

Communicating about PrEP and MTN 001

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MTN-001 Study Drug

- TENOFOVIR
 - Oral
 - Vaginal
 - Oral + Vaginal

WHAT IS PREP?

**WHAT IS THE RATIONALE FOR
STUDYING TENOFOVIR AS PREP?**

What is PrEP?

- **Pre Exposure Prophylaxis**
 - A drug taken to PREVENT HIV infection BEFORE exposure
 - Can be administered ORALLY or TOPICALLY (microbicide)

- The idea of PrEP is not new...
 - Prophylaxis (e.g. mefloquine) for malaria prevention
 - Neviripine for preventing MTCT



Why PrEP?

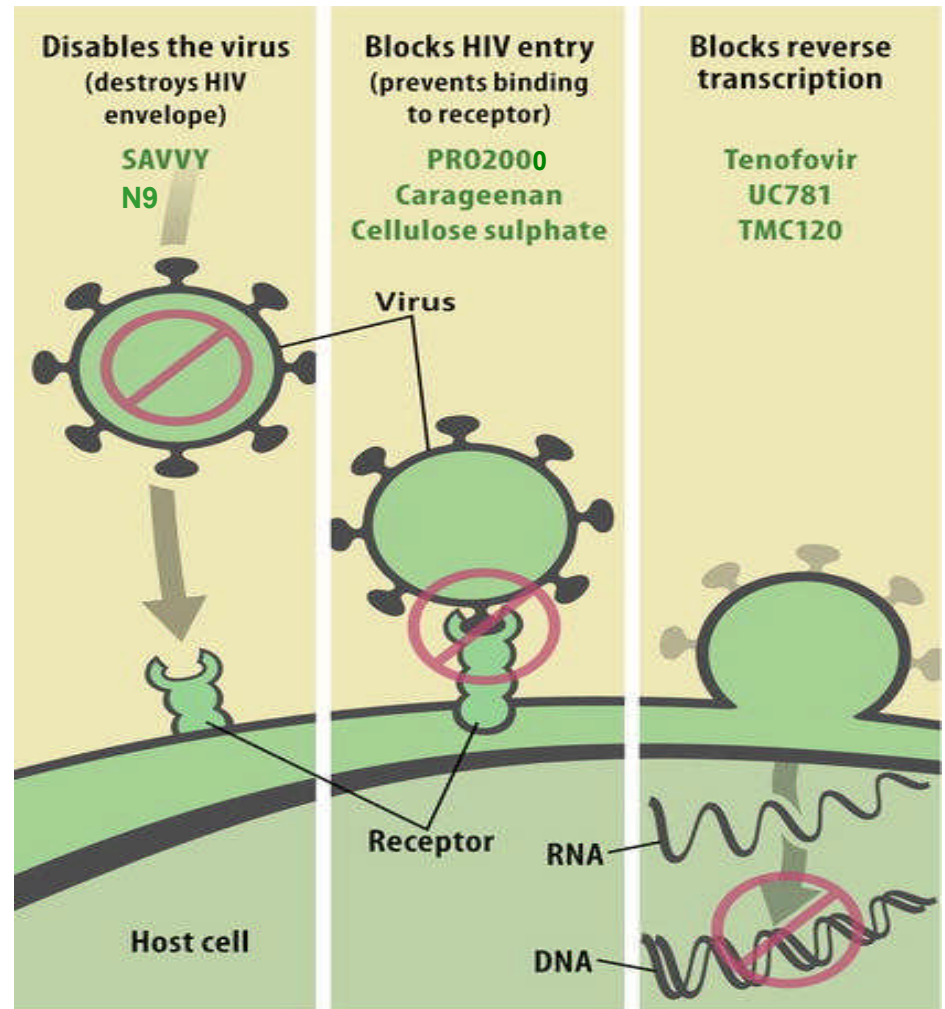
- Condom use and behavioral interventions not always feasible/negotiable
- Need a female-controlled strategy for HIV Prevention
- Vaccine may be a long time away
- Biomedical interventions are promising and have worked in the past

Microbicide Gel Evolution

First Generation
Surfactant

Second Generation
high molecular weight
anionically charged
sulphated polymers

Third Generation
Antiretroviral
compounds



Why Antiretroviral Compounds?

