

# Complete protection against rectal transmission of an FTC-resistant SHIV162p3<sub>M184V</sub> mutant by intermittent prophylaxis with Truvada

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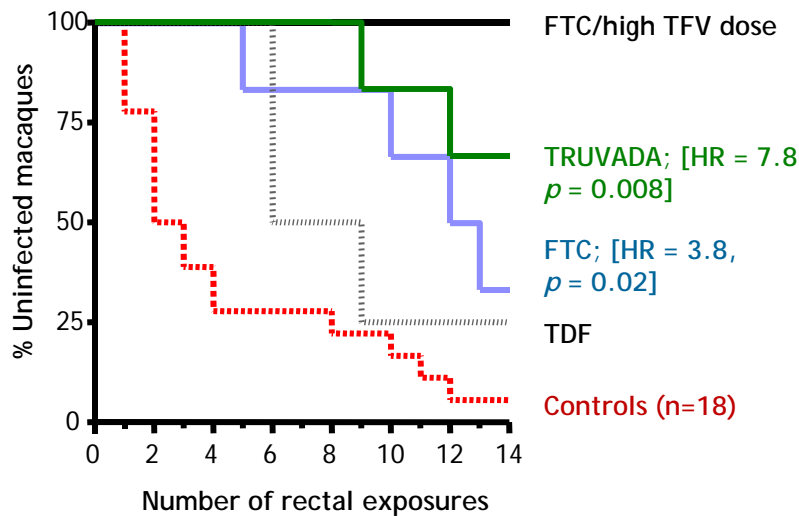
# Oral pre-exposure prophylaxis (PrEP)

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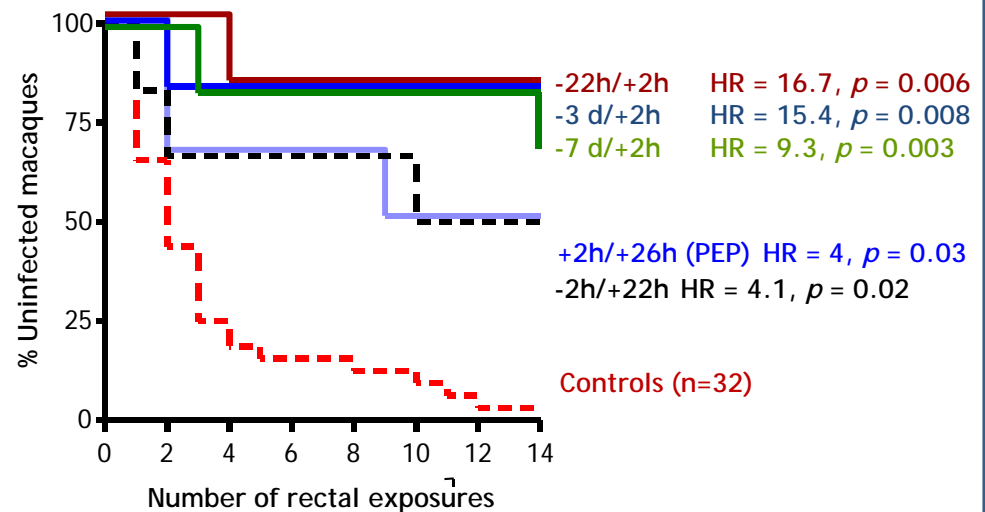
- Promising HIV prevention strategy
- Several clinical trials with daily TDF or Truvada ongoing with first results anticipated this year
- Animal models are important tools for preclinical PrEP research
  - Possibility to study different drugs and drug dosing strategies
  - Investigate relationship between protection and drug PK/PD
  - Explore viral and immunological dynamics in breakthrough infections including kinetics of drug resistance emergence

# Efficacy of daily and intermittent PrEP in a repeat low-dose rectal SHIV transmission model

## Daily PrEP



## Intermittent PrEP with Truvada



# Drug resistance emergence in PrEP failures

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- Protection by PrEP was not complete
- Animals continued treatment after confirmed infection
  - Daily TDF failures (n=3) monitored for 31 wks (range, 20-25)
  - Daily FTC (n=4) and Truvada (n=2) failures monitored for 23 wks (range, 13-29)
  - Intermittent Truvada failures (n=7) monitored for 13 wks (range 8-18)
- Resistance monitored by sequencing and allele-specific PCR

