmacokinetic (PK) assessment in penis tissues following human-equivalent oral FTC/TDF dosing in macaques

Immune characterization of HIV target cells in penile tissue



Enrichment method



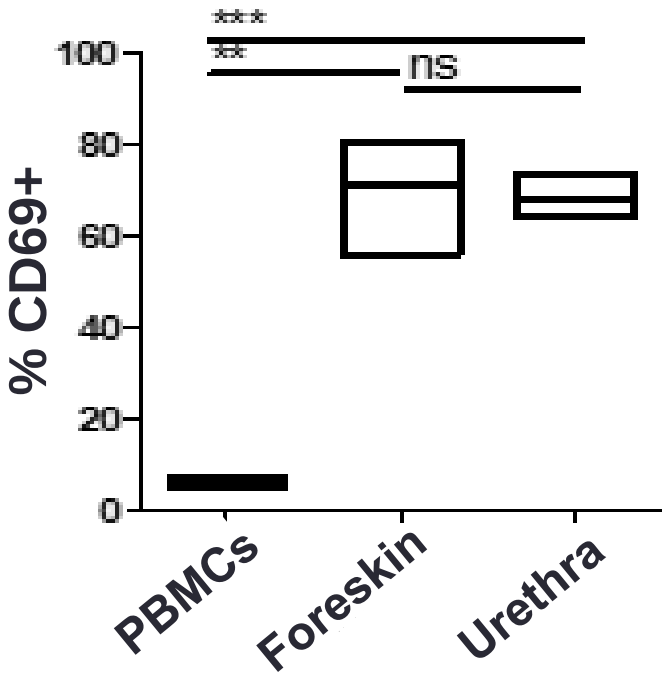
Cell characterization

- ❑ CD4 and CD8 T cells
- ❑ B cells
- ❑ NK cells
- ❑ Monocytes
- ❑ Conventional dendritic cells (CDC)
- ❑ Plasmacytoid dendritic cells (PDC)

- CCR5
- α4β7
- HLA-DR
- CX3CR1

Picture adapted from
http://www.medicitalia.it/public/uploadedfiles/minforma/luigilaino_hiv_circoncisione_laino.jpg

