GS-7340 Demonstrates Greater Declines in HIV-1 RNA than Tenofovir Disoproxil Fumarate During 14 Days of Monotherapy in HIV-1 Infected Subjects

M Markowitz,[1] A Zolopa,[2*] P Ruane,[3] K Squires,[4] L Zhong,[5] BP Kearney,[5] and W Lee[5]

[1]Aaron Diamond AIDS Research Center, New York, NY; [2]Stanford University Positive Care Clinic, Palo Alto, CA; [3]Lighthouse Medical, Los Angeles, CA; [4]Thomas Jefferson University, Philadelphia, PA; [5]Gilead Sciences, Foster City, CA

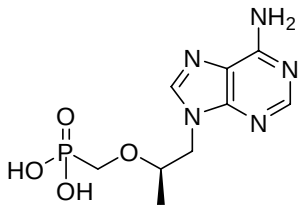
18th Conference on Retroviruses and Opportunistic Infections
March 2, 2011
Paper # 152LB

Introduction

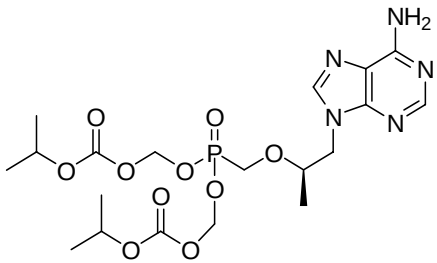
- **GS-7340 is a novel amidate prodrug that was designed to deliver high concentrations of tenofovir diphosphate to lymphoid cells**
- **The targeted delivery to lymphatic tissue should allow for a low dose and minimal systemic levels of tenofovir**
- **Chronic safety studies in dogs and rats demonstrate a greater therapeutic index relative to TDF**

M Markowitz, et al., CROI 2011; Paper # 152LB.

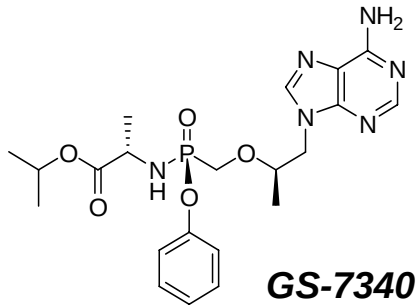
GS-7340: Targeting Lymphoid Cells



Tenofovir



TDF



GS-7340

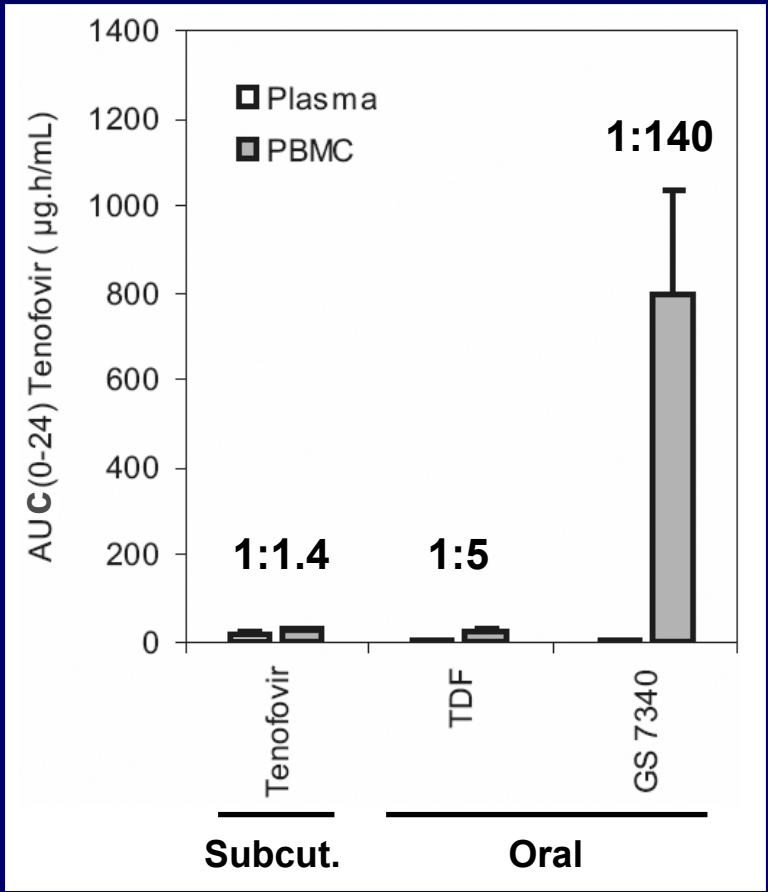
EC_{50} HIV-1 *(PBMCs)*	1.2 µM	0.015 µM	0.003 µM

