Macaque models of PEP: current knowledge and gaps

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Disclosure

Named in a US Gov patent on “HIV Post-exposure Prophylaxis”

Macaque models of HIV PrEP and PEP

- ❑ **Virus exposures done under controlled conditions**
- ❑ **Gold standard for preclinical evaluation of PrEP**
  - Repeat low-dose SHIV exposure models (rectal, vaginal, penile) enabled proof-of-concept studies
  - Strong predictor of clinical efficacy (daily, on-demand oral PrEP; LA injectables)
  - Extensively used to evaluate ARVs and novel PrEP delivery systems
- ❑ **For PEP, early studies with TFV informed development of guidelines**
  - First proof of concept demonstrated the importance of treatment duration and timing of initiation
  - Models may help to investigate new PEP agents and potential impact on HIV diagnostics and resistance
  - Models may support ranking of candidate PEP products and prioritization for human testing

Tsai, Science 1995; Tsai, J Virol 1998; Otten, J Virol 2000; Garcia-Lerma, Current Op HIV/AIDS 2022

Early infection, PrEP, and PEP

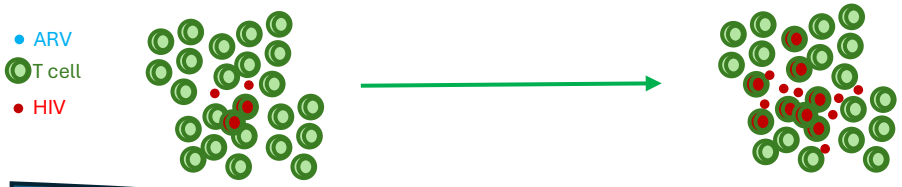
Hours to ~7 days

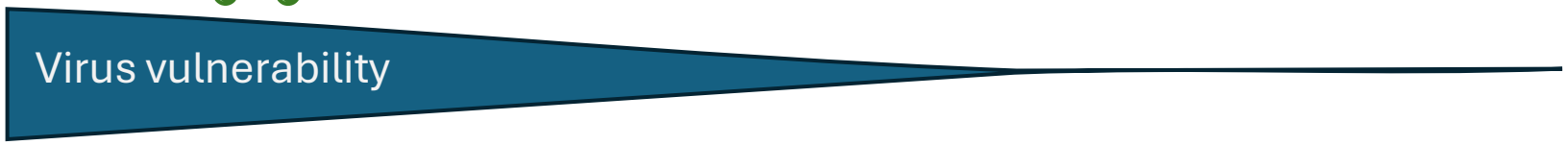
Small founder population
Infection rapidly established within 2h-3 days
Mainly in cervicovaginal tissues
Highly focal - small clusters of productively infected cells (40-50 cells)
Extremely small quantities in systemic lymphoid tissue within 1-3 days

Local expansion
Locally/draining lymph nodes
Immune activation/recruitment of susceptible target cells → **signal amplification.**

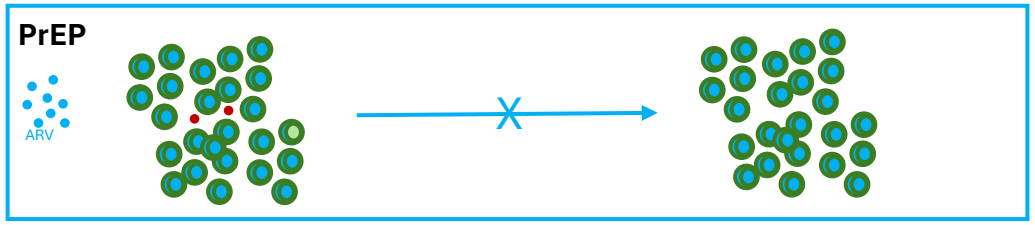
7-10 days

Systemic dissemination
Self-propagating infection in peripheral lymph nodes → **systemic spread/viremia.**

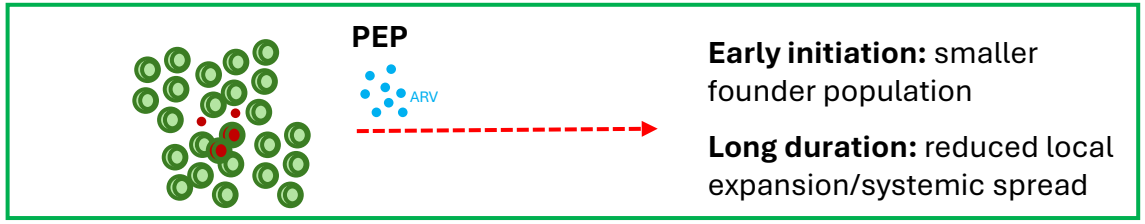




HIV target cells are already protected



HIV target cells are not protected



Early initiation: smaller founder population

Long duration: reduced local expansion/systemic spread

Success is a function of timing of initiation and duration of treatment

Haase, Nature 2010, Annu Rev Med 2011; Hu, J Virol 2000; Miller, J Viol 2005

Understanding SIV/SHIV challenge models

Model	Eclipse phase	Number of T/F variants	Innate immune activation	Rate of infection
High SIV/SHIV dose (usually >1,000 $TCID_{50}$)	~4 days	>10	High	1
Low SIV/SHIV dose (usually 10-50 $TCID_{50}$)	7-9 days	1-2	Low	0.5-0.25
HIV infection	8-10 days	1 (~70-80%) 2-5 (20-30%)	Low	0.0138-0.0004*