- Blunted (1-2 log<sub>10</sub>) wild type acute viremias
- 2 of the 6 daily FTC/Truvada failures developed M184V/I (one FTC and one Truvada) after 3-10 weeks
- No resistance in failures with intermittent Truvada (2 weekly drug doses)
- No K65R selection

# Can circulating FTC and TFV-resistant viruses compromise the efficacy of prophylaxis with Truvada?

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## **M184V**

- Common in patients failing treatment
- Frequently seen in SDRM (despite high fitness cost)
- Confers >100-fold resistance to FTC

## **K65R**

- Less prevalent in treated and untreated
- Confers resistance to both TFV (~2-4 fold) and FTC (~9 fold)
- B/non-B



- ✓ Drug concentrations at the virus portal of entry
- ✓ Transmission fitness
- ✓ Levels of drug resistance
- ✓ Residual antiviral activity
- ✓ Mutational interactions and complex phenotypic profiles (i.e., TFV hyper susceptibility mediated by M184V)

# Objective

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To investigate if Truvada maintains prophylactic efficacy against an FTC-resistant virus containing the M184V mutation

# Methods

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- **Generation of an FTC-resistant virus stock for macaque challenge studies**
  - R5-tropic SHIV162p3 isolate used in the repeat-low dose model of rectal/vaginal transmission
  - M184V introduced by site-directed mutagenesis (ATG→GTT)
  - In vitro and in vivo characterization of SHIV162p3<sub>M184V</sub>
- **Analysis of the prophylactic efficacy of Truvada against SHIV162p3<sub>M184V</sub>**
  - 2 dose intermittent Truvada regimen administered orally
  - Weekly rectal SHIV162p3<sub>M184V</sub> exposures

# Characteristics of SHIV162p3<sub>M184V</sub>

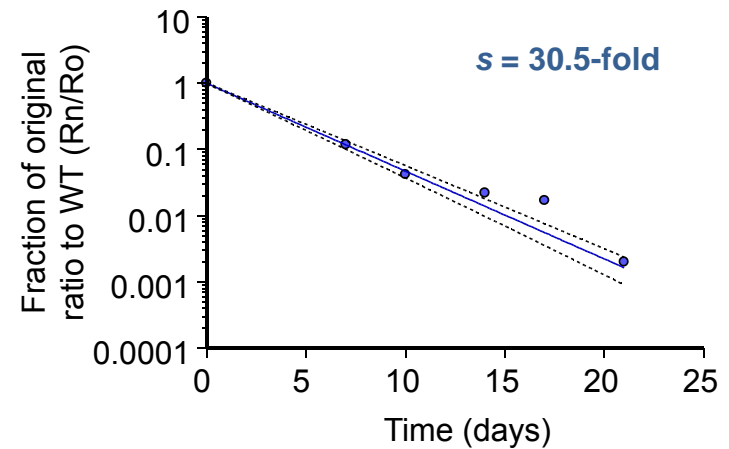
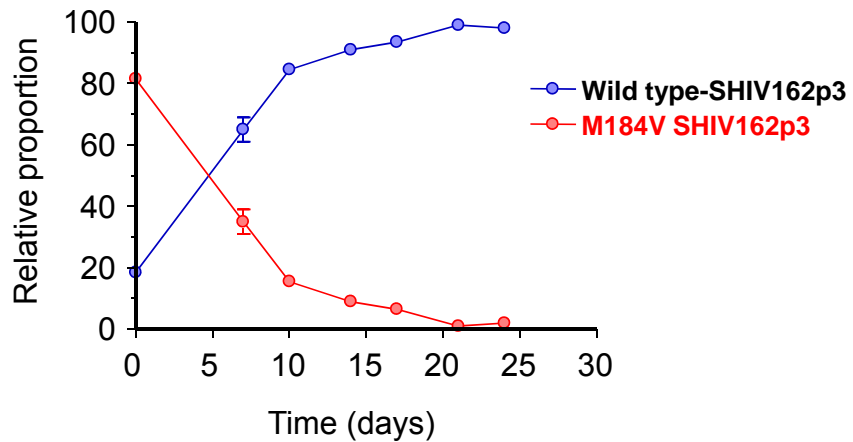
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Isolate	RNA copies/ml	TCID <sub>50</sub> / ml*	TCID <sub>50</sub> / RNA (x10 <sup>6</sup> )	IC <sub>50</sub> (fold)	
				FTC	TFV
SHIV162P3 <sub>wt</sub>	2.57 x 10 <sup>9</sup>	10,160	3.96	0.10	1.67
SHIV162P3 <sub>M184V</sub>	2.62 x 10 <sup>9</sup>	2,540	0.97	78.2 (>100)	0.50 (0.3)