- **GS-7340 is 400-fold more potent than tenofovir in PBMCs[1]**
- **GS-7340 is 200-fold more stable in plasma than TDF resulting in circulating levels of prodrug[1]**
- **GS-7340 is rapidly metabolized inside the lysosomes of lymphoid cells by the enzyme cathepsin A[2]**

[1] Lee et al. Antimicrob Agents Chemother 2005
[2] Birkus et al. Antimicrob Agents Chemother 2007

Increased Distribution to PBMCs *In Vivo*

Plasma to PBMC ratio following administration of TFV, TDF or GS-7340 to dogs (10 mg-eqv/kg)[1]



M Markowitz, et al., CROI 2011; Paper # 152LB.

[1]Lee et al. Antimicrob Agents Chemother 2005

Objectives

- **Primary Objectives**
  - **To evaluate the antiviral potency of 2 different doses of GS-7340 as compared to TDF**
    - **Primary endpoint: DAVG at Week 2**
  - **To determine the safety of GS-7340 over 14 days**

- **Secondary Objectives**
  - **To determine the plasma and intracellular PK of GS-7340**
  - **To determine the viral dynamics of HIV-1 RNA in plasma**

M Markowitz, et al., CROI 2011; Paper # 152LB.

Study Design

- **HIV-1-infected adults**
  - **ART Treatment-naïve**
  - **HIV-1 RNA ≥ 15,000 c/mL**
  - **CD4 count ≥ 200 cells/mm^3**
- **Randomized, double-blind 3 arm study**
  - **TDF 300 mg (active control arm)**
  - **GS 7340 - 50mg**
  - **GS 7340 - 150 mg**
- **Monotherapy for 14-day once-daily dosing**

M Markowitz, et al., CROI 2011; Paper # 152LB.

Baseline Characteristics

	TDF 300mg (N=10)	GS-7340 50 mg (N=10)	GS-7340 150 mg (N=10)
Age (mean)	34.8 ± 7.6	36.6 ± 9.7	35.4 ± 6.5
Sex (males)	9	9	9
Ethnicity			
Caucasian	6	3	4
Black	2	4	3
Latino	2	2	3
Asian	0	1	0
Mean HIV-1 RNA (log_{10} copies/mL)	5.03 ± 0.77	4.73 ± 0.58	4.72 ± 0.30
Mean CD4 cell count	384 ± 153	454 ± 201	432 ± 108

M Markowitz, et al., CROI 2011; Paper # 152LB.

Primary Efficacy Endpoint

Treatment (10 pts/arm)	Mean $DAVG_2$ [log_{10} c/mL]	p-value vs. TDF 300 mg
TDF 300 mg	- 0.54 ± 0.32	-
GS-7340 50 mg	- 0.95 ± 0.32	0.0211
GS-7340 150 mg	- 1.07 ± 0.14	0.0002

