Maria Curtis, MS
Gilead Sciences, Inc.

I have financial relationship(s) within the last 12 months relevant to my presentation with Gilead Sciences, Inc. (employment, stock options)

AND

My presentation does include discussion of off-label or investigational use

FTC for the treatment of HBV

HBV rtN236T Mutant Subpopulations Respond Like Wild-Type During Tenofovir DF (TDF) Monotherapy or Combination Therapy with Emtricitabine (FTC): an Evaluation of Early Viral Load Decay Kinetics

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Oral #134

Introduction

- HBV pol/RT resistance mutations have been identified following administration of most oral anti-HBV agents (lamivudine, adefovir dipivoxil, entecavir, and telbivudine)

- No amino acid substitutions associated with resistance to tenofovir DF detected in the HBV pol/RT following 192 weeks of TDF treatment for HBeAg- and HBeAg+ subjects in Studies 102 and 103[1]

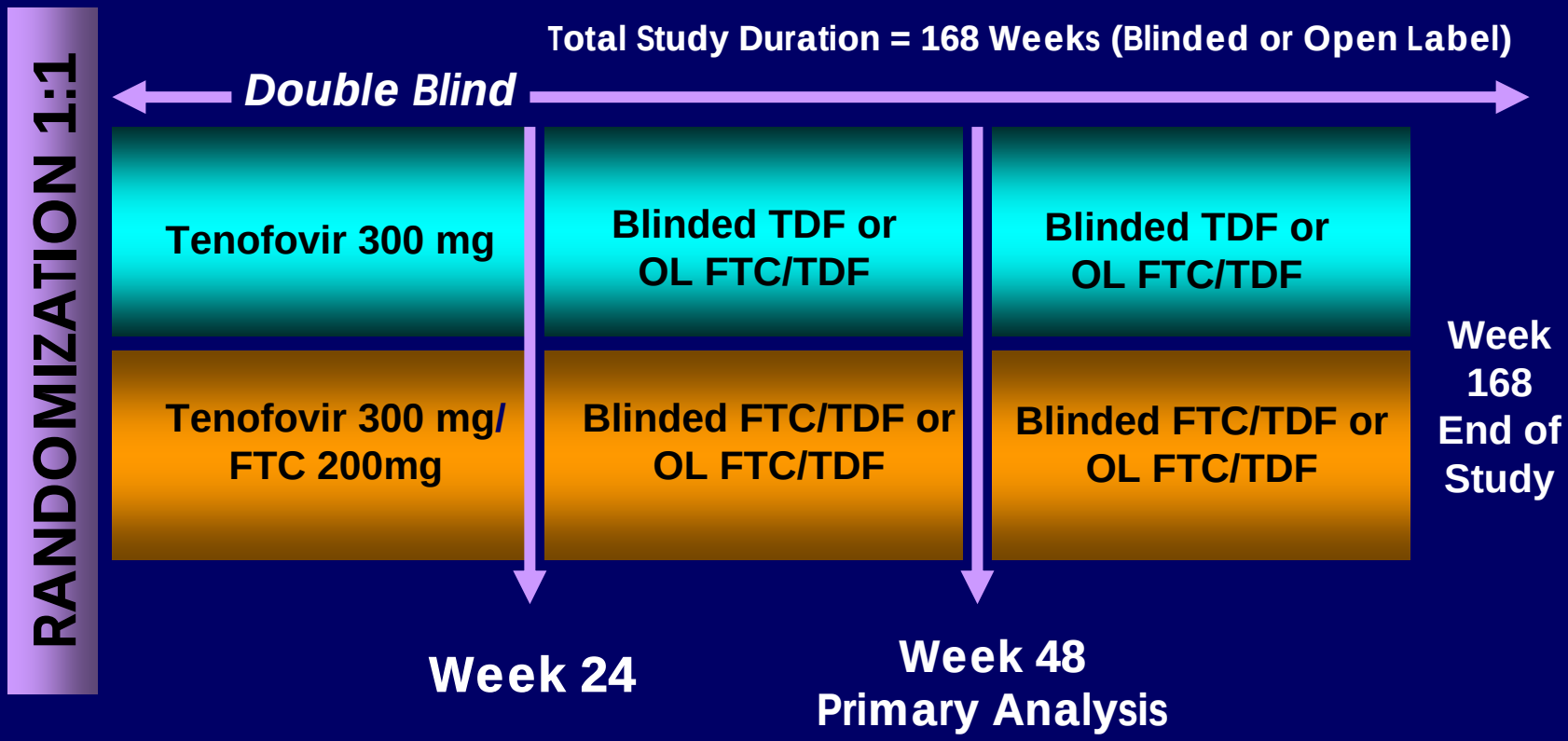
- In vitro, the rtN236T ADV-associated resistance mutation confers low-level cross-resistance (2.5-12-fold) to tenofovir[2]

