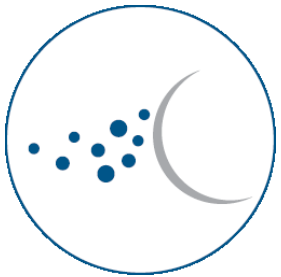
Post exposure prophylaxis with single doses of combination EVG/COBI/FTC/TAF protect macaques against Rectal SHIV Infection

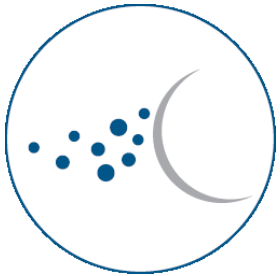
Ivana Massud Ph.D.

Centers for Disease Control and Prevention, Atlanta, GA. USA



Conflicts of Interest

Disclosure: named in a US Government patent application on HIV- post-exposure prophylaxis



On demand PEP for HIV prevention

- Post exposure prophylaxis (PEP) reduces risk of HIV acquisition following occupational and non-occupational exposure (28 days ART regimen)

- On-demand PEP regimens that do not require daily adherence or anticipation of sex may be a preferred and cost-effective prevention option against sexual HIV acquisition

- On-demand PrEP with 2 pills of TDF/FTC 24h prior to sexual activity followed by 1 pill 24h after first dose and a fourth pill 24h later was associated with 86% reduction in the risk of infection *(Molina et.al 2015)*

On demand PEP for HIV prevention

- Integrase inhibitors are attractive candidates for PEP
  - Act in a late stage of the replicative cycle
  - Previous studies showed protection using RAL gel applied as PEP 3h after vaginal exposure in macaques*(Dobard, et. al 2014)*
- Focus on elvitegravir (EVG)
  - Penetrates more efficiently than DTG/RAL in rectal and vaginal tissues after oral dosing in macaques; also highest antiviral activity *(Massud et.al 2015)*
  - High adherence and low adverse events in clinical studies of EVG for PEP *(Valin et.al 2016, Inciarte et.al 2017, Mayer et.al 2017)*

Objective

Investigate if a short and potent on demand regimen containing 1-2 oral doses of combination EVG/COBI/FTC/TAF can prevent rectal SHIV infection in macaques

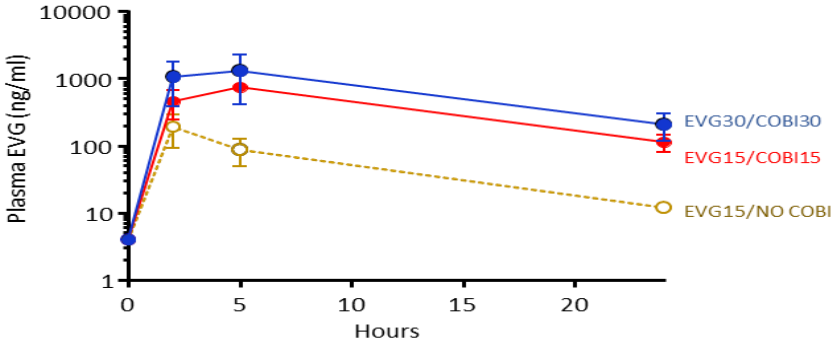
- Identify drug doses that result in plasma/intracellular drug concentrations that are within the range seen in humans
- Define window for an effective post exposure intervention

Methods

- Clinical equivalent doses for EVG, COBI, TAF, and FTC
  - Rhesus macaques (n=3 per dose) received an oral dose by gavage
  - Drug levels measured in plasma, PBMC and rectal biopsies by LC-MS/MS

- Assessment of rectal efficacy
  - Macaques exposed rectally to low doses of $SHIV_{162p3}$ (up to 8 challenges)
  - Challenges done every 2 weeks to minimize residual systemic drug levels
  - Infection monitored by serology and PCR amplification of SHIV RNA in plasma and SHIV DNA in PBMC and lymph nodes