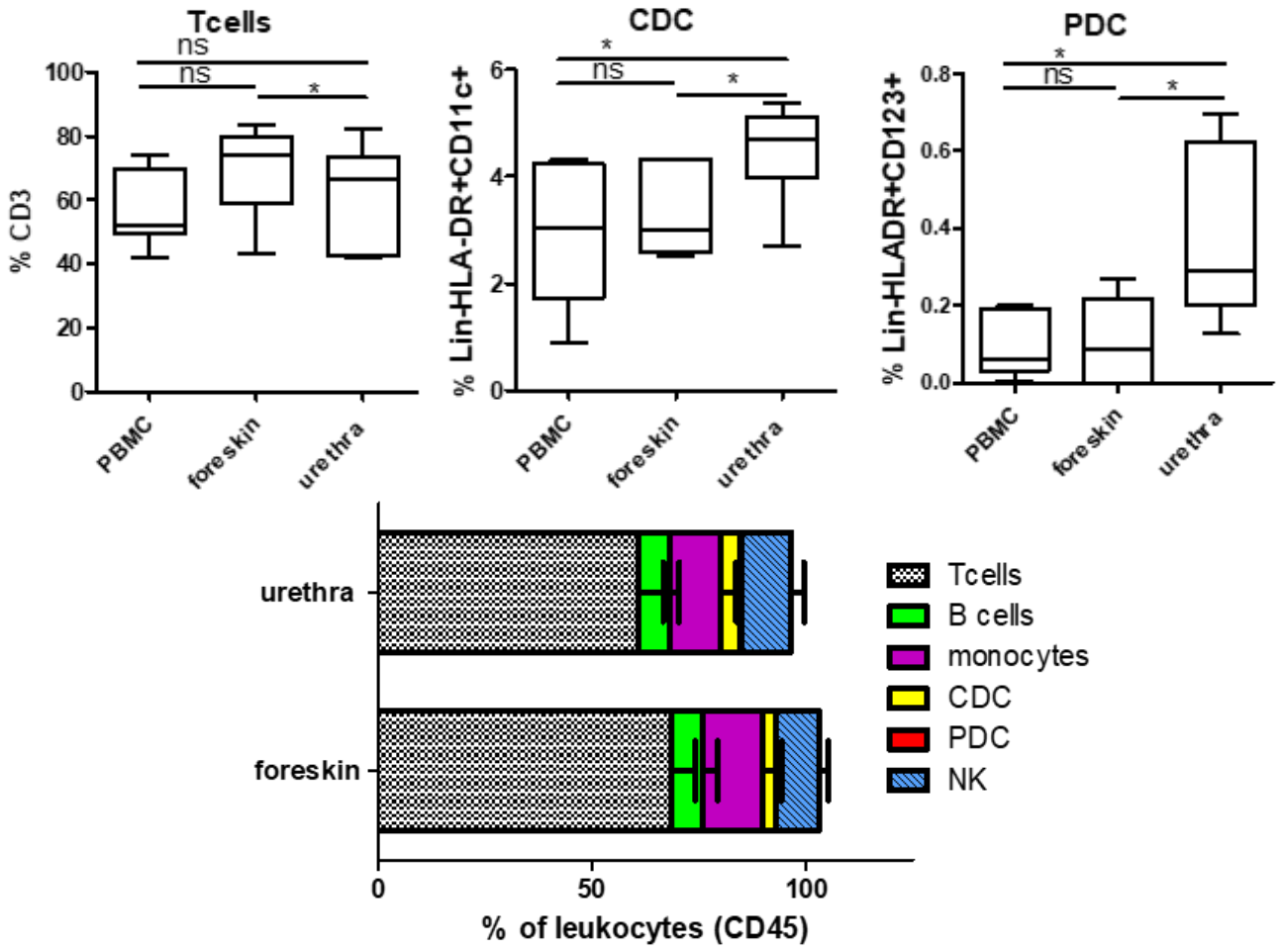
Cellular immune barrier landscapes at urethral and foreskin barriers



Highly enriched local immune populations in foreskin and urethral tissues

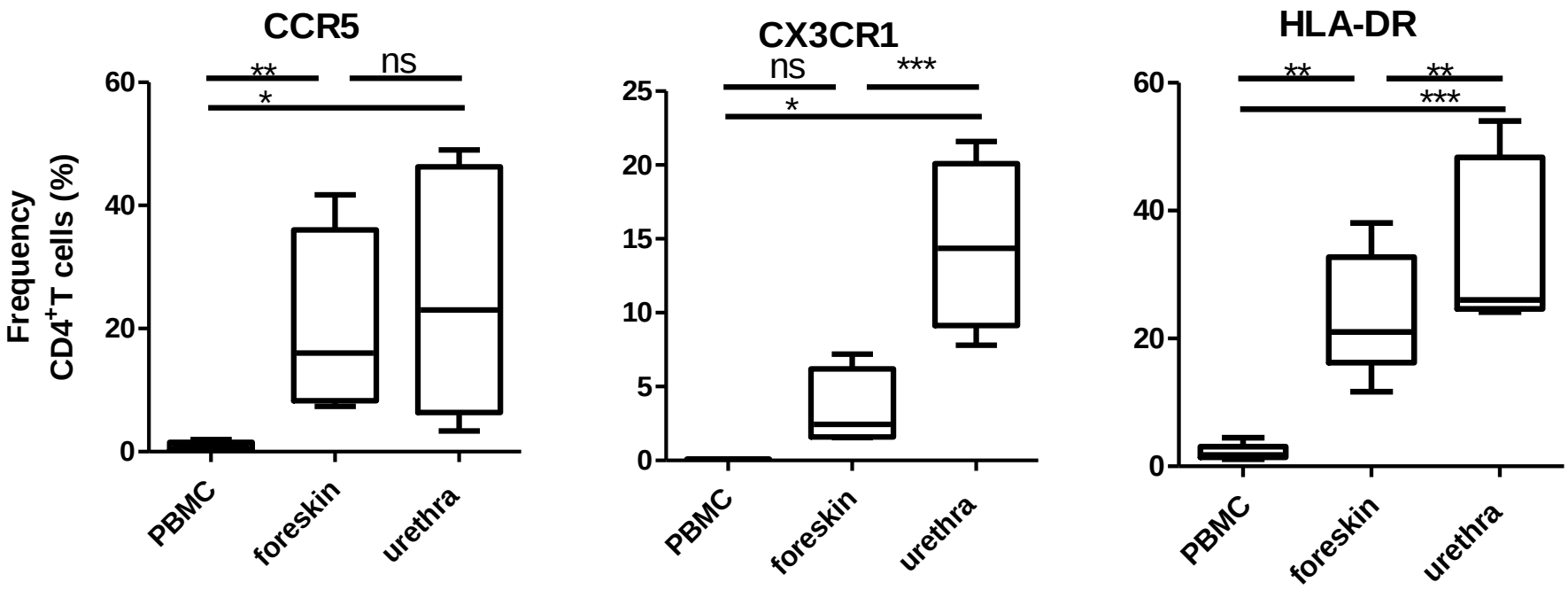
Picture adapted from Farber D, Cell Rep, 2017