* Receptive anal intercourse, insertive penile-vaginal intercourse

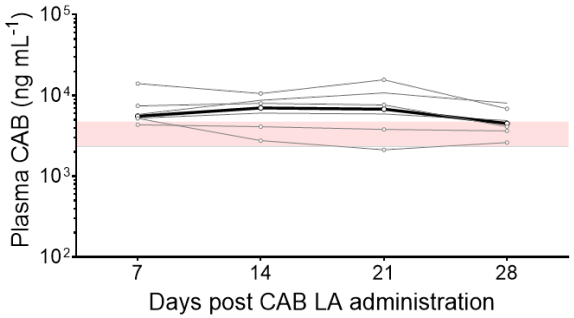
Liu, J Virol 2010; Keele, PNAS 2008

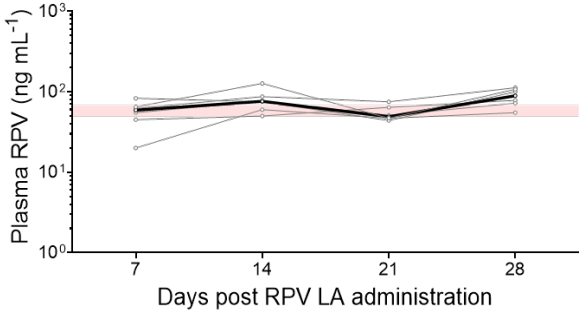
PEP testing in the high-dose SIV/SHIV challenge model

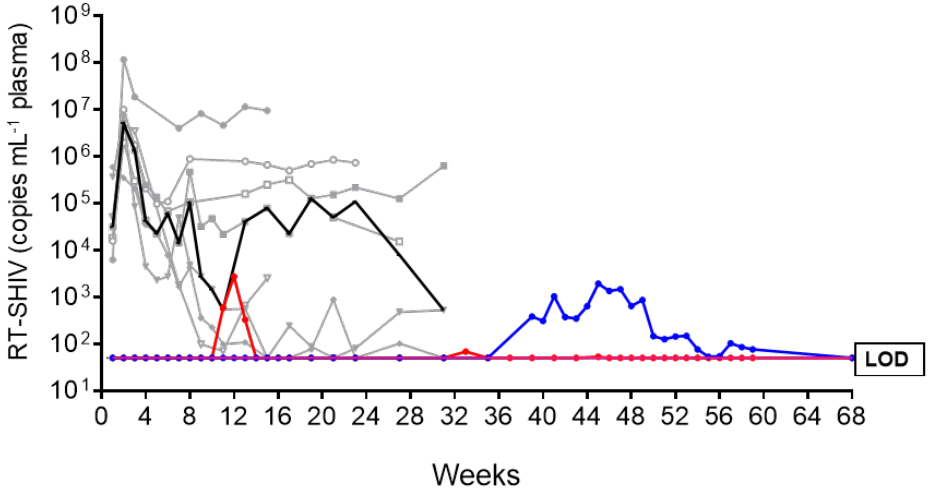
- **Commonly used for preclinical testing of PEP**
  - Controls infected after a single challenge - reduces animal use
  - The preferred macaque model (repeated low-dose virus exposures) not always feasible for PEP due to long drug washout periods or complex animal procedures
- **Several studies completed with long-acting injectables and simplified oral PEP regimens**
  - Injectable CAB LA/RPV LA
  - Weekly oral islatravir
  - Short (7 days) oral combinations; FTC/TAF/EVG/COBI or FTC/TAF/BIC
  - In all studies, PEP was initiated at 24h

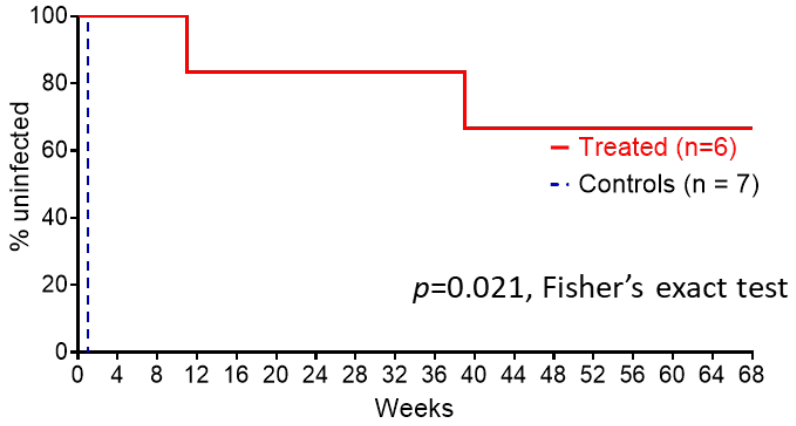
Efficacy of long-acting PEP - injectable CAB/RPV LA