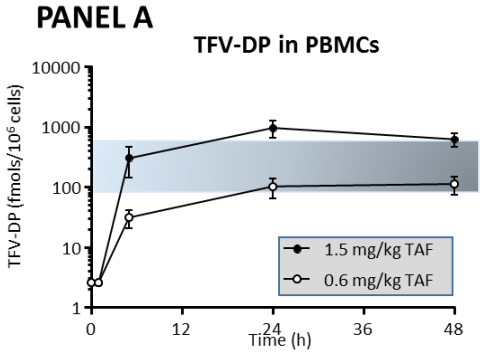
Cobicistat efficiently boosts EVG in plasma

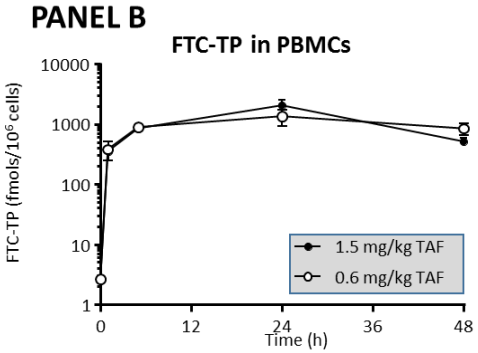


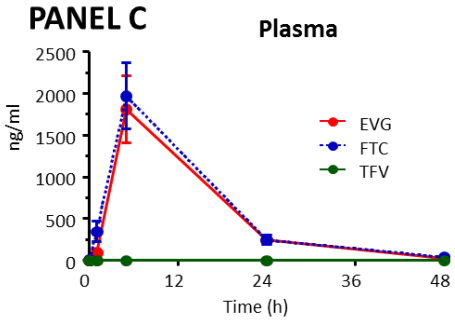
EVG/COBI (mg/kg)	$AUC_{0\text{-}24h}$ (ng*h/ml)	Cmax (ng/ml)	C_{24h} (ng/ml)
15/-	1,749	191	12
15/15	12,161	752	114
30/30	22,720	1,565	238
***Humans 150/150**	**27,000**	**2,660**	**490**

**J Acquir Immune Defic Syndr 2010*

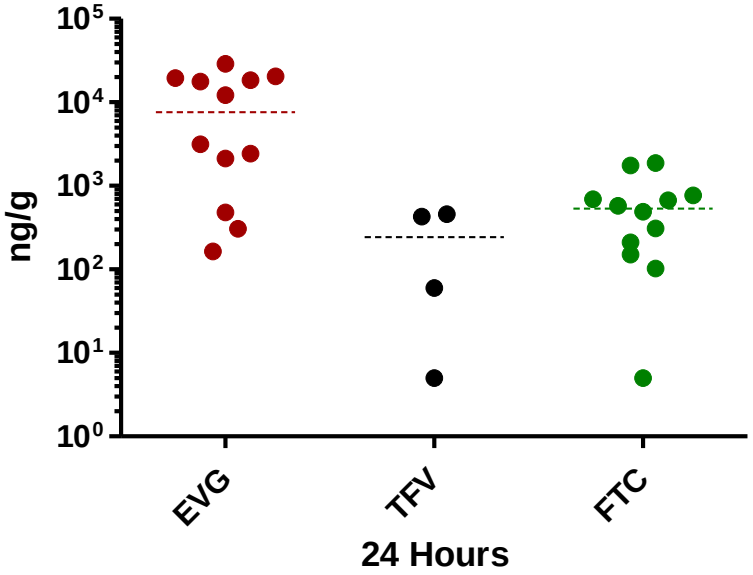
PK profile of EVG/COBI/FTC (30/30/20 mg/kg) with 0.6 or 1.5 mg/kg of TAF