[1]Snow-Lampart et. al. AASLD 2010, Poster #1365
[2]Kitrinos et. al. AASLD 2009, Poster #434

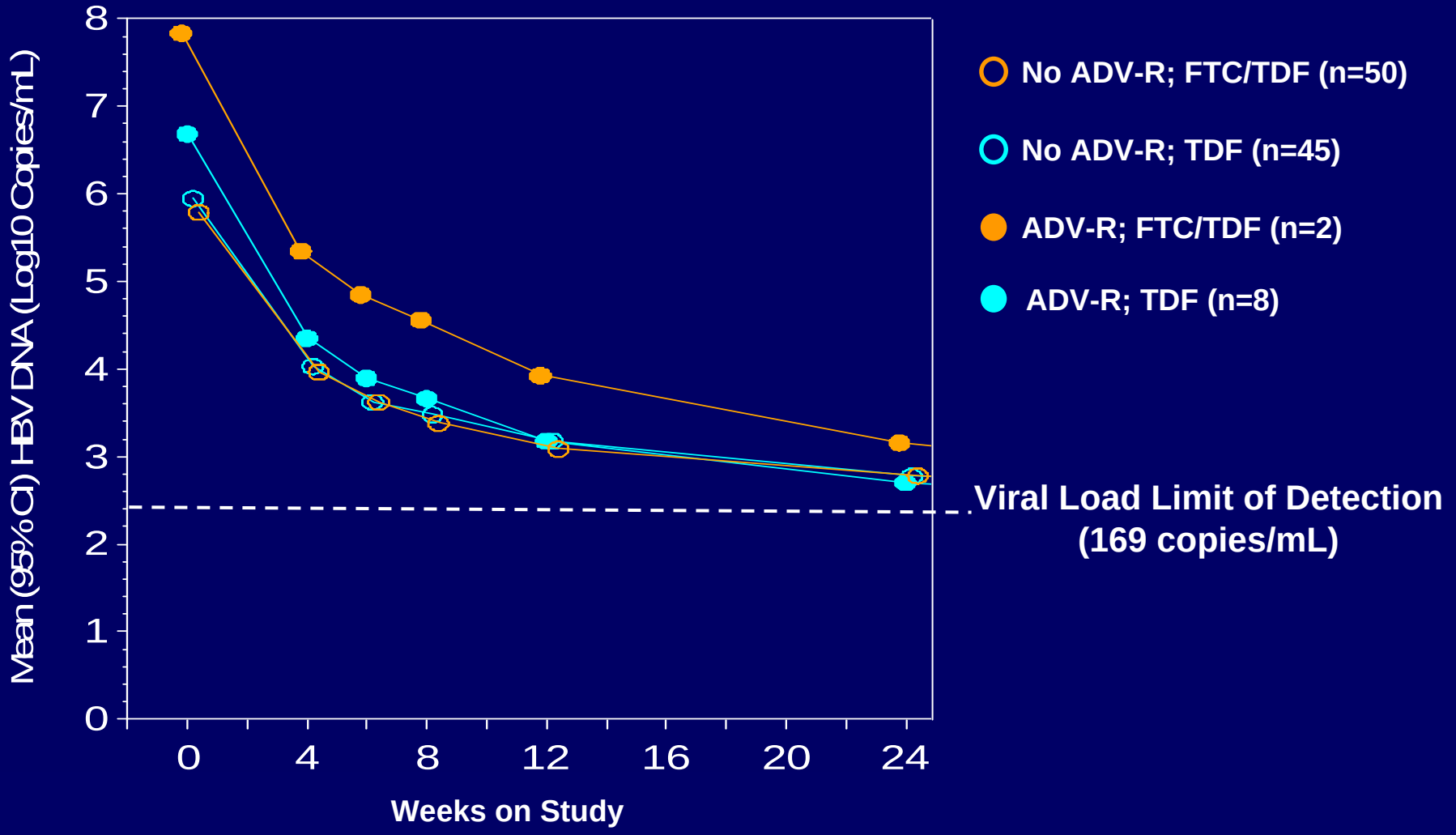
Objective

- Evaluate the clinical response to TDF therapy of the rtN236T mutant virus
- Using allele-specific PCR, detect the rtN236T mutation in patient samples prior to and during TDF or FTC/TDF therapy
- Compare early viral load decay kinetics of mutant vs. wild-type in CHB mono-infected patients harboring rtN236T prior to initiation of TDF or FTC/TDF therapy