Single exposure (rectal) to a high dose of SHIV
PEP initiated at 24h
One IM injection of **CAB/RPV LA**







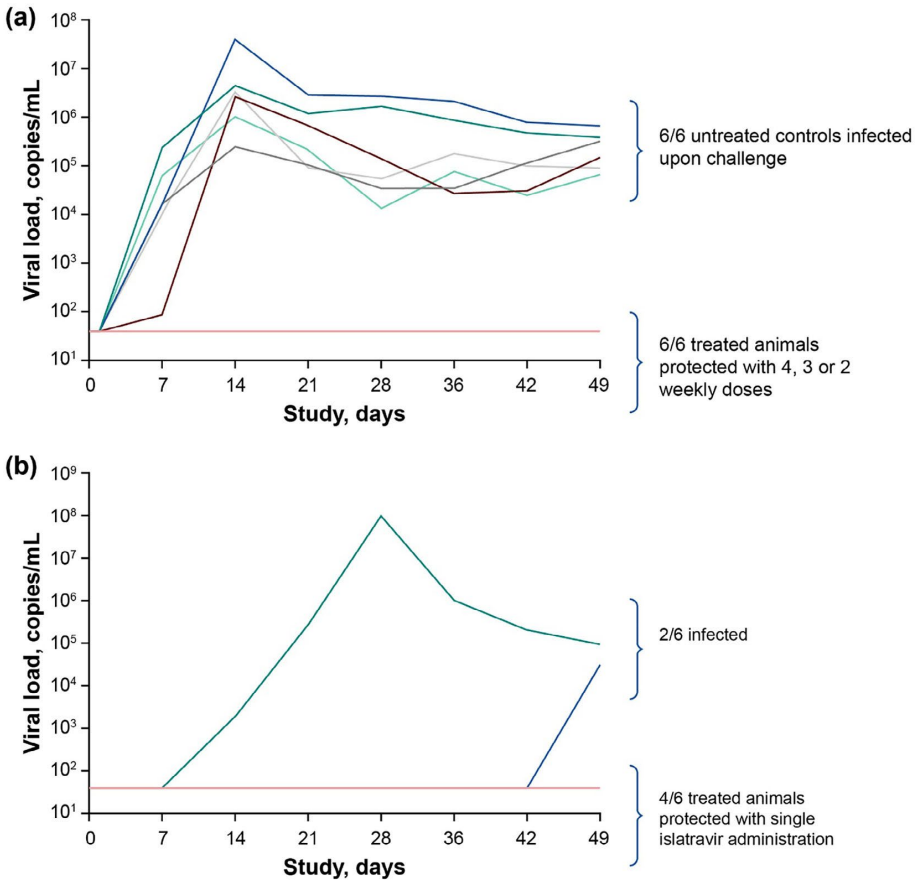


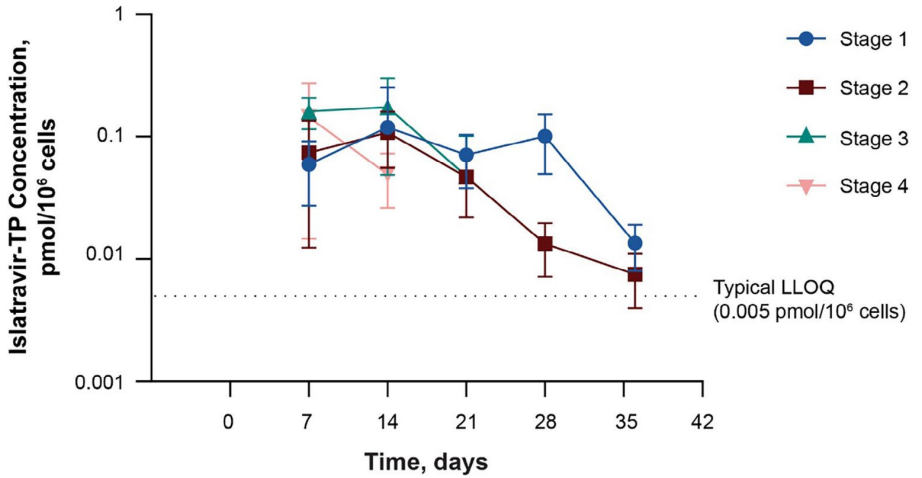
- ✓ Significant protection (estimated efficacy of 66.7%; p=0.057)
- ✓ Delayed SHIV detection and seroconversion in breakthroughs (3-10 months)
- ✓ Selection of RPV resistance

Srinivasan et al., eBioMed 2026

Efficacy of long-acting PEP - weekly oral islatravir

Single exposure (IV) to a high dose of SIV
PEP initiated at 24h
Islatravir given orally once a week