\**Rhesus macaques PBMCs*

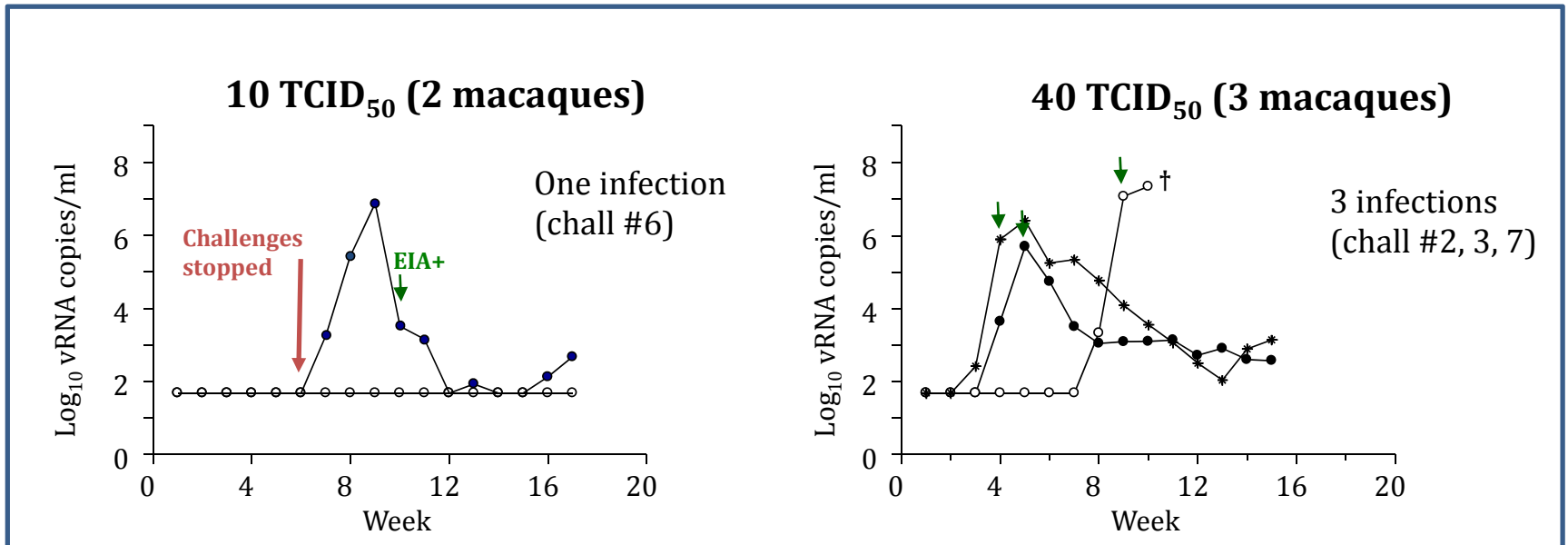
# M184V confers a high fitness cost in SHIV162P3