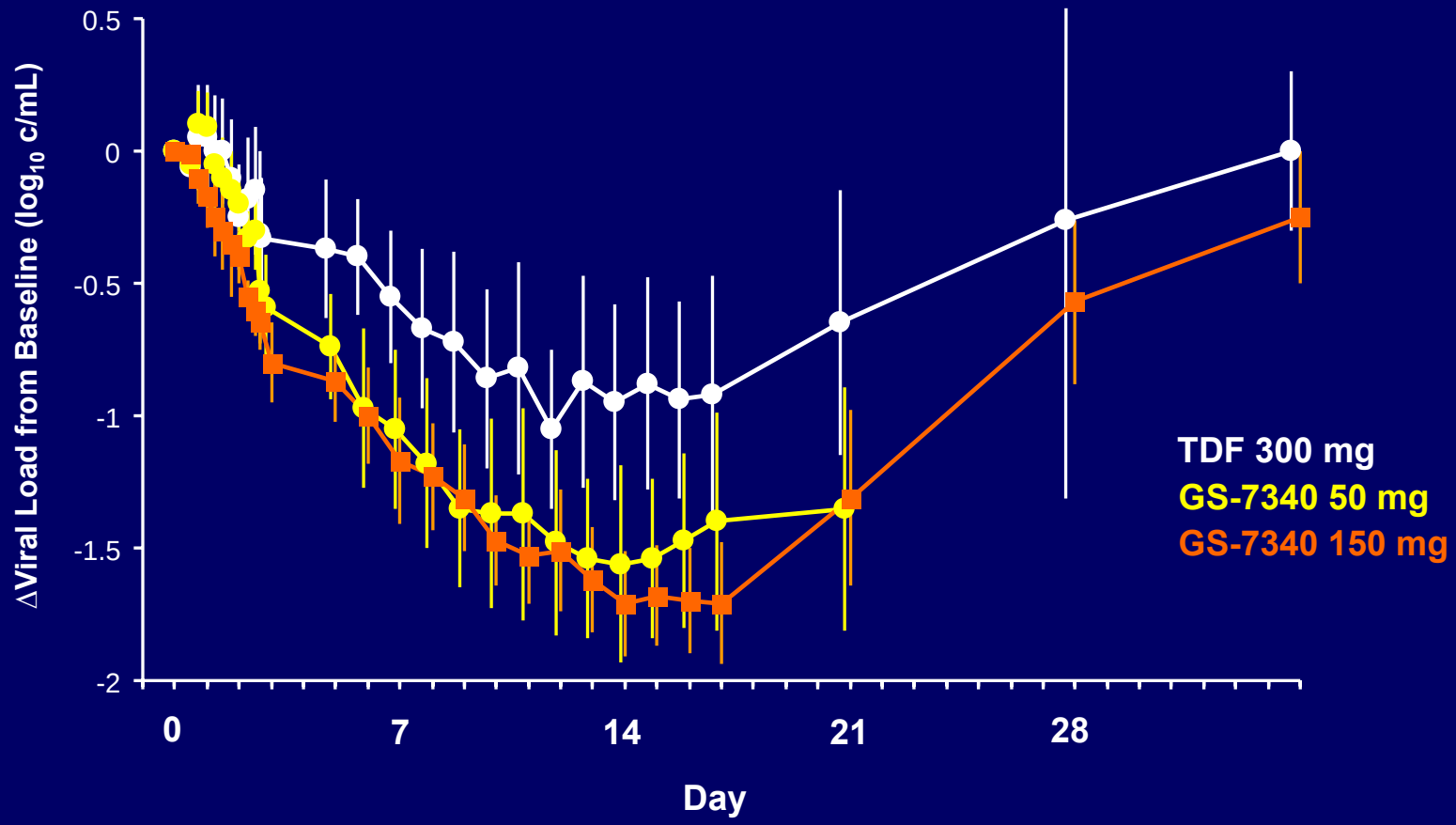
M Markowitz, et al., CROI 2011; Paper # 152LB.

Viral Dynamics

Treatment (10 pts/arm)	Mean ΔVL Day 14 [log_{10} c/mL]	p-value of mean ΔVL vs. TDF 300 mg	Mean first phase decay slope	p-value of mean decay slope vs. TDF 300 mg
TDF 300 mg	- 0.94 ± 0.49	-	- 0.36 ± 0.14	-
GS-7340 50 mg	- 1.57 ± 0.53	0.0257	- 0.63 ± 0.13	0.0003
GS-7340 150 mg	- 1.71 ± 0.24	0.0010	- 0.64 ± 0.13	0.0003