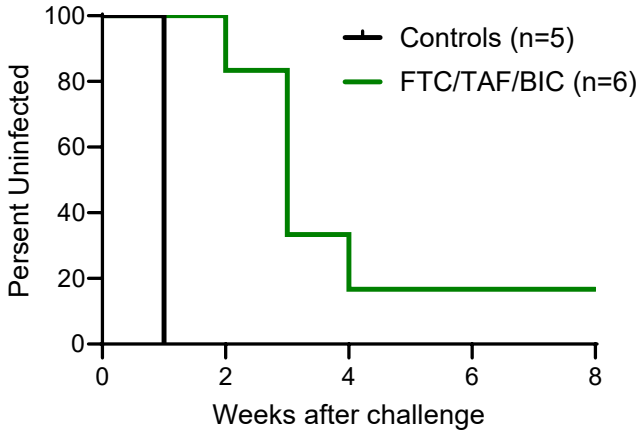


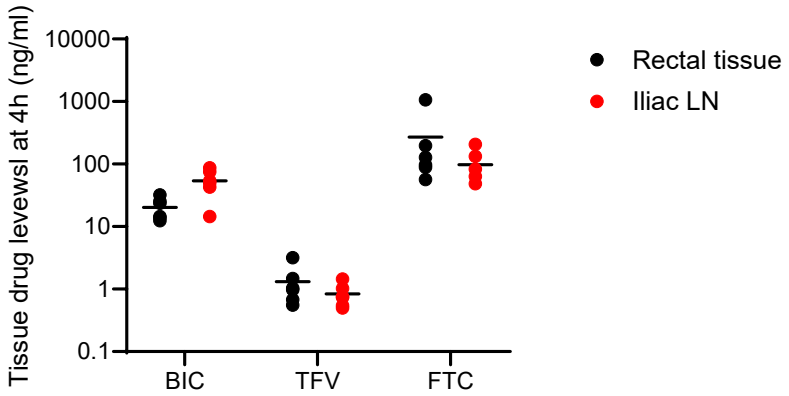
**Macaque ISL dose models the weekly 2 mg human dose*

Markowitz et al., J Int AIDS Soc.2025

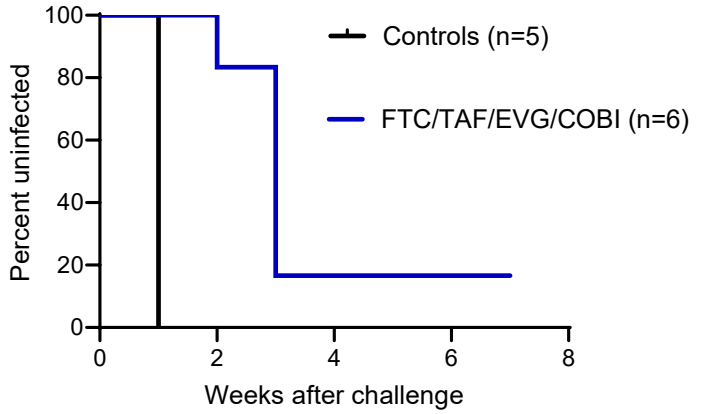
Efficacy of short oral PEP - 7 daily doses

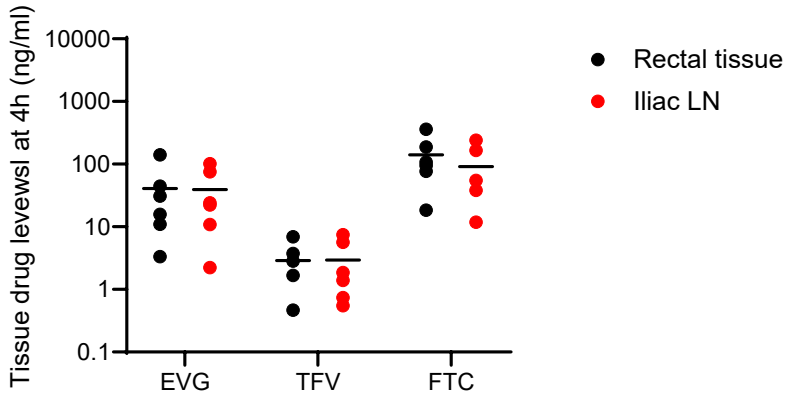
Single exposure (rectal) to a high dose of SHIV
PEP initiated at 24h
FTC/TAF/BIC given for 7 consecutive days





Single exposure (rectal) to a high dose of SHIV
PEP initiated at 24h
FTC/TAF/EVG/COBI given for 7 consecutive days