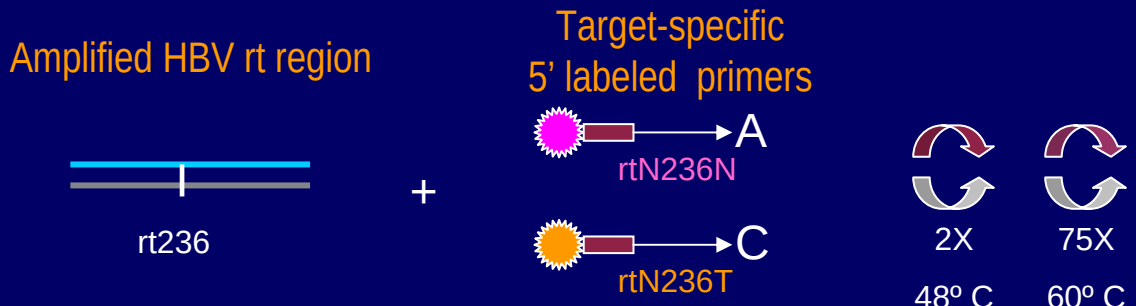
Study 106: TDF vs FTC+TDF in ADV Refractory Patients

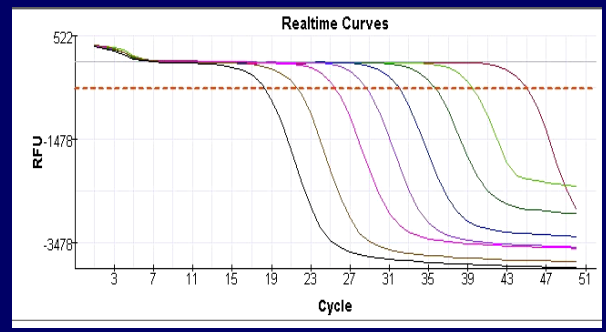


Mean HBV DNA Over Time by Baseline ADV Resistance Mutations

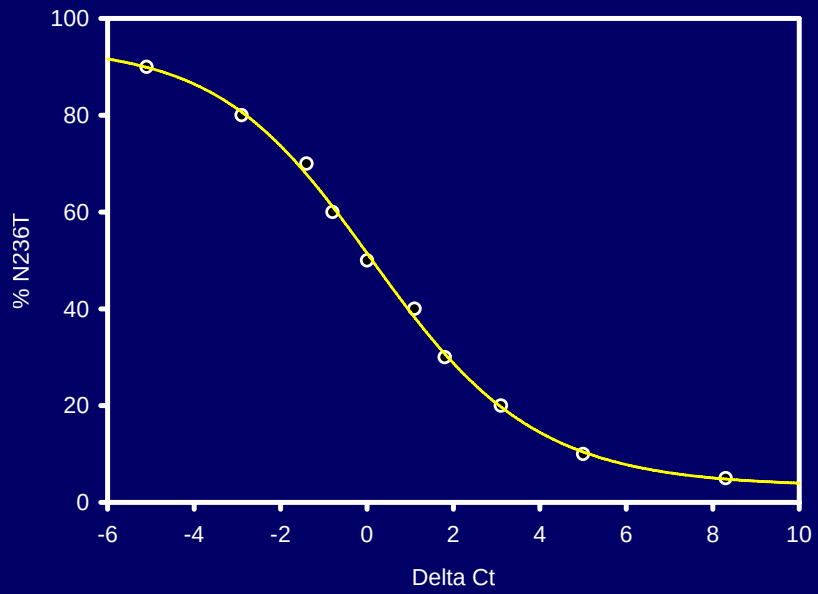


Method Background - Allele-Specific PCR (MULTI-CODE RTx)