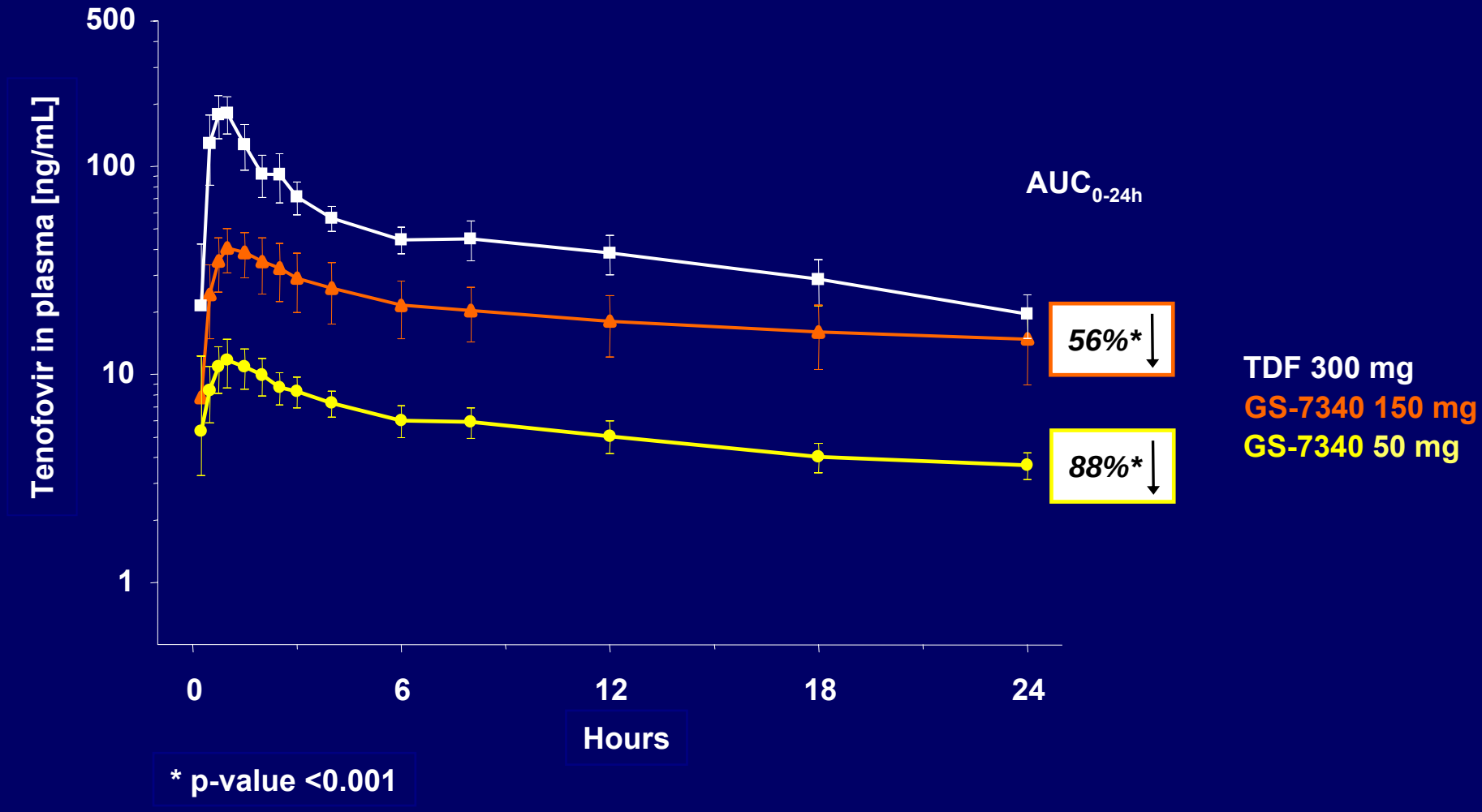
M Markowitz, et al., CROI 2011; Paper # 152LB.