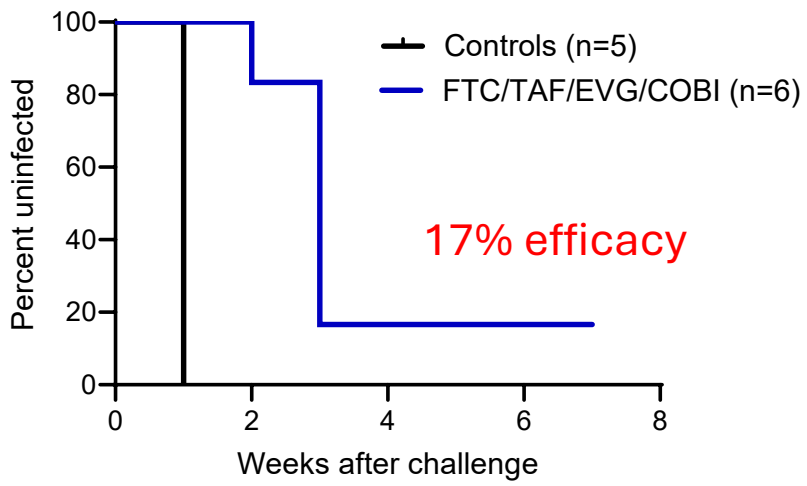




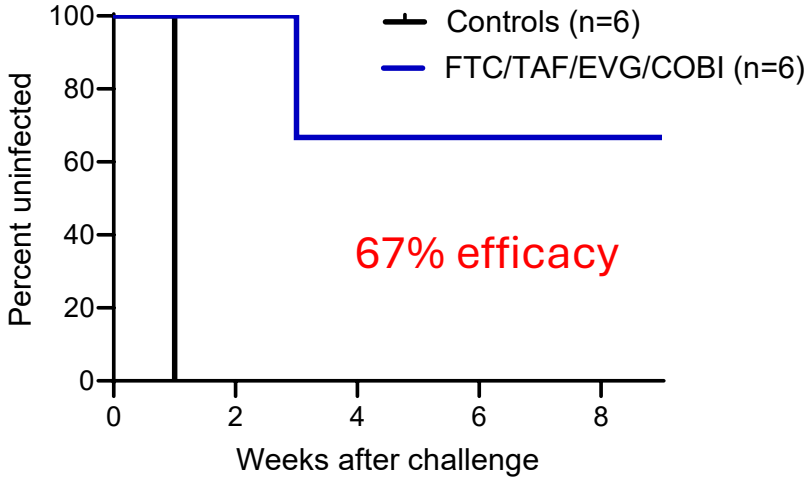
Makarova et al., in preparation

FTC/TAF/EVG/COBI seems more effective against lower SHIV doses

High SHIV dose
(3,000 $TCID_{50}$ RT-SHIV)



Lower SHIV dose
(112 $TCID_{50}$ SHIV162p3)



Makarova et al., in preparation

Efficacy of PEP in the high-dose SIV/SHIV challenge model

	PEP modality	PEP initiation	Drug coverage	Size of virus inoculum	Route of virus inoculation	Efficacy	References
Long PEP	Daily subcut TFV	24h	28 days	SIV, 10^3 $TCID_{50}$	IV	75%-100%	Tsai, J Science 1995 Tsai, J Virol 1998
Long PEP	Weekly oral ISL*	24h	14-28 days	SIV, 10×AID_{50}	IV	100%	Markowitz, J Int AIDS Soc 2025
Long PEP	One injection of CAB/RPV LA	24h	28 days	RT-SHIV, $3x10^3$ $TCID_{50}$	Rectal	66.7%	Srinivasan, eBioMed 2026
Short PEP	Oral FTC/TAF/BIC	24h	7 days	RT-SHIV, $3x10^3$ $TCID_{50}$	Rectal	No efficacy	Makarova et al., unpublished
Short PEP	Oral FTC/TAF/EVG/COBI	24h	7 days	RT-SHIV, $3x10^3$ $TCID_{50}$	Rectal	No efficacy	Makarova et al., unpublished

Summary and gaps

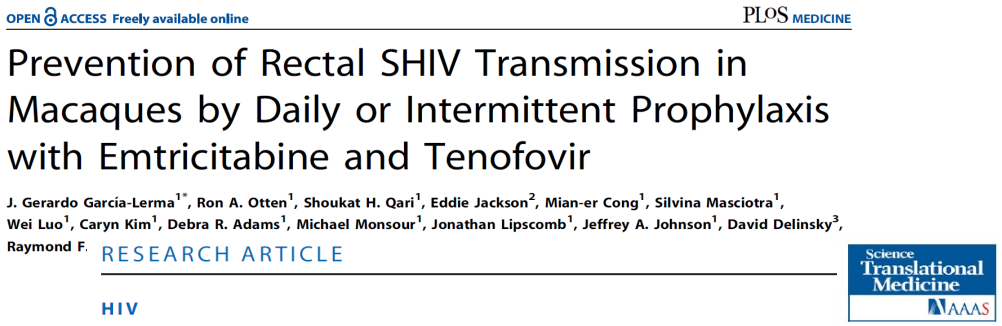
- **When initiated at 24h, long-acting PEP seems more effective than short-duration oral PEP**
  - Significant protection with CAB/RPV LA and weekly ISL under high SHIV challenge doses is remarkable
  - LA injectables may introduce diagnostic challenges and require extended follow up testing
- **SHIV model matters**
  - Short PEP with FTC/TAF/EVG/COBI provided some protection at lower virus inoculum (though infection rates in untreated controls remained high)
  - Unclear how FTC/TAF/BIC would perform at lower SHIV doses
- **ISL data supports the evaluation of next-generation approaches**
  - Weekly ISL/LEN or single-dose MK-8527
  - Important to determine if timing of PEP initiation is more forgiving with these agents