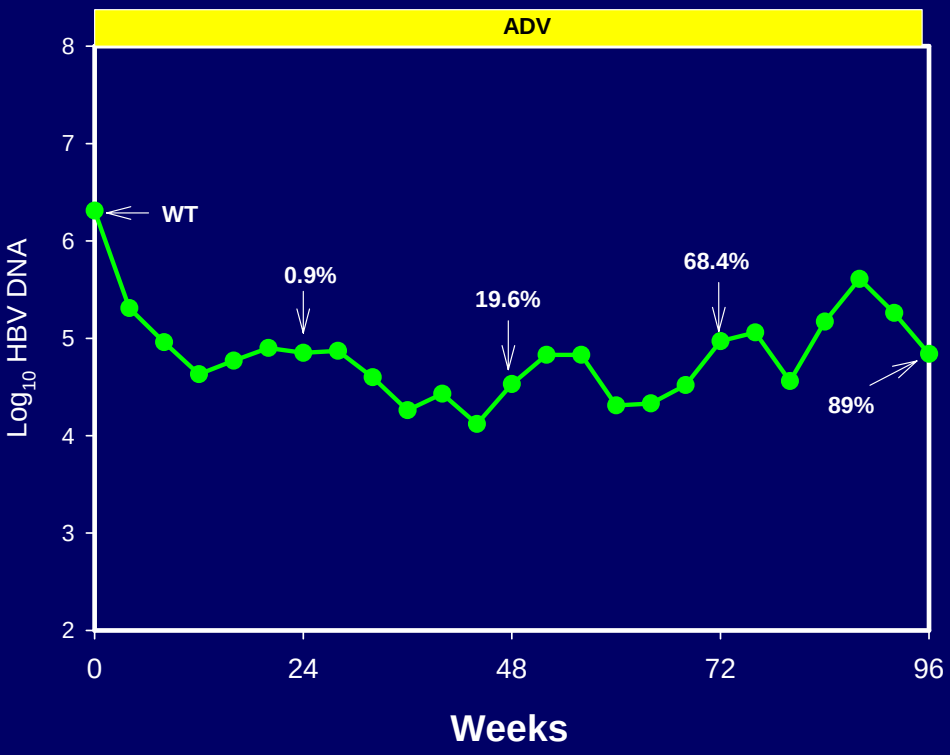
Standard Curve for AS-PCR



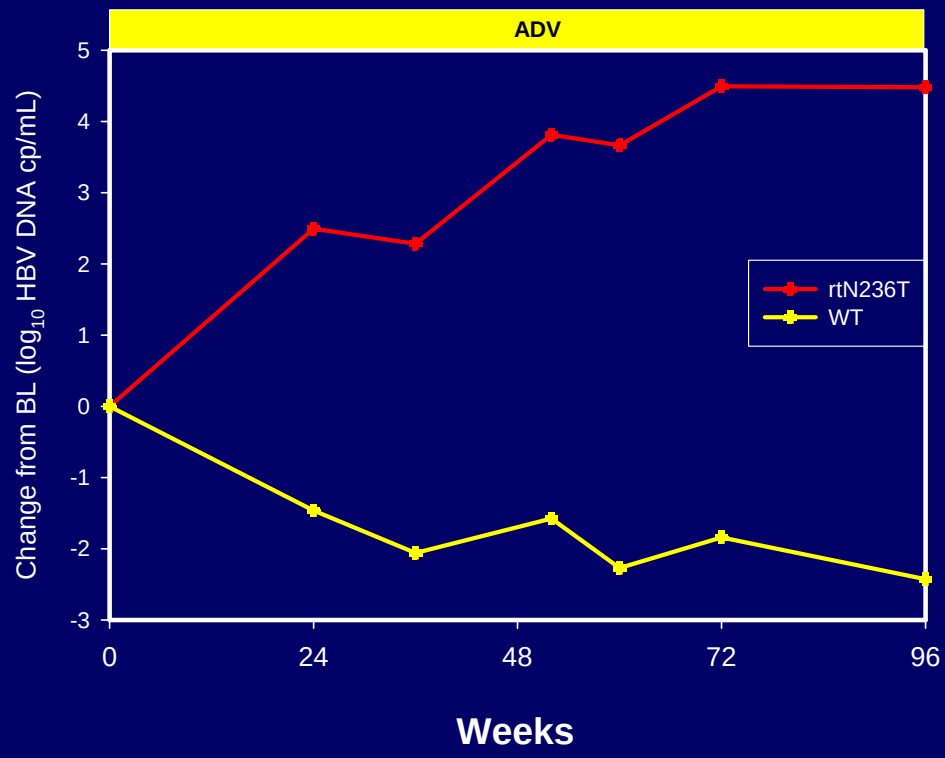
- limit of 0.5% for detection of the mutation
- dynamic range from 0.5% to 95%
- Viral Load cut-off 1000 cp/mL

Assay Validation - Detection of rtN236T in a Patient on Long Term Adefovir Therapy*

Total HBV DNA



Change in rtN236T vs. WT



***Previous studies have shown increased selection of the rtN236T in patients during ADV therapy (Pallier et.al. 2009, Hepatology 49;50-9)**