Cellular immune barrier landscapes at urethral and foreskin barriers



Increased frequency of inflammatory mediators in urethral barrier

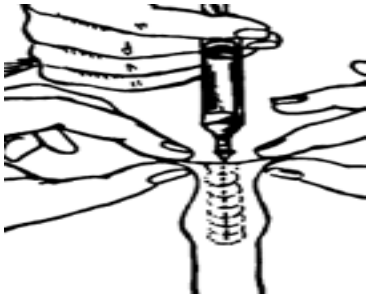
HIV target cells at urethral and foreskin barriers



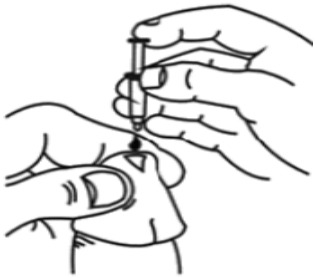
- Increased HIV target cells in foreskin and urethra tissues compared to blood
- Higher expression of activation markers HLA-DR and fractalkine receptor in target cells in urethra tissue

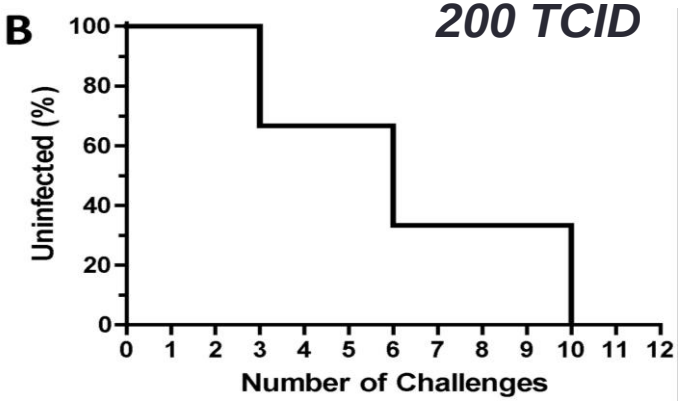
Urethral and inner foreskin barriers: susceptibility following SHIV challenge