- May be advantageous to protect **cells** before exposure to virus
 - Mucosal tissue early site for HIV replication and CD4+ T-cell destruction (Veazy 03, Veazy 07)
 - Can be independent of coitus
- Target specific stage in HIV replication
- Can be modified to other delivery forms – oral/vaginal/rectal

Advantages of licensed ARV

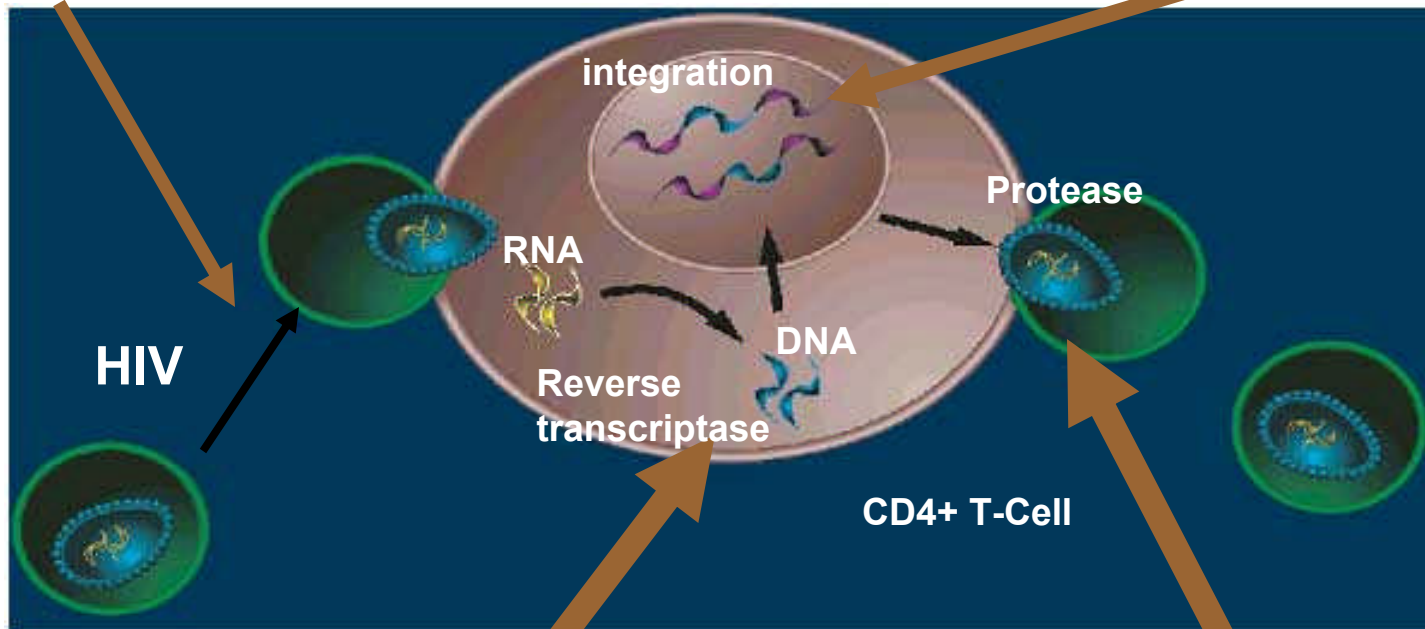
- Newer agents are very potent at low doses
- Documented efficacy as therapeutics
- Extensive preclinical/clinical data available



Multiple Targets for Intervention

Fusion/Entry Inhibitors
Fusion (T20), Maraviroc

Integrase Inhibitor
Raltegravir



Reverse transcriptase inhibitors
Nucleoside/tide analogs (**tenofovir**)
Non-nucleoside RT inhibitors (UC781, TMC120)

Protease inhibitors

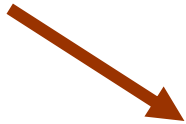
Ideal Candidate for PrEP

- Once daily dosing
- Potent antiretroviral
- Established safety as HIV treatment
- Long duration of action
- Low levels of resistance

