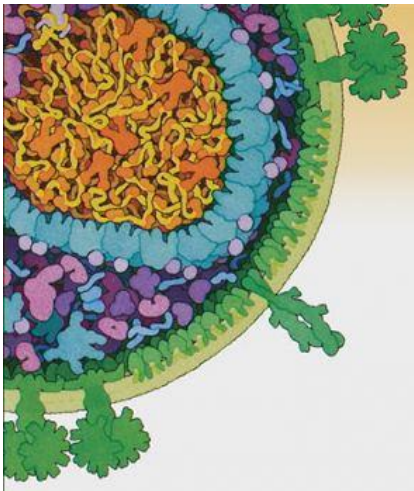

MODERATE EFFICACY OF ORAL SINGLE-AGENT TAF AGAINST VAGINAL SHIV INFECTION IN MACAQUES

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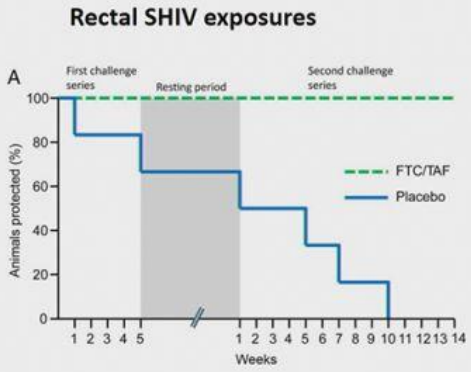
Tenofovir alafenamide (TAF) for PrEP

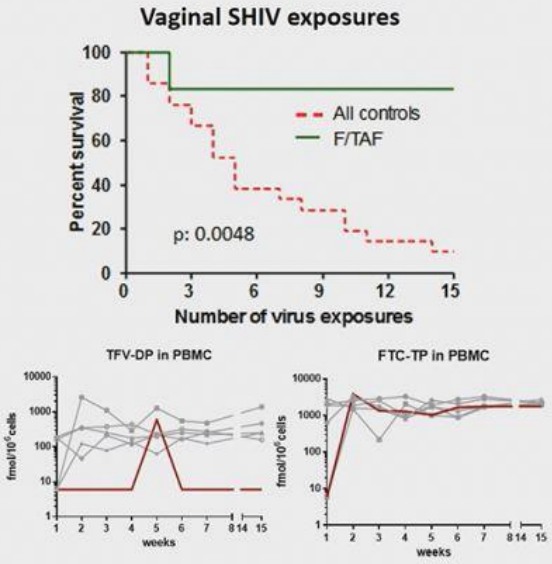
- Daily PrEP with FTC/TDF is a safe and effective option to prevent HIV acquisition among men and women
- TAF is considered an alternative to TDF for oral tenofovir-based PrEP
  - Higher TFV-diphosphate concentrations in PBMC; prolonged drug persistence
  - Significantly lower dose and ~10-fold lower TFV in plasma
- Under evaluation as a long-acting single agent delivered from implants

Preclinical studies with TAF for PrEP

- No protection with a low 0.1 mg dose of oral TAF in newborn macaques exposed orally to SIVmac251 *(Van Rompay et al, J AIDS 2006)*
- No protection with a high 13.7 mg/kg dose of oral TAF administered 3 days before rectal SHIV exposure *(Garcia-Lerma et al., J Virol 2011)*
- High efficacy with a clinically equivalent dose of oral FTC/TAF combination against vaginal and rectal SHIV infection *(Massud et al., CROI 2018 and JID 2016)*

High efficacy of FTC/TAF against vaginal and rectal SHIV infection





Massud et al., JID 2016

Massud et al., CROI 2018

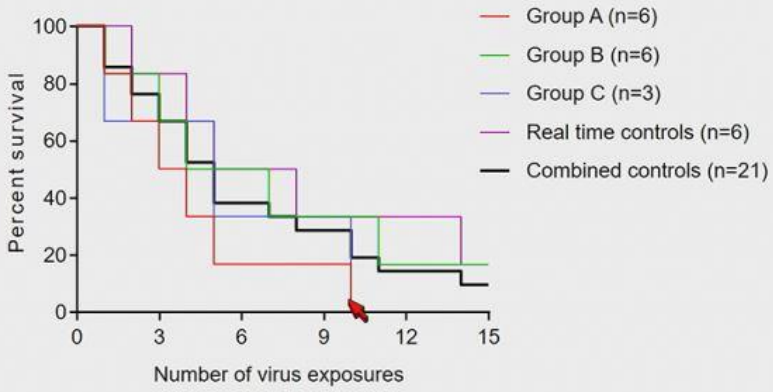
Objective

To investigate if single-agent TAF is effective in preventing vaginal SHIV infection