Methods

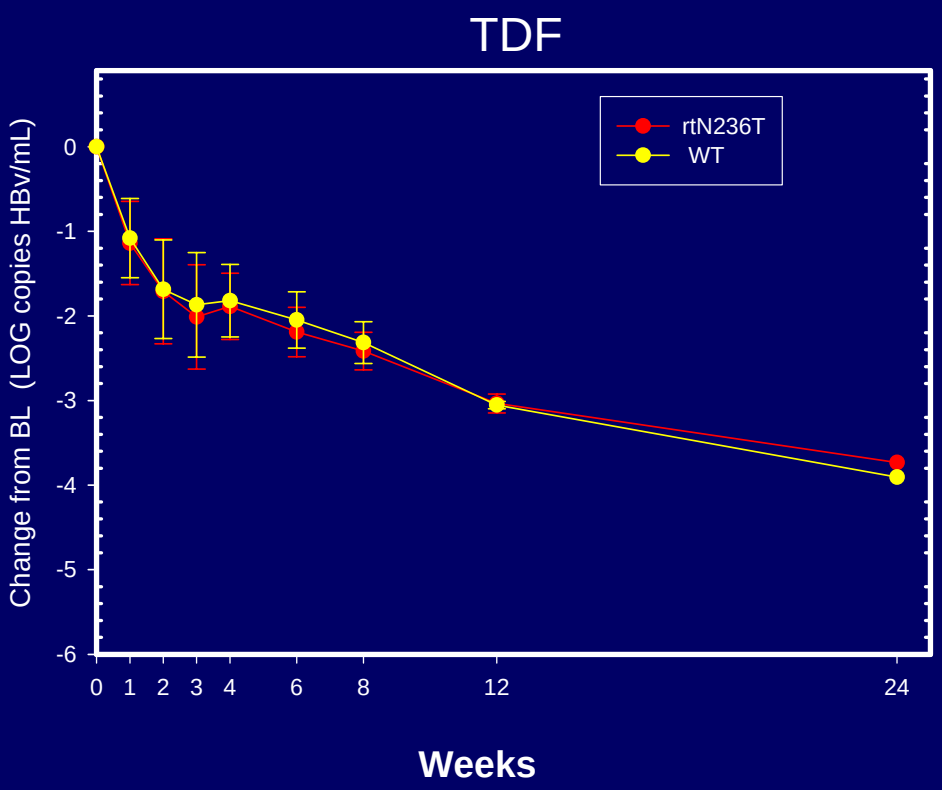
- Baseline samples (n=105) from patients enrolled in Study 106 were tested for rtN236T using AS-PCR
- Patients with rtN236T at baseline were evaluated for levels of rtN236T and rtN236N at each visit through week 24 (or until HBV DNA <1000 copies/mL)
- Differences in viral load decline through week 4 were evaluated using a Wilcoxon signed rank and rank sum test

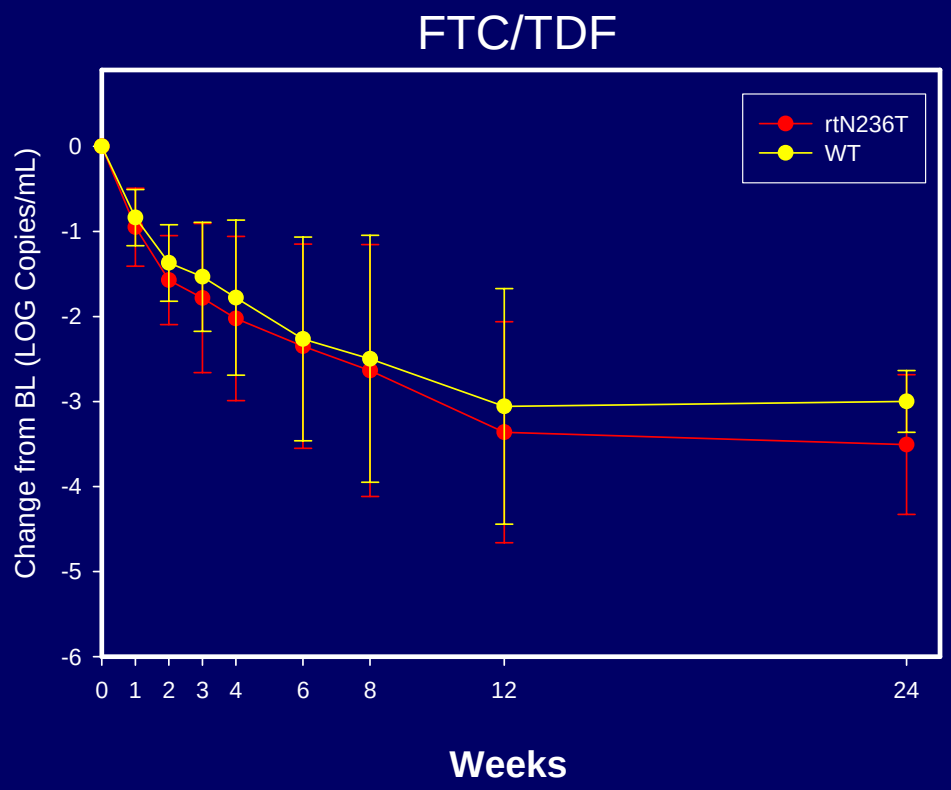
The rtN236T Mutation was Detected in 14 (13.3%) Patients Prior to Initiating TDF or FTC/TDF