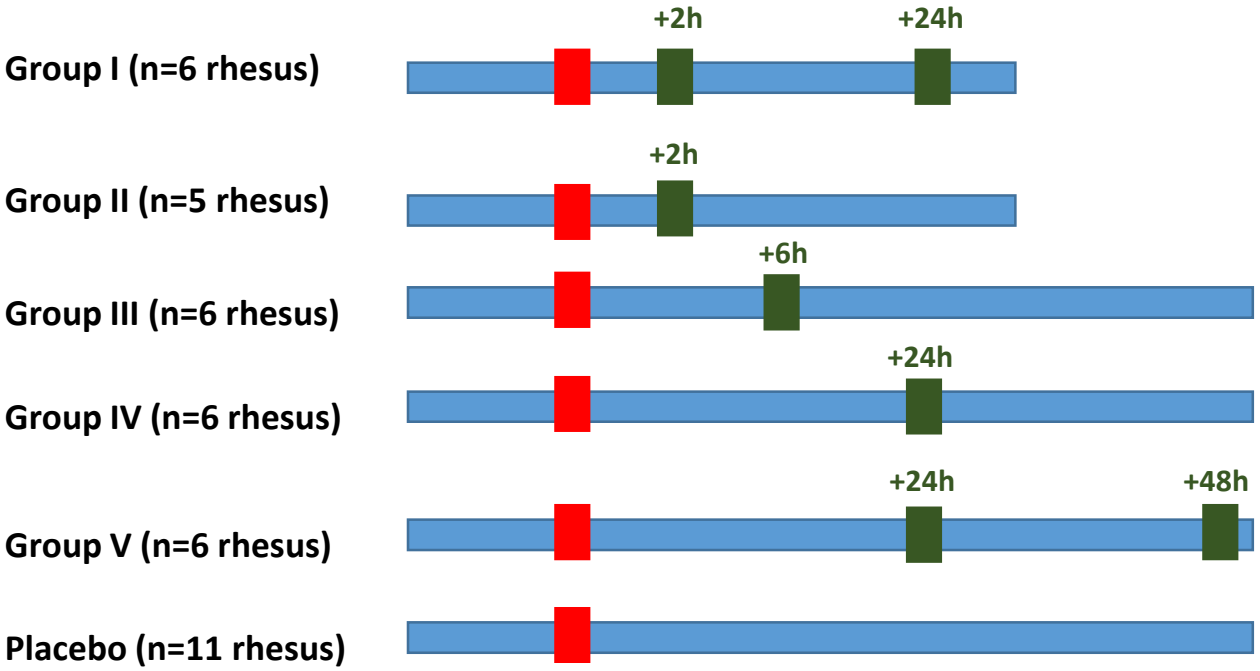




Drug penetration in rectal tissues after an oral dose of EVG/COBI/FTC/TAF (30/30/20/1.5 mg/kg)



Efficacy of EVG/COBI/FTC/TAF as PEP against rectal SHIV infection: study design



- Up to 8 rectal virus exposures
- Exposures done every 2 wks to minimize residual drug