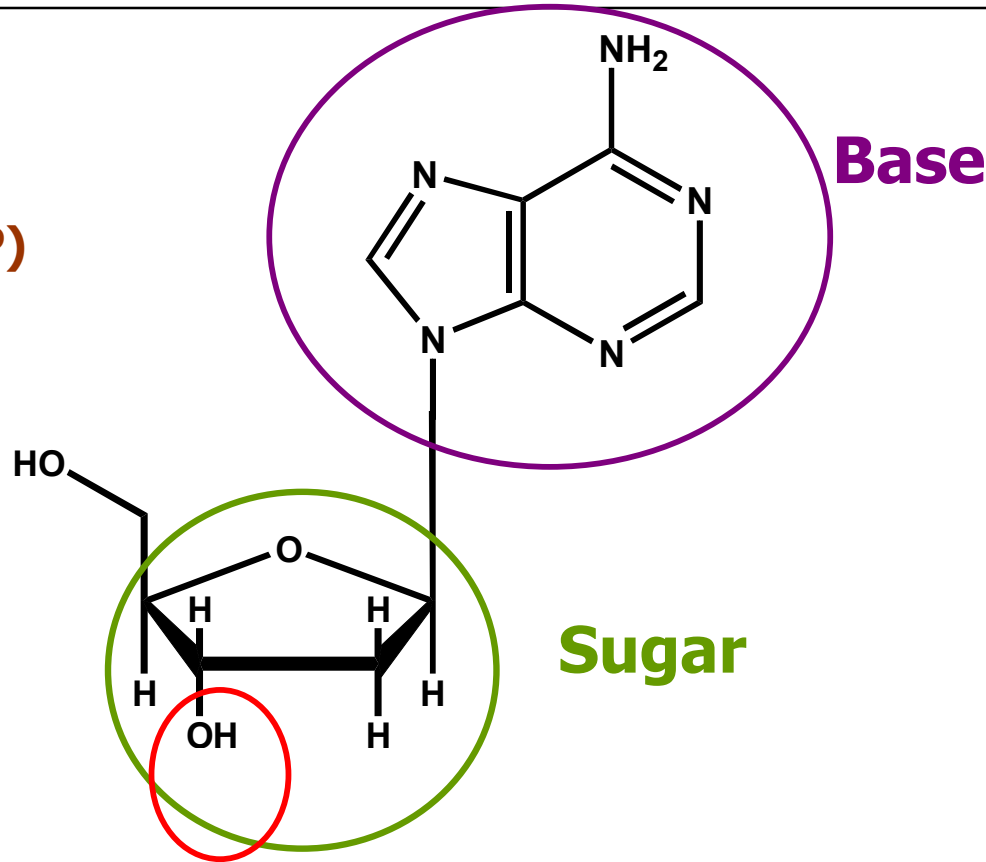
Tenofovir

What is Tenofovir?

Phosphates
(nucleotide or dNTP)



**Hydroxyl
Group**

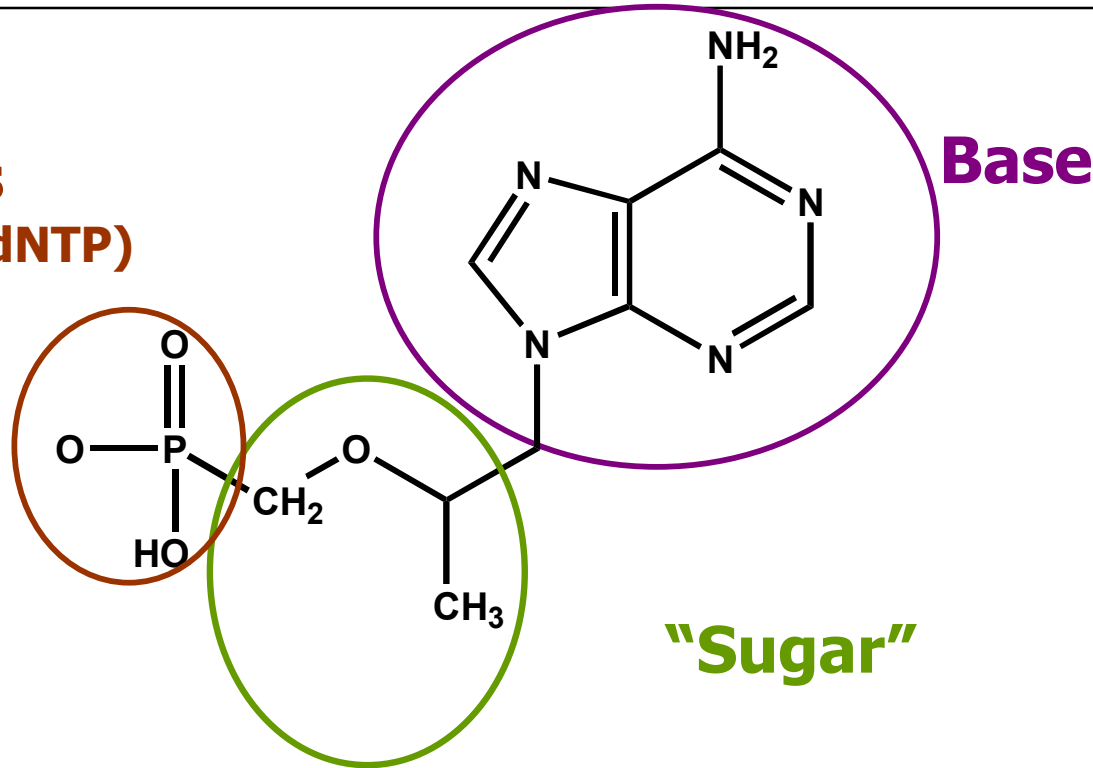
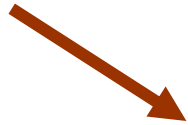


2'-Deoxyadenosine (A)

What is Tenofovir?