Pt	ORIGINAL COHORT	BL HBV DNA Log_{10} cp/mL	BL MUTATIONS (population sequencing)	BL % rtN236T (AS-PCR)
A	**TDF**	**6.1**	**rtA181A/T,rtN236N/T**	**17.7%**
B	**TDF**	**6.7**	**rtN236N/T**	**34.3%**
C	**TDF**	**6.1**	**rtA181V/A,rtN236T/N**	**52.5%**
D	**TDF**	**8.8**	**rtA181A/T/V,rtN236T/N**	**56.4%**
E	**TDF**	**6.9**	**rtA181T,rtN236T**	**93.2%**
F	**FTC/TDF**	**6.0**	**None**	**0.5%**
G	**FTC/TDF**	**5.2**	**None**	**0.5%**
H	**FTC/TDF**	**6.1**	**None**	**1.0%**
I	**FTC/TDF**	**5.8**	**Unable to genotype***	**1.3%**
J	**FTC/TDF**	**4.9**	**rtL180Mrt/M204M/V**	**3.2%**
K	**FTC/TDF**	**7.3**	**rtA181V**	**3.3%**
L	**FTC/TDF**	**7.4**	**None**	**8.2%**
M	**FTC/TDF**	**6.6**	**None**	**14.3%**
N	**FTC/TDF**	**8.4**	**rtN236N/T**	**17.0%**

*rtA181V/A, rtN236N/T detected by INNO LiPA

Average Decline in rtN236T and WT Populations in Patients on TDF or FTC/TDF

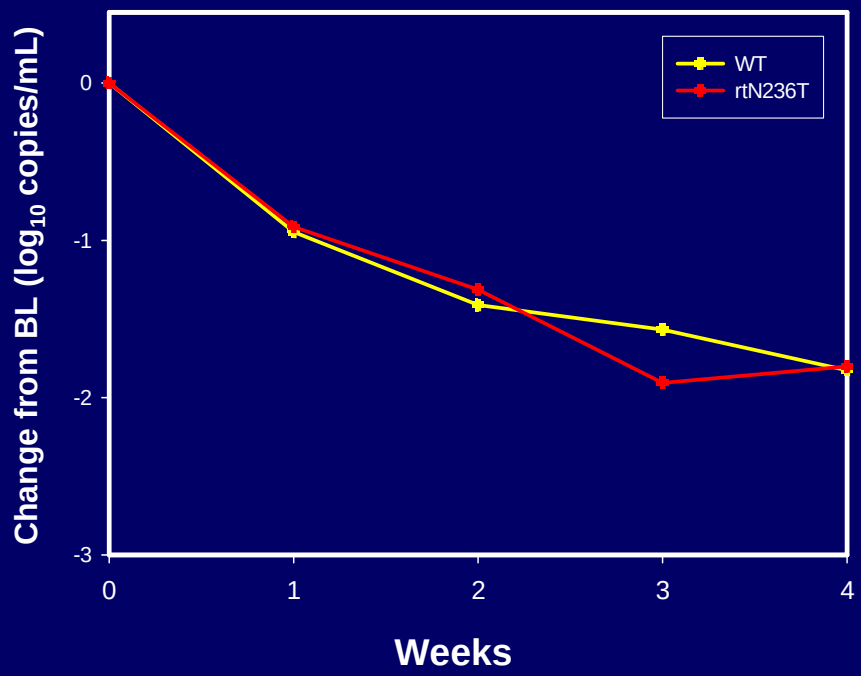




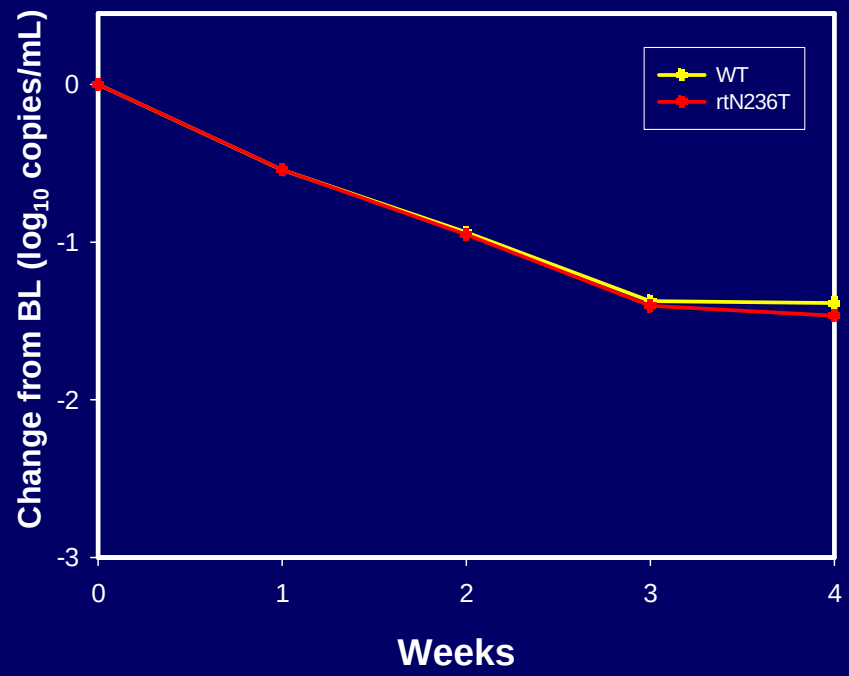
- **3/5 TDF patients had HBV DNA <1000 cp/mL at W24**
- **6/9 FTC/TDF patients had HBV DNA <1000 cp/mL at W24**
- **no significant difference in rates of viral load decline at W4 for the rtN236T virus comparing TDF and FTC/TDF treatment (p=0.933)**