Dual infection competition assay  
in rhesus PBMCs



# Infectivity of SHIV162p3<sub>M184V</sub> in macaques

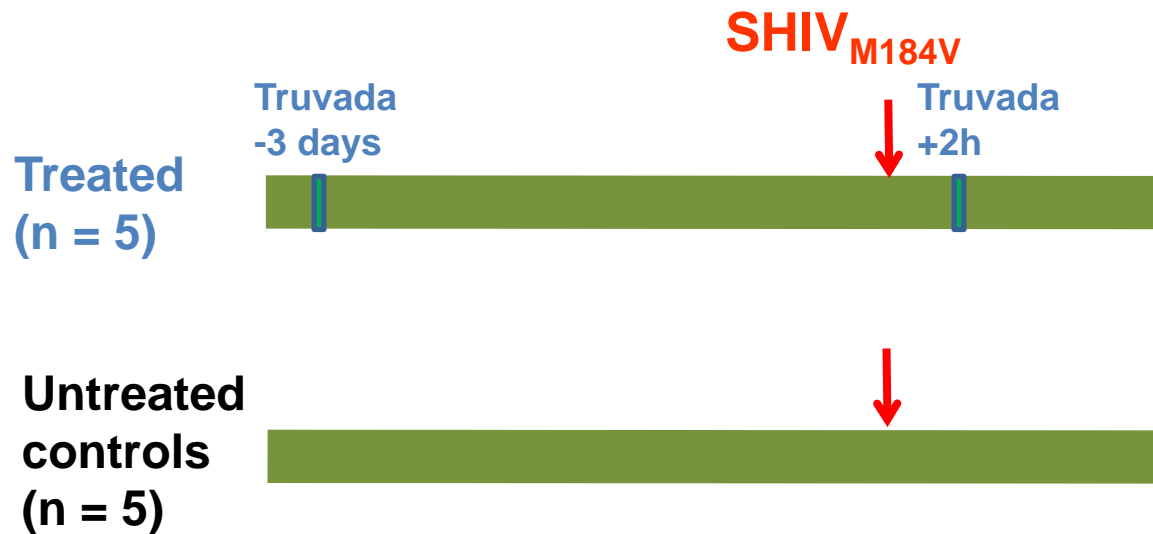
- Weekly rectal virus challenges
- Initial dose of 10 TCID<sub>50</sub> to mimic exposures with original WT SHIV162p3



# Efficacy study: design

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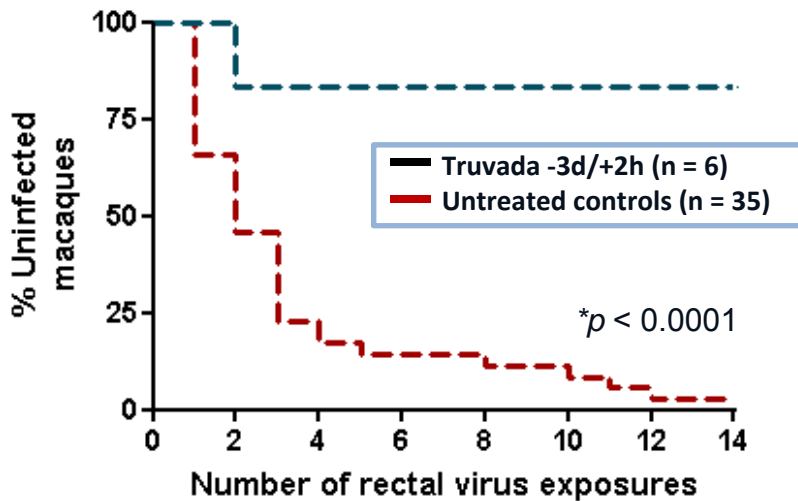
- Two arm efficacy study in Indian rhesus macaques



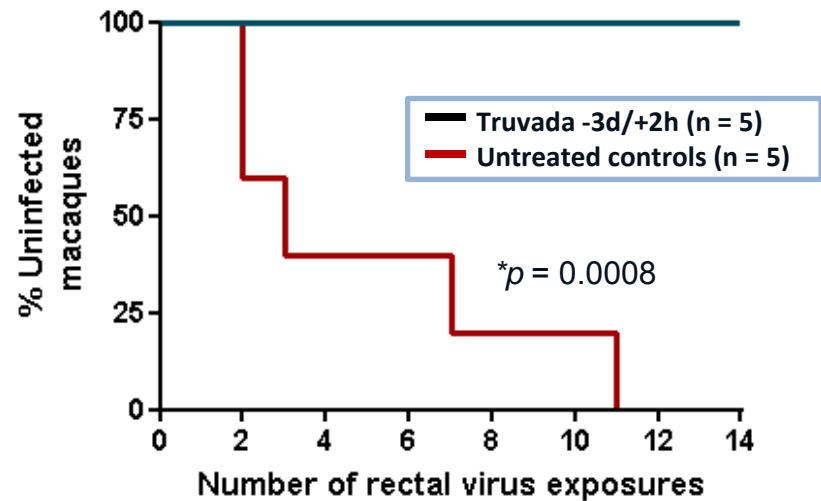
- Virus dose increased to 40 TCID<sub>50</sub>
- Weekly rectal SHIV162p3<sub>M184V</sub> exposures repeated for up to 14 weeks
- Infection monitored by serology and PCR amplification of viral RNA and DNA