PEP testing using the repeat low dose model

Model	Eclipse phase	Number of T/F variants	Innate immune activation	Rate of infection
Low SIV/SHIV dose (usually 10-50 $TCID_{50}$)	7-9 days	1-2	Low	0.5-0.25
HIV infection	8-10 days	1 (~70-80%) 2-5 (20-30%)	Low	0.0138-0.0004*

* Receptive anal intercourse, insertive penile-vaginal intercourse

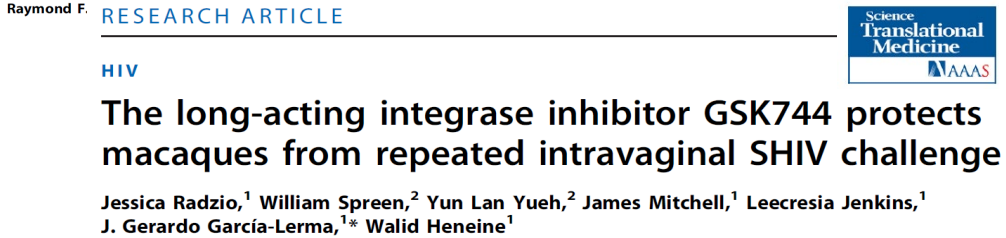
Extensively used and validated for PrEP



OPEN ACCESS Freely available online PLOS MEDICINE

Prevention of Rectal SHIV Transmission in Macaques by Daily or Intermittent Prophylaxis with Emtricitabine and Tenofovir

J. Gerardo García-Lerma[1*], Ron A. Otten[1], Shoukat H. Qari[1], Eddie Jackson[2], Mian-er Cong[1], Silvina Masciotra[1], Wei Luo[1], Caryn Kim[1], Debra R. Adams[1], Michael Monsour[1], Jonathan Lipscomb[1], Jeffrey A. Johnson[1], David Delinsky[3], Raymond F.



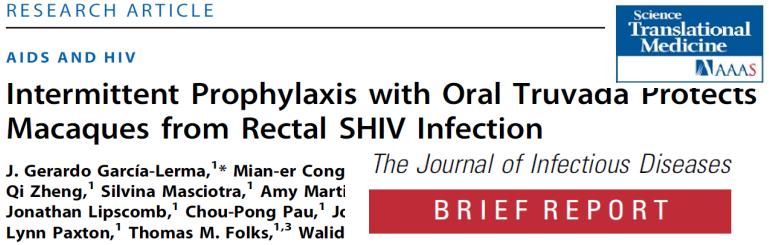
RESEARCH ARTICLE

HIV

Science Translational Medicine AAAS

The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge

Jessica Radzio,[1] William Spreen,[2] Yun Lan Yueh,[2] James Mitchell,[1] Leecresia Jenkins,[1] J. Gerardo García-Lerma,[1*] Walid Heneine[1]



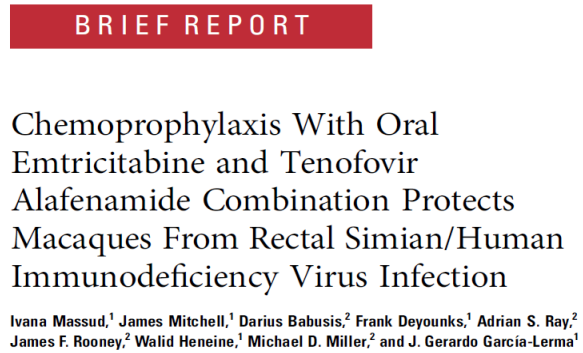
RESEARCH ARTICLE

AIDS AND HIV

Science Translational Medicine AAAS

Intermittent Prophylaxis with Oral Truvada Protects Macaques from Rectal SHIV Infection

J. Gerardo García-Lerma,[1*] Mian-er Cong Qi Zheng,[1] Silvina Masciotra,[1] Amy Marti Jonathan Lipscomb,[1] Chou-Pong Pau,[1] Jo Lynn Paxton,[1] Thomas M. Folks,[1,3] Walid



The Journal of Infectious Diseases

BRIEF REPORT

Chemoprophylaxis With Oral Emtricitabine and Tenofovir Alafenamide Combination Protects Macaques From Rectal Simian/Human Immunodeficiency Virus Infection

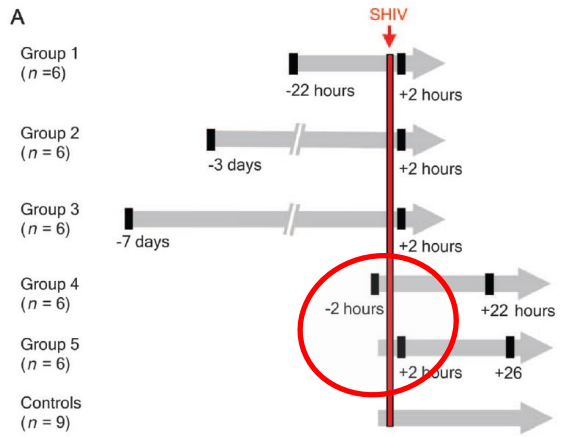
Ivana Massud,[1] James Mitchell,[1] Darius Babusis,[2] Frank Deyounks,[1] Adrian S. Ray,[2] James F. Rooney,[2] Walid Heneine,[1] Michael D. Miller,[2] and J. Gerardo García-Lerma[1]