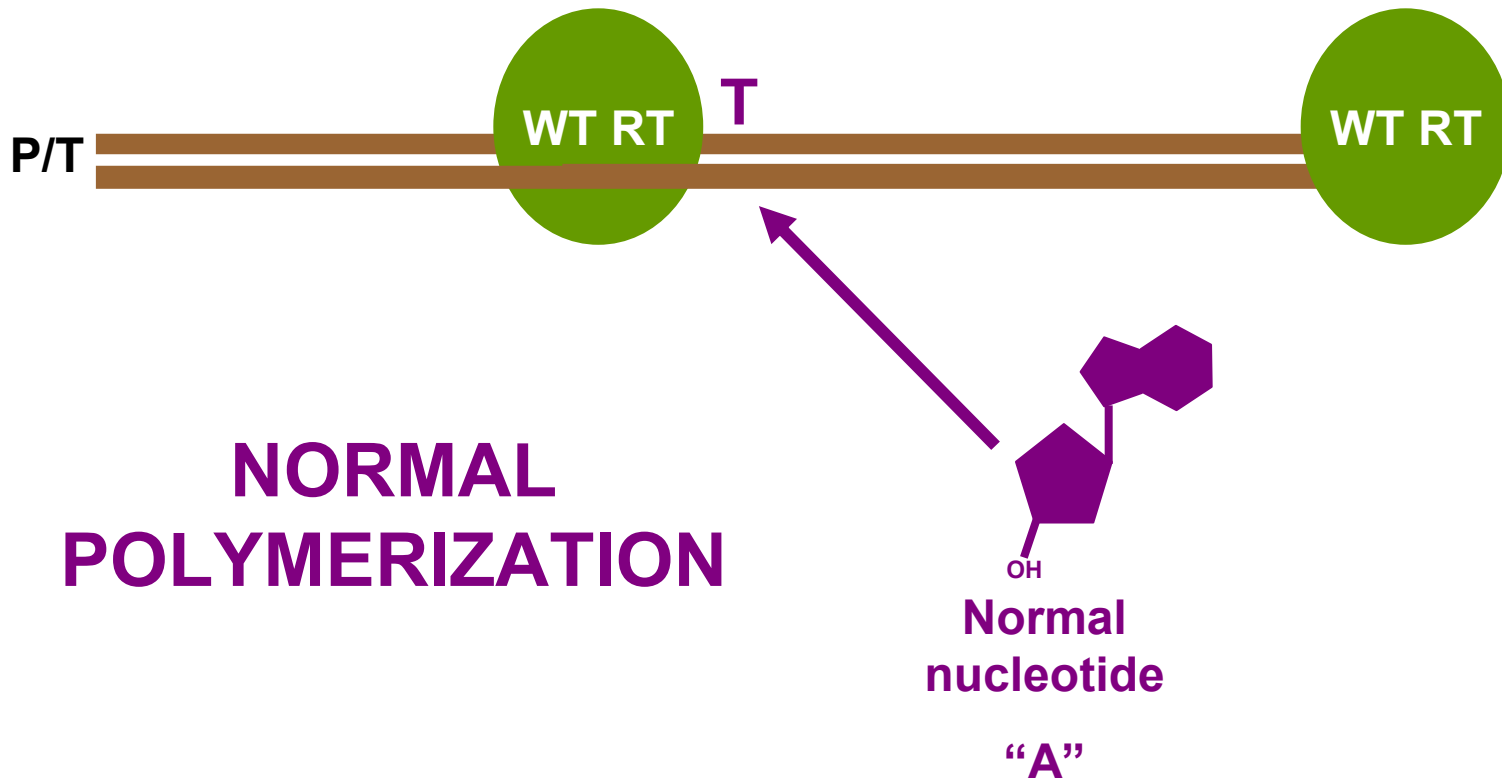
Phosphates

(nucleotide or dNTP)