The rtN236T Virus Showed Similar Rates of Decline to WT at W4 with TDF

TDF Subject A
(18% rtN236T by AS-PCR; rtA181A/T±rtN236N/T by pop.seq.)



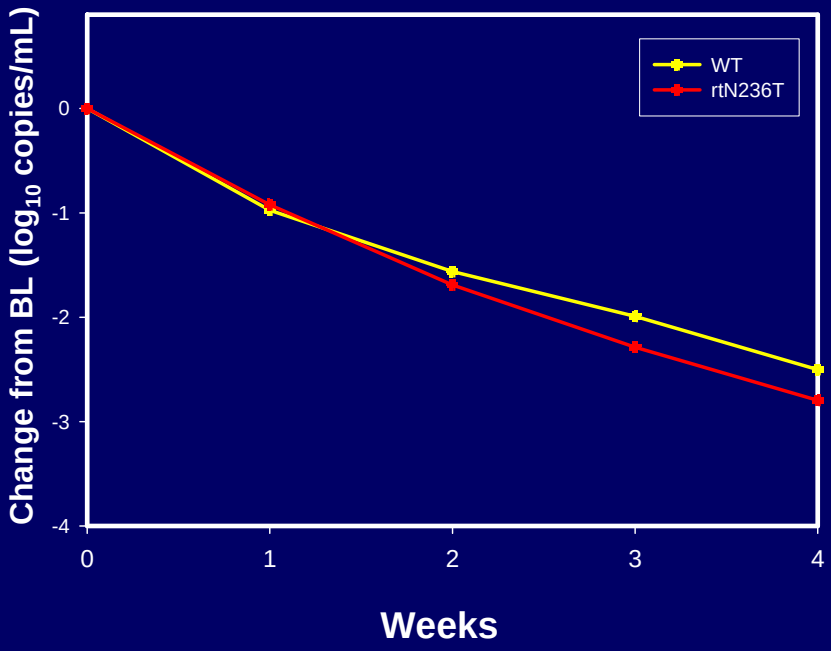
TDF Subject E
(93% rtN236T by AS-PCR; rtA181T ± N236T by pop.seq.)



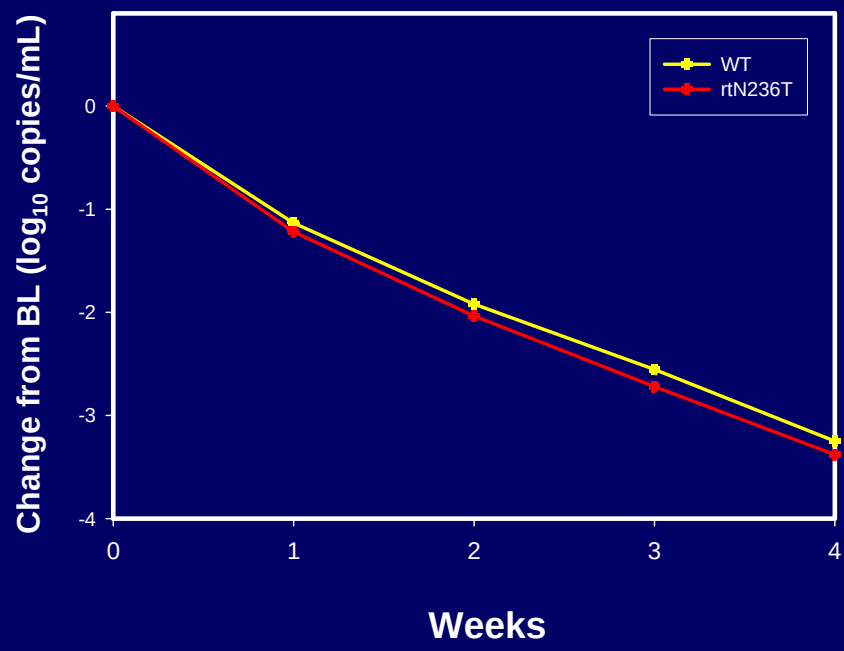
- **Overall, no significant difference between rtN236T and WT rates of early viral load decline (p=0.109)**

The rtN236T Virus Showed Similar Rates of Decline to WT at W4 with TDF/FTC

TDF/FTC Subject H
(1% rtN236T by AS-PCR; WT by pop.seq)