PEP testing in the repeat-low dose SIV/SHIV challenge model

- ❑ More robust model validated with PrEP
- ❑ Higher statistical power and less animal numbers
  - Repeated virus exposures
  - Controls not infected after a single virus challenge
  - Evaluates protection against multiple virus exposures
- ❑ For PEP testing, only feasible for drugs with short half-lives
- ❑ Studies done with 1-2 oral doses “on-demand” and two/three drug combinations
  - FTC/TAF and FTC/TDF
  - FTC/TAF/EVG/COBI

Two-drug combination

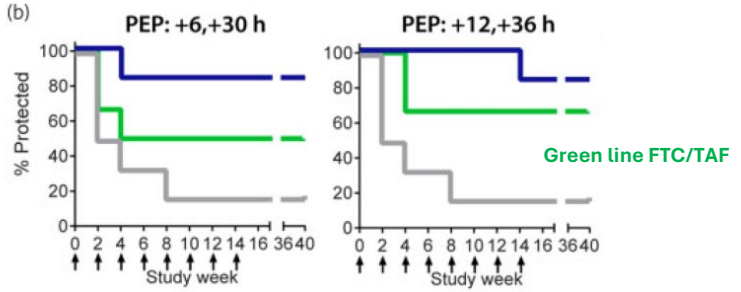
Repeated exposures (rectal) to low dose SHIV
PEP initiated at 2h
Two doses of FTC/TDF



PrEP (efficacy of ~75%; boosted to 100% with double dose)
PEP (efficacy of ~75%)

✓75% efficacy if initiated early (+2h/+24h)
✓Unknown if double dose or longer duration (5-7 days) can boost efficacy

Repeated exposures (rectal) to low dose SHIV
PEP initiated at 6-48h
Two doses of FTC/TAF



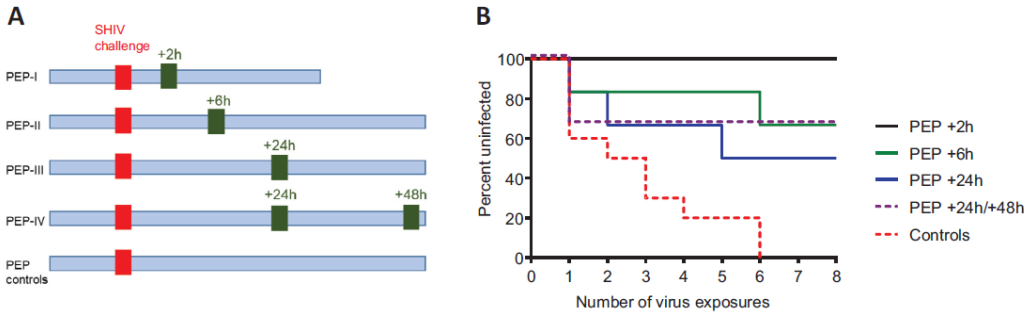
PEP dose	Efficacy	p value
+6h/+30h	57.8%	0.241
+12h/36h	78.2%	0.071
+24h/+48h	51.6%	0.251
+48h/+72h	2.7%	0.965

✓No efficacy if initiated as early as +6h/+30h suggests a short window for protection
✓Unknown if double dose of longer duration (5-7days) can provide protection

Garcia-Lerma et al., Sci Trans Med 2010; Bekerman et al., J Antimicrob Chemother 2021

Three-drug combination

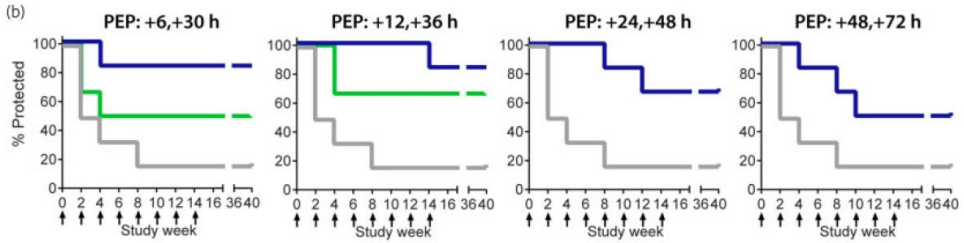
Repeated exposures (rectal) to low dose SHIV
PEP initiated at 2-24h
One/two doses of FTC/TAF/EVG/COBI



PEP dose	Efficacy	p value
+2h	100%	**0.001**
+6h	80.1%	**0.011**
+24h	64.6%	0.057
+24h/+48h	77%	**0.013**

- ✓ 80-100% efficacy with one dose given within +6h
- ✓ Efficacy reduced if initiated at 24h
- ✓ If initiated at +24h, protection may require 2-7 doses