Study design

- Female pigtail macaques (n=9) with regular menstrual cycles
  - Two macaques did not dose well with TAF and excluded (15 to 16 fmols/10^6 cells)
- Clinically equivalent dose of TAF (1.5 mg/kg) given orally by gavage before and after SHIV challenge (24h/+2h)
  - Macaques exposed to a low dose of SHIV162p3 once a week for up to 15 weeks
- TFV-DP and dATP levels measured in PBMC by LC-MS/MS
- Infection monitored by serology and PCR amplification of SHIV RNA and DNA
- Infection outcome compared to 21 untreated controls; 6 real-time and 15 historical exposed to the same virus stock and dose

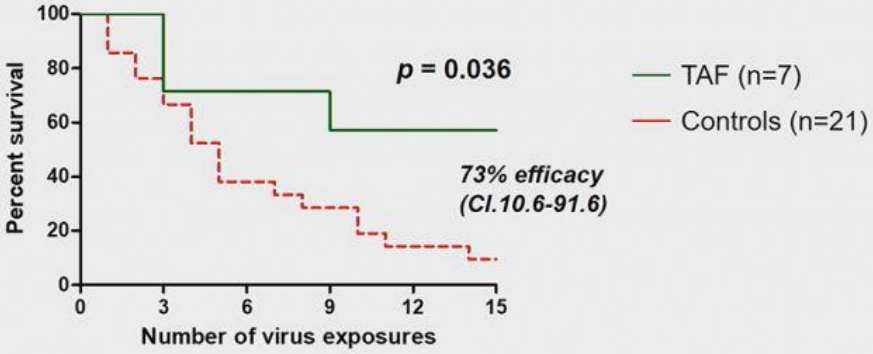
Similar infection outcome in real time and historical controls



- ❑ No difference in infection rates (p=0.5, Fisher's Exact test)
- ❑ No difference in time to RNA detection (p=0.32, Log-Rank Test)

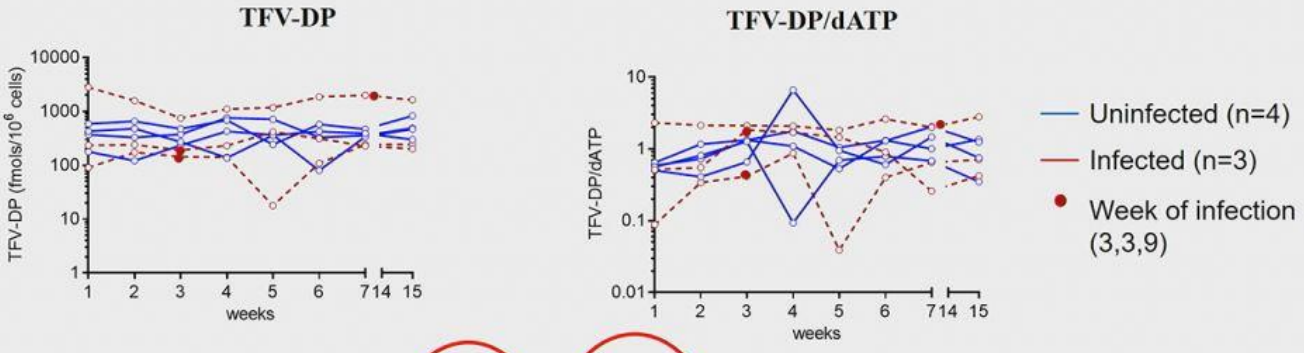
Radzio et al., PLoS One 2012
Srinivasan et al., PloS One 2016
Ross et al., ARHR 2014

Efficacy of single-agent TAF against vaginal SHIV infection



(p=0.194 vs real time controls only)

Similar TFV-DP levels and TFV-DP/dATP ratios in PBMCs among protected and infected animals



	TFV -DP	TFV-DP/dATP ratio
Infected (n=3)	351 (143 -1568)	0.68 (0.37 -2.1)
Uninfected (n=4)	331 (236 -584)	1.04 (0.70 -1.2)
	p = 0.36	p = 0.98

Conclusions

- A clinically equivalent dose of TAF administered orally -24h/+2h after virus exposure resulted in higher TFV-DP levels in PBMCs compared to TDF but conferred moderate vaginal protection
  - High (~350 fmols/10^6 cells) TFV-DP levels in protected and infected animals
  - dATP levels not related to the lack of protection seen in some animals
  - Threshold for high protection likely above 350 fmols/10^6 cells

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- Findings point to an important contribution of FTC in the protection seen with FTC/TAF
- Results highlight the importance of defining the TFV-DP levels in PBMC associated with complete vaginal protection from single agent TAF

Study limitations

- Only 2 doses of TAF (-24h/+2h) per week
  - Limited TFV-DP accumulation in PBMC and vaginal tissues possible
  - Unknown if TDF alone given at -24h/+2h confers vaginal protection in the macaque model
- Unknown if other routes of TAF delivery (i.e implants) would increase efficacy