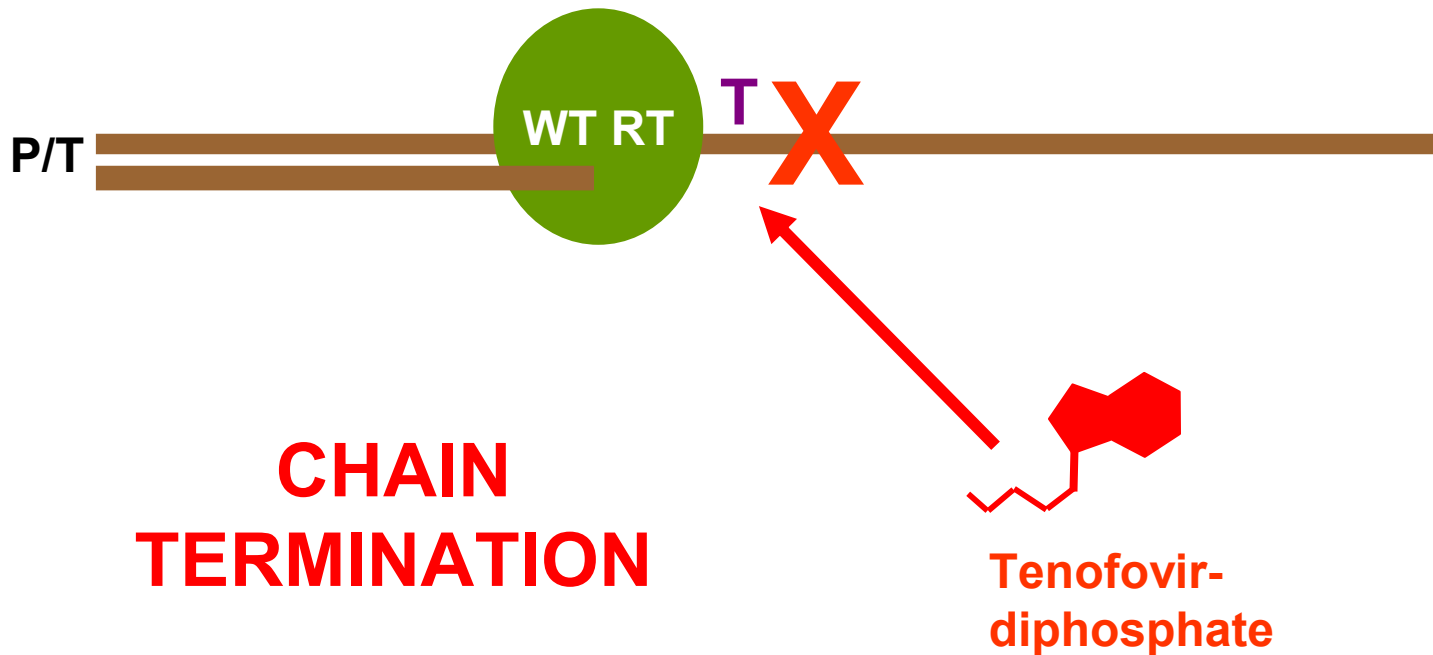


Tenofovir (A Analog)

How Does Tenofovir Work?



How Does Tenofovir Work?



Is Tenofovir Safe?

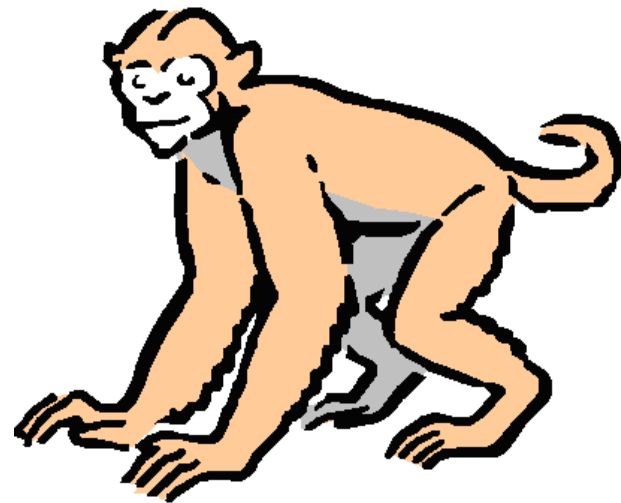
- Oral is well-tolerated with few side effects
- Chronic administration of tenofovir to rhesus macaques (birth – 13 yr + pregnancy):
 - No PRTD (proximal renal tubular dysfunction)
 - Only occurred in animals treated with 7X human dose, older age (reduced clearance)
 - No new toxicities identified
 - No teratogenic effects (one monkey on TFV treatment since birth had 3 healthy offspring up to 5 yr)
-(Van Rompey AAC 2008)
- 1% gel is safe and accepted by women and men
-(Mayer 2006, Carballo-Diequez 2007)

Is Tenofovir Long-Lasting?