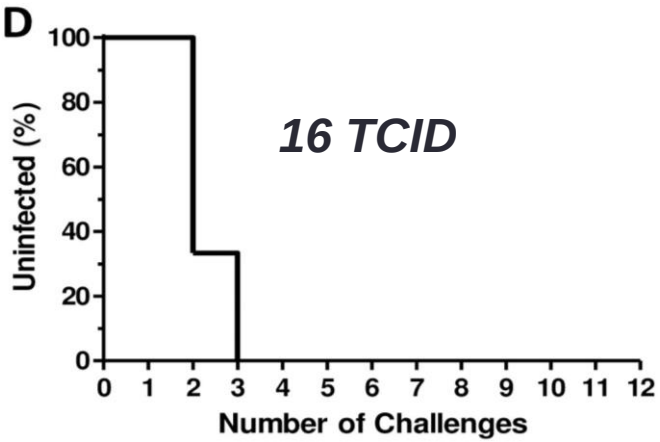
Foreskin



Urethra







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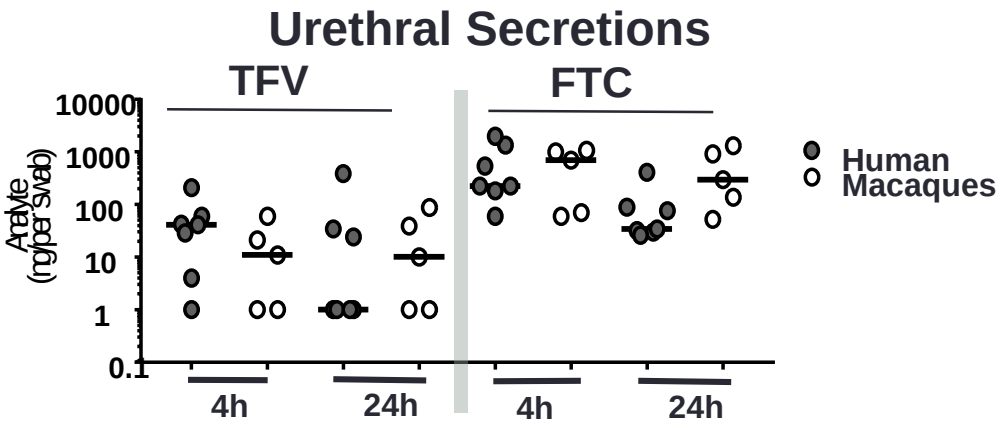
The urethral barrier exhibits greater vulnerability to SHIV infection

1-Garber, PLoS One, 2018

Penile PK assessment in humans and macaques

Human and Macaques

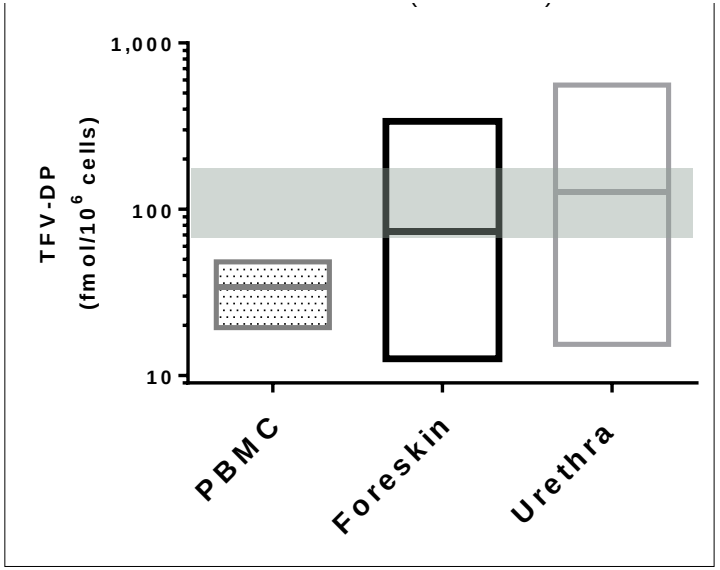
- Oral Truvada (FTC/TDF)
  -Human (**n=7**); 200/300 mg
  -Macaques (**n=5**); 20/22 mg/kg
- Collect urethra swabs 4 and 24 hours post dosing
- TFV and FTC levels (ng/swab)



Similar levels in humans and macaques

Macaques

- Collect penile tissues at necropsy 24 post dosing
  - Isolate lymphocytes from urethral and foreskin tissue
  - Measure intracellular TFV-DP



TFV-DP associated with *in vivo* efficacy

Conclusions

- **Defined differences in immune cell composition in urethral and foreskin tissues**
  - Distinct barrier compositions in urethral compared to foreskin tissues defined by increased inflammatory function and peripheral immune surveillance
  - Consistent with penile transmission studies in macaques, findings suggest urethral barrier is more vulnerable to SHIV infection than the foreskin barrier

- **Validated urethra sampling methods in macaques to assess penile PK**
  - Similar drug penetration in urethra secretions in humans and macaques following oral TDF/FTC dosing
  - High concentrations of TFV-DP in both urethral and foreskin tissues support the protective efficacy seen with oral TDF regimens