Viral Dynamics



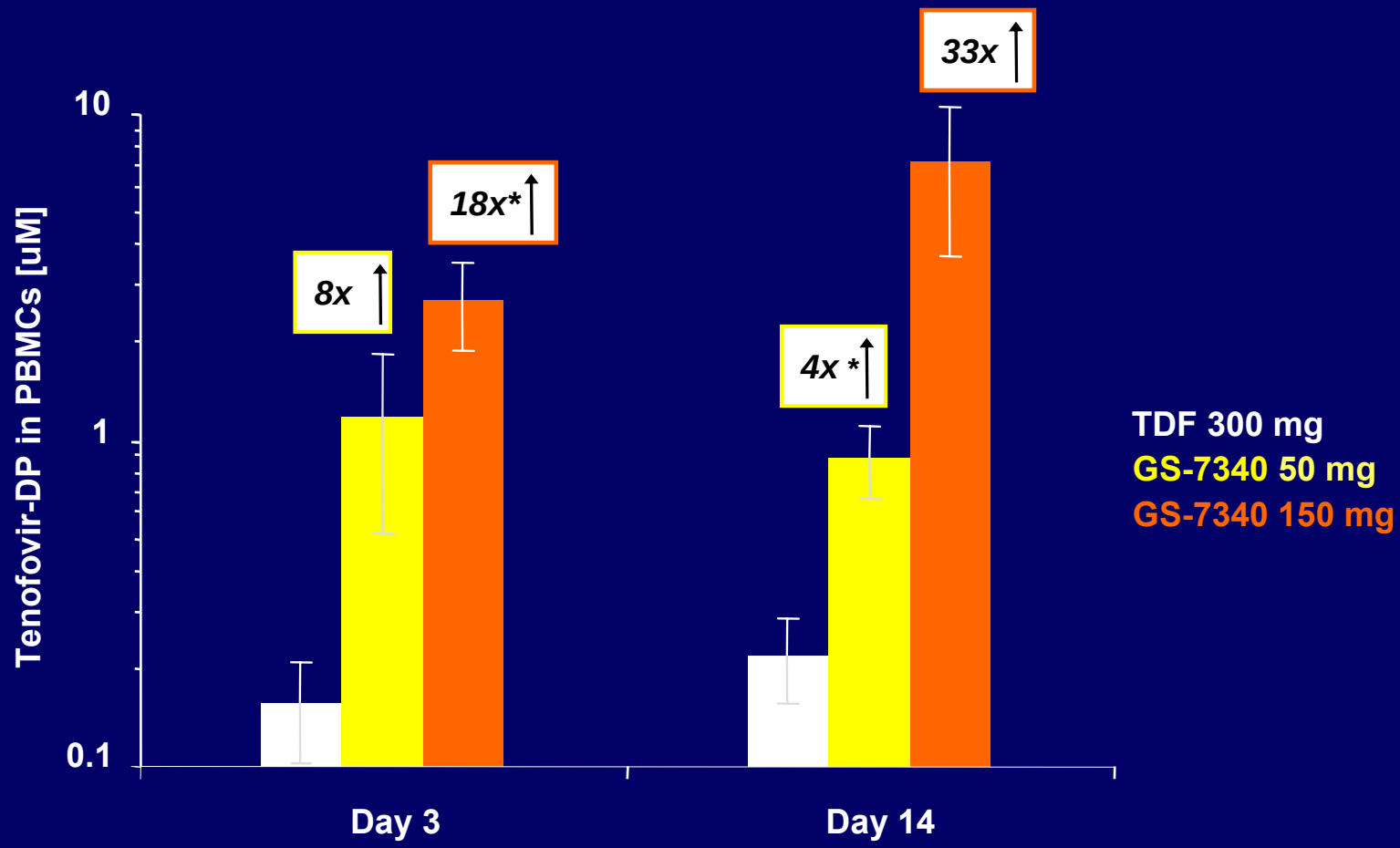
M Markowitz, et al., CROI 2011; Paper # 152LB.

Tenofovir Levels in Plasma: PK Profile on Day 1



M Markowitz, et al., CROI 2011; Paper # 152LB.

Tenofovir Diphosphate in PBMCs



* p-value <0.05

M Markowitz, et al., CROI 2011; Paper # 152LB.

Safety and Resistance

- **No dose interruptions or discontinuations**
- **No serious adverse events**
- **No clinically significant laboratory abnormalities**
- **Most frequent adverse events were mild to moderate headache and nausea**
- **No resistance mutations to GS-7340 or TDF were detected at day 14 in any subject**

M Markowitz, et al., CROI 2011; Paper # 152LB.

Summary

- **Monotherapy with GS-7340 at 50 or 150 mg led to significantly greater decreases in HIV-1 RNA and at lower systemic tenofovir exposures than with TDF 300 mg**
- **GS-7340 is a next generation oral prodrug of tenofovir that has the potential to improve upon the efficacy and safety of TDF for the treatment of HIV**
- **The lower dose of GS-7340 will permit the development of new single tablet regimens that are not possible today**
- **GS-7340 has the potential of making tenofovir more widely available in resource limited settings given the relative manufacturing expense compared to TDF**

M Markowitz, et al., CROI 2011; Paper # 152LB.