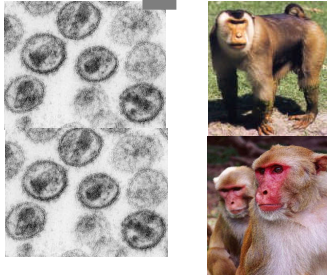
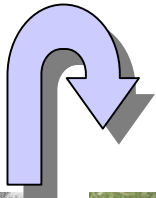
	Intracellular Halflife	Serum halflife
Viread (TFV)	>50 hr	17 hr
Emtriva (FTC)	39 hr	10 hr
Zidovudine (AZT)	3 hr	1.1 hr

Is Tenofovir effective in prevention?

- Limited data from macaque studies:
 - Different macaques used
 - Study designs different
 - Route of drug administration/virus inoculation different
- However, all show that tenofovir has potential



SHIV Challenge Models

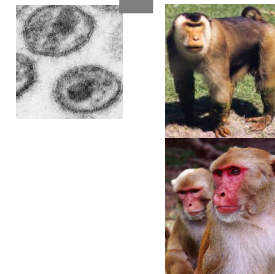
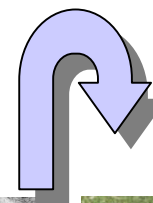
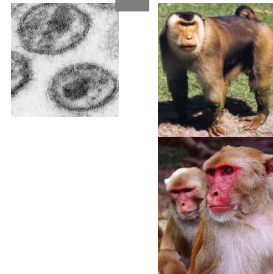
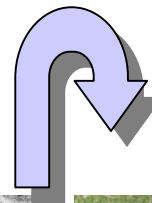
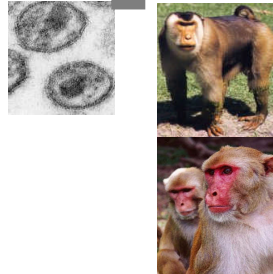
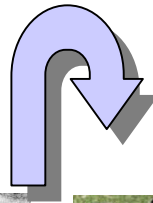
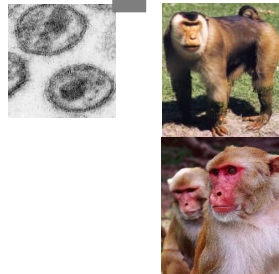
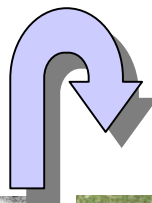
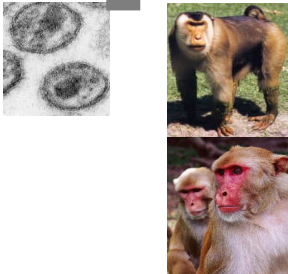
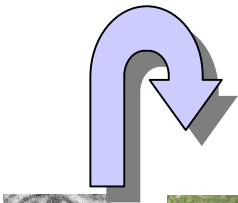


Single high-dose model

SIVmac_{251/32H} at 19,000 TCID₅₀ rectally once

Repeated low-dose model

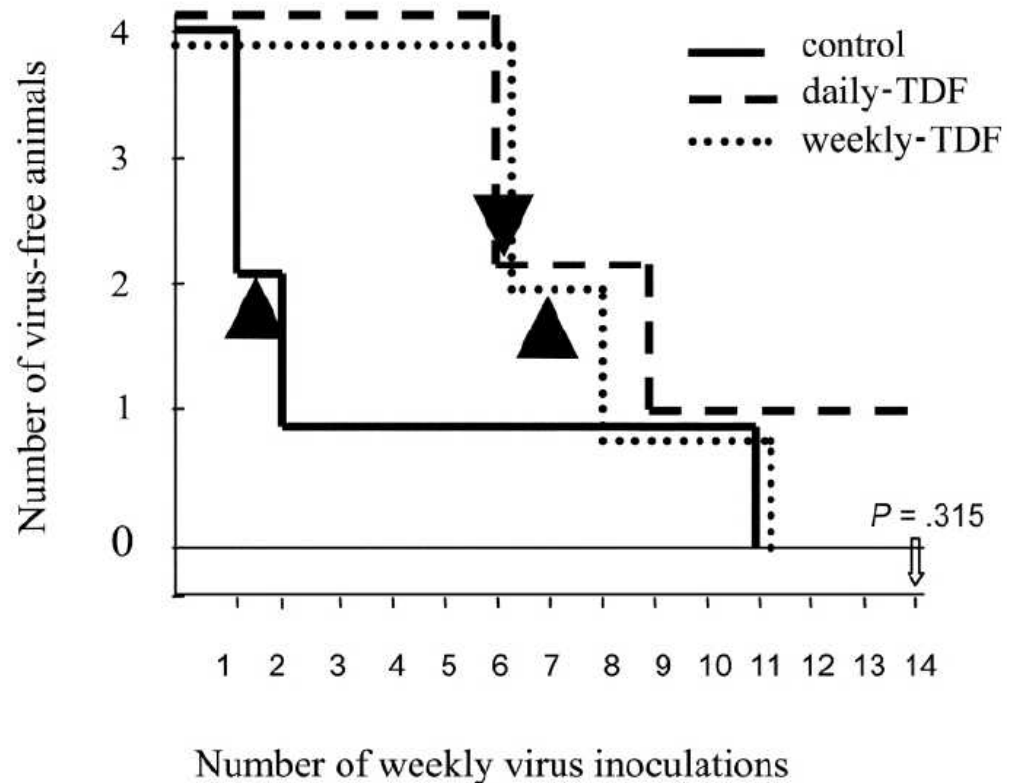
SIVmac_{162p3} at 10 TCID₅₀ multiple times