# Efficacy of intermittent prophylaxis with Truvada against wild type and FTC-resistant SHIV

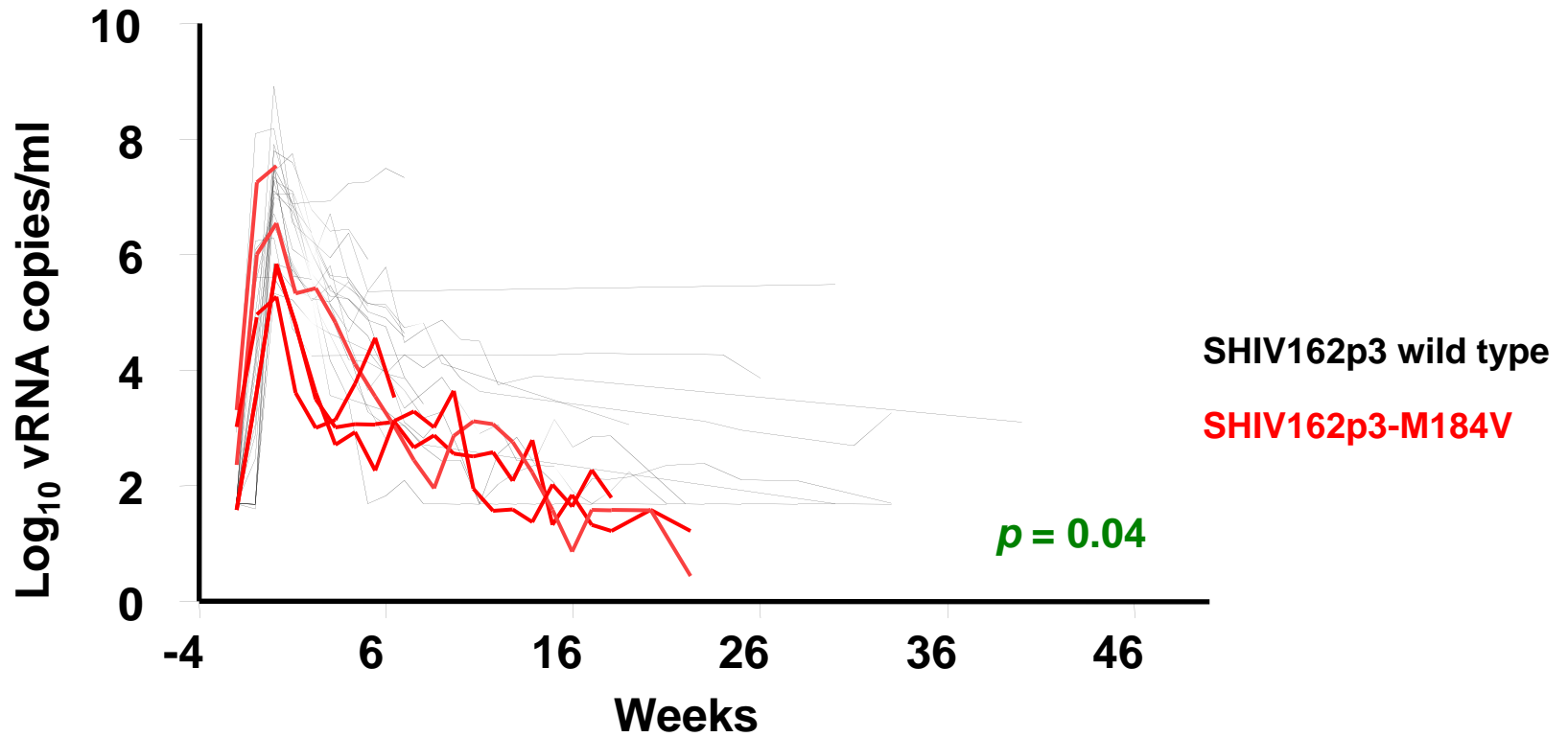
## Wild type SHIV162p3



## FTC-resistant SHIV162p3<sub>M184V</sub>



# Blunted acute M184V virus loads



# Summary

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- Intermittent prophylaxis with Truvada maintains efficacy against an FTC-resistant mutant in macaques
  - TFV hyper susceptibility conferred by M184V
  - Increased threshold for establishment of a productive infection due to low fitness of M184V viruses
  - Residual antiviral activity of FTC on M184V viruses
  - High FTC and TFV levels in rectal tissues (drug PK/PD dependence, PrEP modality, route of transmission)

# Summary

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- Findings suggest that high fitness cost of M184V may impact early acute viremias. Potential impact on early virus diversification and maturation of immune responses

# Acknowledgements

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