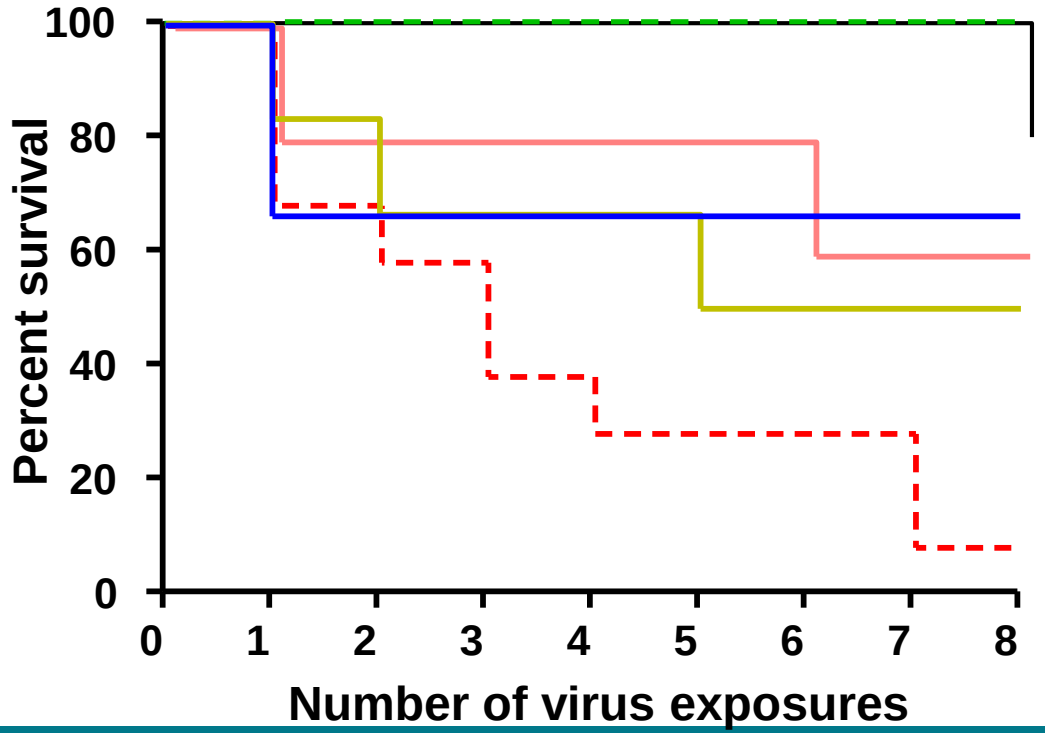
SHIV challenge

EVG/COBI/TAF/FTC

Efficacy of EVG/COBI/FTC/TAF as PEP against rectal SHIV infection

- **Oral FTC/TDF +2h+24h:** 80% efficacy in preventing rectal SHIV infection (p:0.03)
- **Subcutaneous FTC/TFV +24+48:** Lack of efficacy in preventing rectal SHIV infection

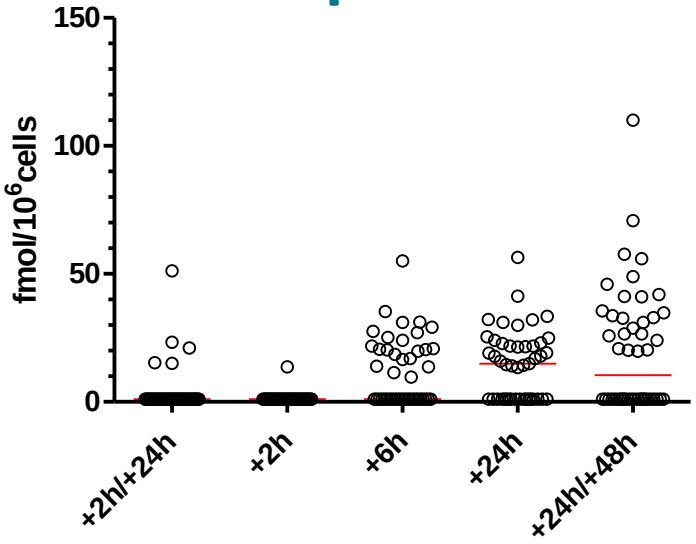
(Garcia Lerma, et. al Sci Transl Med 2010)



	Efficacy
Controls	
+2h/+24h; p=0.0019	92%
+2h; p=0.0005	100%
+6h; p=0.011	80%
+24h; p=0.057	65%
+24h/+48h; p=0.013	77%

P>0.05

Intracellular drug levels in PBMC at the time of virus exposure



	+2h+24h	+2h	+6h	+24h	+24h+48h
TFV-DP (median/range)	**BLOQ**	**BLOQ**	**7.6** (BLOQ-25)	**17.5** (BLOQ-21)	**13.8** (BLOQ-110)

FTC-TP were undetectable at all time points

Conclusions

- High efficacy with 1 or 2 EVG/COBI/TAF/FTC oral doses initiated within 24h after rectal virus exposure
- EVG/COBI/FTC/TAF oral dose is currently under evaluation as PrEP in a macaque model
- These results identify novel on-demand PEP regimens with a wide dosing window and support efficacy studies in humans

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For more information please contact Centers for Disease Control and Prevention
1600 Clifton Rd NE, Atlanta, GA 30333
Phone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov
Web: http://www.cdc.gov