Oral TDF with Rectal Challenge

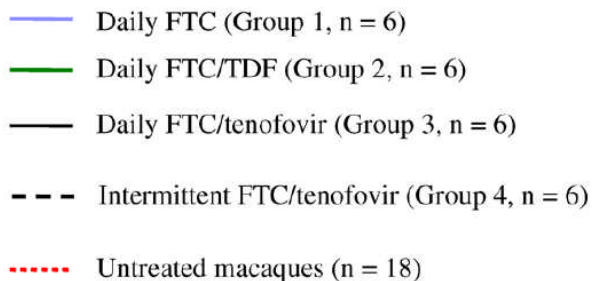
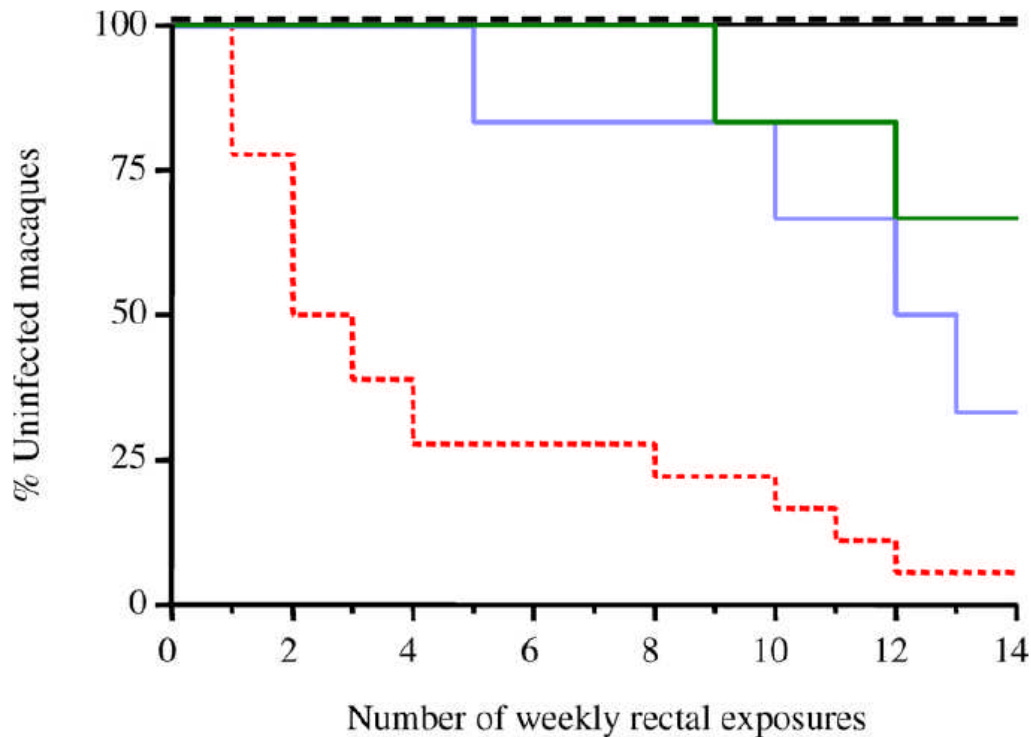
- 12 male Chinese rhesus
- Number infected:
 - 4/4 control
 - 4/4 weekly TDF
 - 3/4 daily TDF
- Infection delayed
- No development of drug resistance after 31 weeks