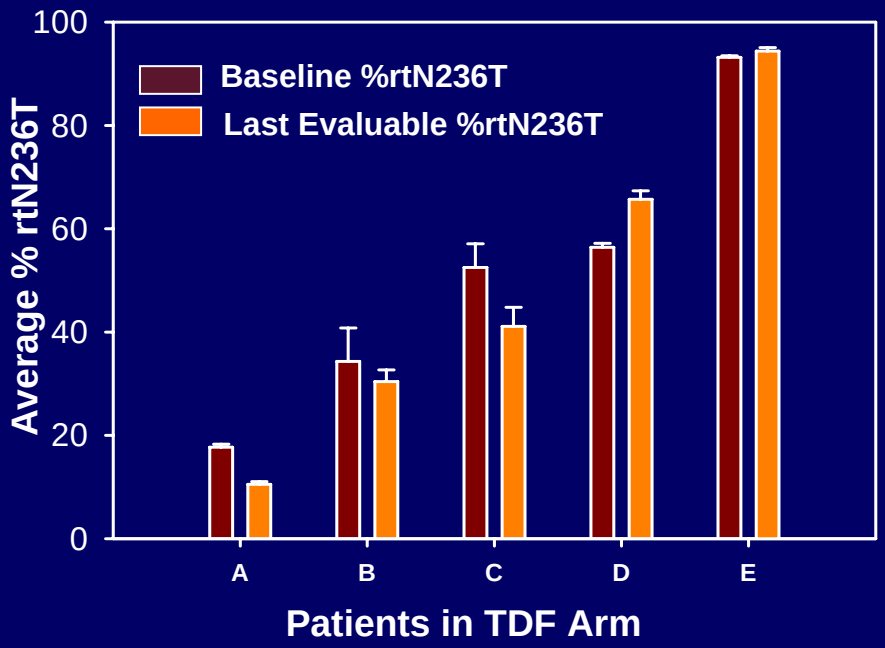
TDF/FTC Subject N
(17% rtN236T by AS-PCR; N236N/T by pop.seq)



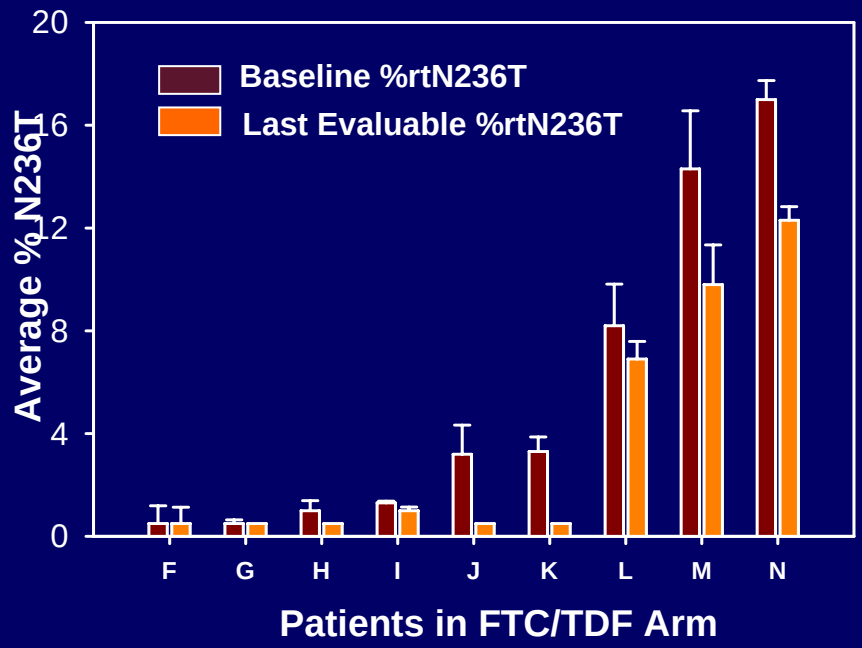
- **Overall, no significant difference between rtN236T and WT rates of early viral load decline (p=0.375)**

Relative Proportions of rtN236T to WT did not Increase During Therapy with TDF or FTC/TDF

% rtN236T at Baseline and Last Evaluable Time Point for patients in TDF arm



% rtN236T at Baseline and Last Evaluable Time Point for Patients in FTC/TDF Arm



Average % N236T is from n=2 AS-PCR runs

Conclusions

- **The rtN236T mutant virus showed similar early viral load kinetics of HBV DNA decline to that of WT virus**
- **No statistical differences in the rate of viral load decline between rtN236T and wild-type virus at W4 on either TDF or FTC/TDF**
- **Despite low levels of cross resistance observed in vitro, TDF equally suppresses WT and rtN236T viruses in vivo**

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