Repeated exposures (rectal) to low dose SHIV
PEP initiated at 6-48h
Two doses of FTC/TAF/BIC



PEP dose	Efficacy	p value
+6h/+30h	90.1%	**0.036**
+12/+36h	81.7%	**0.046**
+24h/+48h	80.3%	0.055
+48h/+72	66.9%	0.134

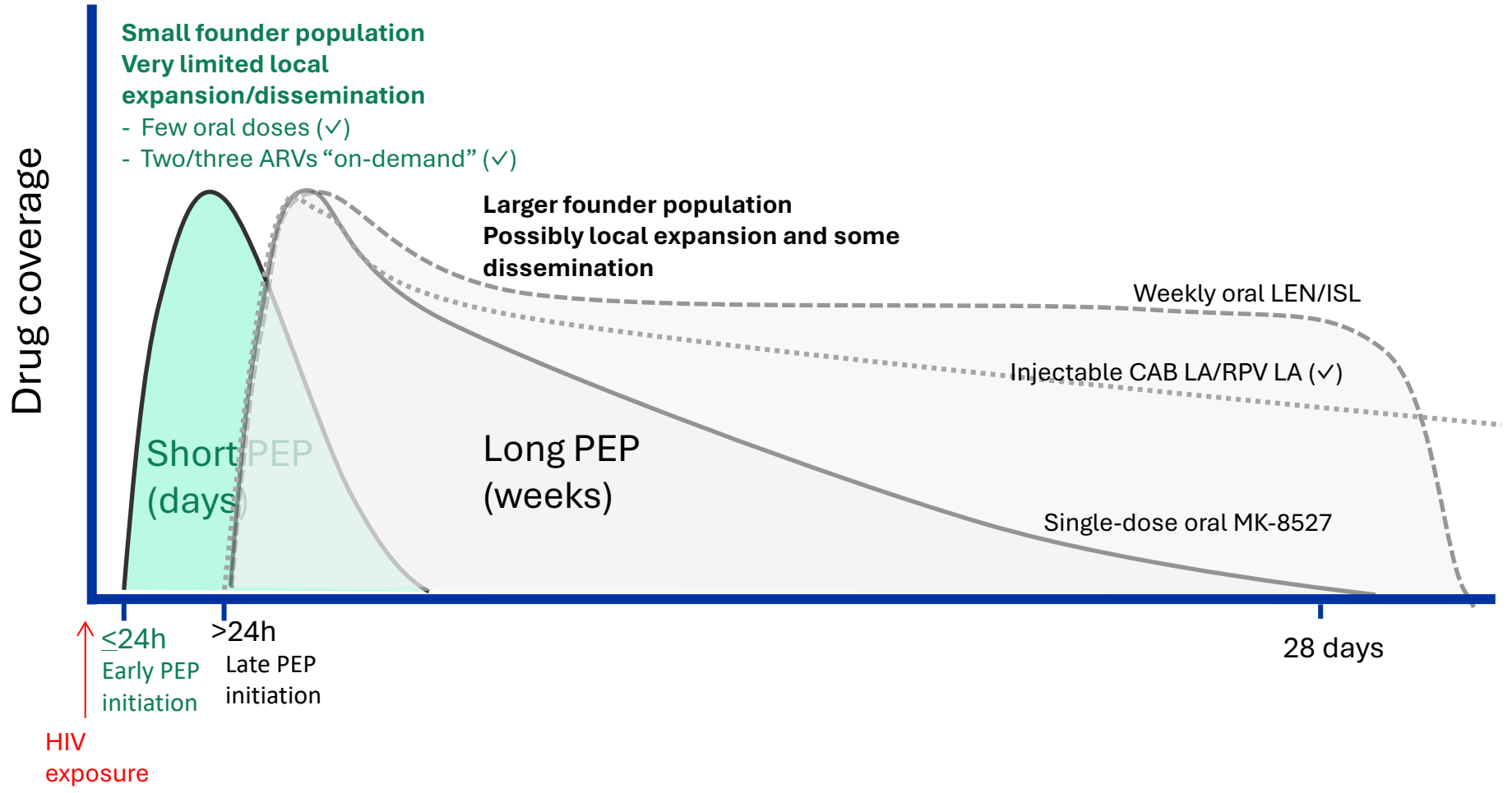
- ✓ 80-90% efficacy with two doses if initiated within 12h
- ✓ Efficacy reduced if initiated later
- ✓ If initiated at +24h, protection may require more that 2 doses

Massud et al., EBioMed 2020; Bekerman et al., J Antimicrob Chemother 2021

Summary and gaps

- Data suggest that 3-drug PEP may be more effective than two drugs in a short regimen
  - Unknown if double doses of FTC/TDF or FTC/TAF or a 5 to 7-day regimen can be protective
- For short-acting oral drugs, PEP initiation close to exposure is likely key
- For long-acting oral drugs like ISL or MK-8527, timing of PEP initiation may be more forgiving
  - Further evaluation needed
- Long-acting injectables may pose diagnostic challenges requiring long testing follow ups – also drug resistance concerns

Lessons learned from macaques



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