-Subbaro et al JID 2006



2 hr post

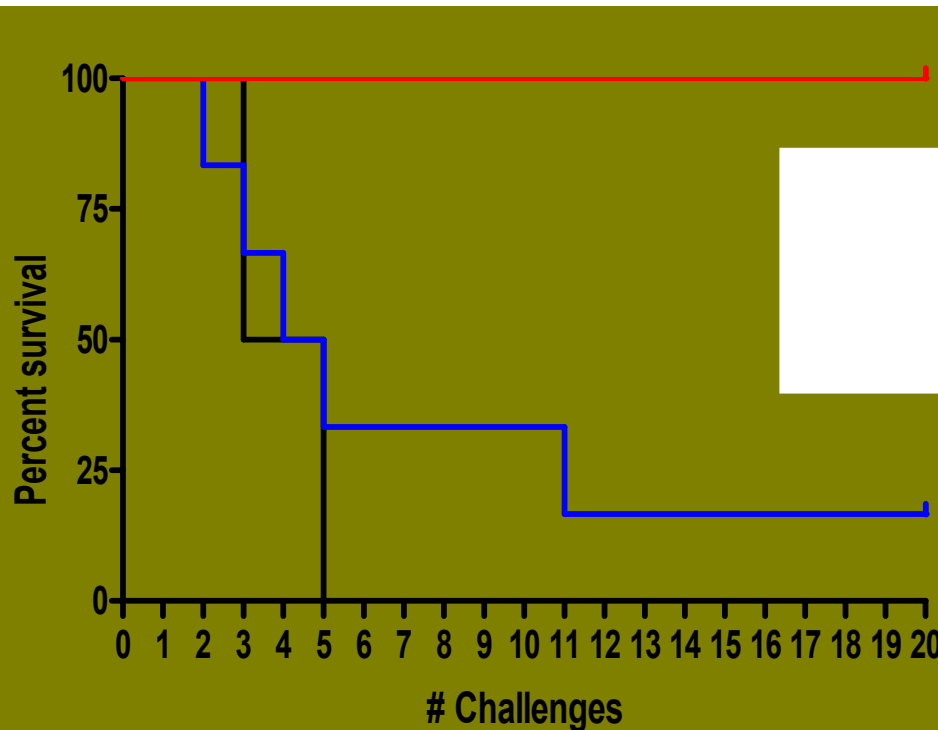
TDF/FTC with Rectal Challenge



- Rhesus macaques
- Number Infected:
 - 17/18 control
 - 2/6 daily oral Truvada
 - 0/6 daily subQ Truvada
 - 0/6 subQ Truvada 2/24
- Drug resistance:
 - No K65R
 - 2 with 184V (FTC) I (Tru)
- Delayed infection
- Blunted viremia

-Garcia-Lerma PLoS Med 2008

TFV/FTC with Vaginal Challenge



— no gel (n=2)
— placebo gel (n=6)
— FTC/TFV gel (n=6)

- Pigtail macaques
- Vaginal challenge 2X/week
- Number Infected:
 - 2/2 no gel
 - 5/6 placebo
 - 6/6 FTC/TFV gel
- Tenofovir alone in progress

-Parikh AIDS Conf 2008

Rectal TFV with Rectal Challenge

Study	Group	Animal # Infected	Animal Number	Procedure
Evaluation of protective efficacy of rectal tenofovir	A	2/6	D3, D30, D37, D39, D43, D79	Tenofovir 15 min before virus
	B	3/4	C57, D9, D26, D68	Placebo 15 min before virus
	C	4/4	D77, D83, E73, E81	No treatment before virus
	D	1/3	D14, D69, D56	Tenofovir 2 h before virus
	E	2/3	D15, D18, D29	Tenofovir 2 h after challenge

- 6/9 macaques protected from infection
- 2/3 infected while on tenofovir had modified outcomes compared to control



Drug Resistance Concerns

- Can the same drug be used for treatment and prevention?
- Will using tenofovir limit treatment options if resistance occurs?

Treatment vs Prevention

- In treatment, **tenofovir** is **ALWAYS** used in **COMBINATION**
- **Tenofovir** as PrEP can only be used by **UNINFECTED** persons.
- There is a risk for drug resistance if:
 - A positive person uses **tenofovir** only
 - **Tenofovir** does not protect and the participant becomes infected
- Using **tenofovir** as PrEP does not eliminate the possibility of using tenofovir for treatment.

Risk with Tenofovir Monotherapy

- Tenofovir: K65R <3-fold
 - Humans: no resistance after 28 d monotherapy 300 mg daily (Barditch-Crovo 01)
 - Monkeys: RT-SHIV-infected – 8 wk monotherapy (Van Rompay 07)
- Nevaripine: Y181C >100-fold
 - 38% after single dose (no other post-partum ARV) (Arrivé 07)
- AZT: TAMS >200-fold
 - requires multiple mutations – occurs within 6 months (Luckashov 01)

Why use TENOFOVIR for PrEP?

- PrEP is a potentially important prevention strategy
- Tenofovir is a promising antiretroviral
 - Well-tolerated, once-daily, potent, minimal resistance
- **If PrEP is successful, could have a large impact on preventing new infections**





Thank You!

Questions?
