

In Vitro Susceptibility of HBV Polymerase Encoding Mutations Acquired During Adefovir Dipivoxil Therapy to Other Anti-HBV Agents

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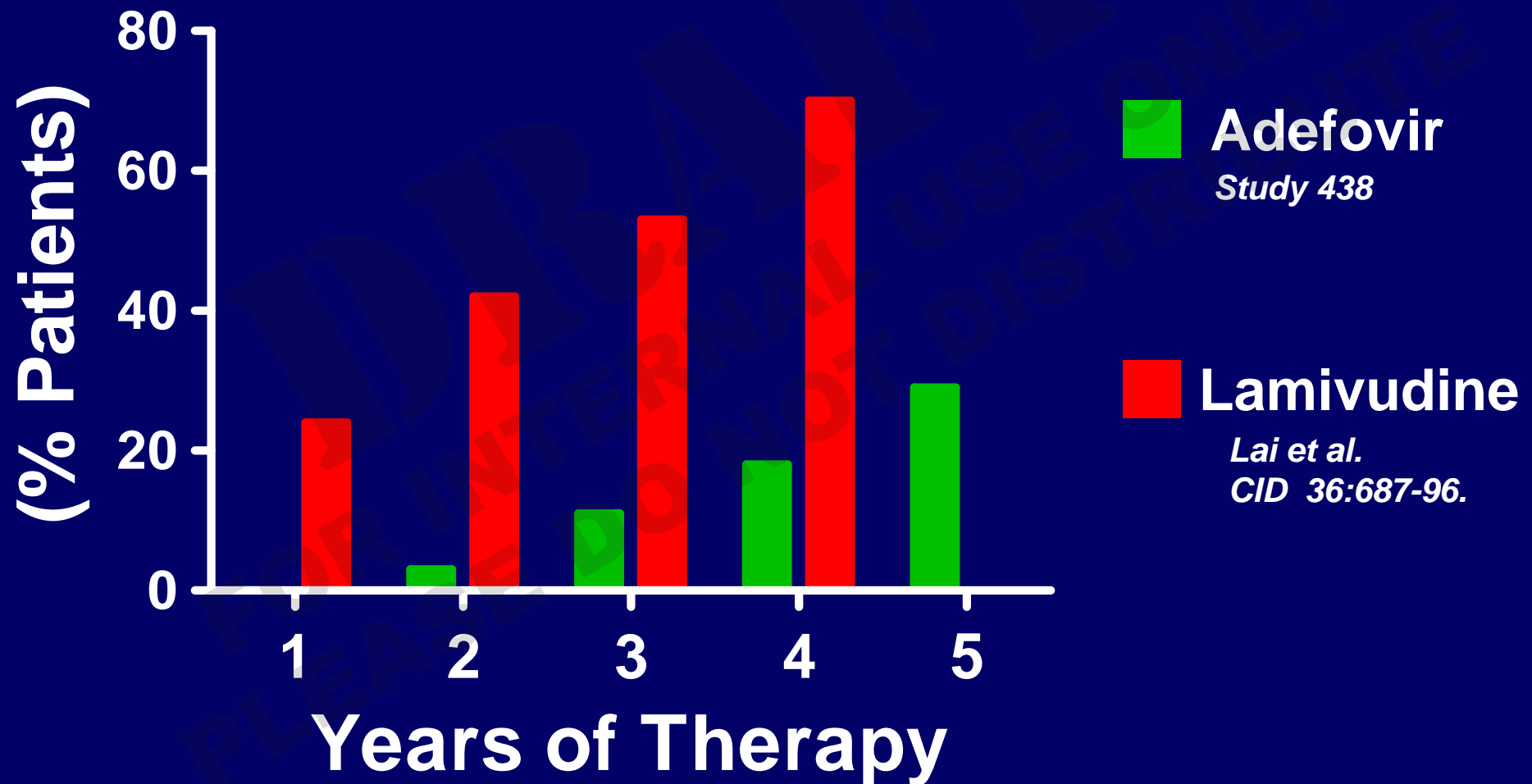
- * I have financial relationship with Gilead that is relevant to my presentation.
- * My presentation does include discussion of off-label or investigational use.
Tenofovir, Emtricitabine, Telbivudine, Clevudine, Torcitabine

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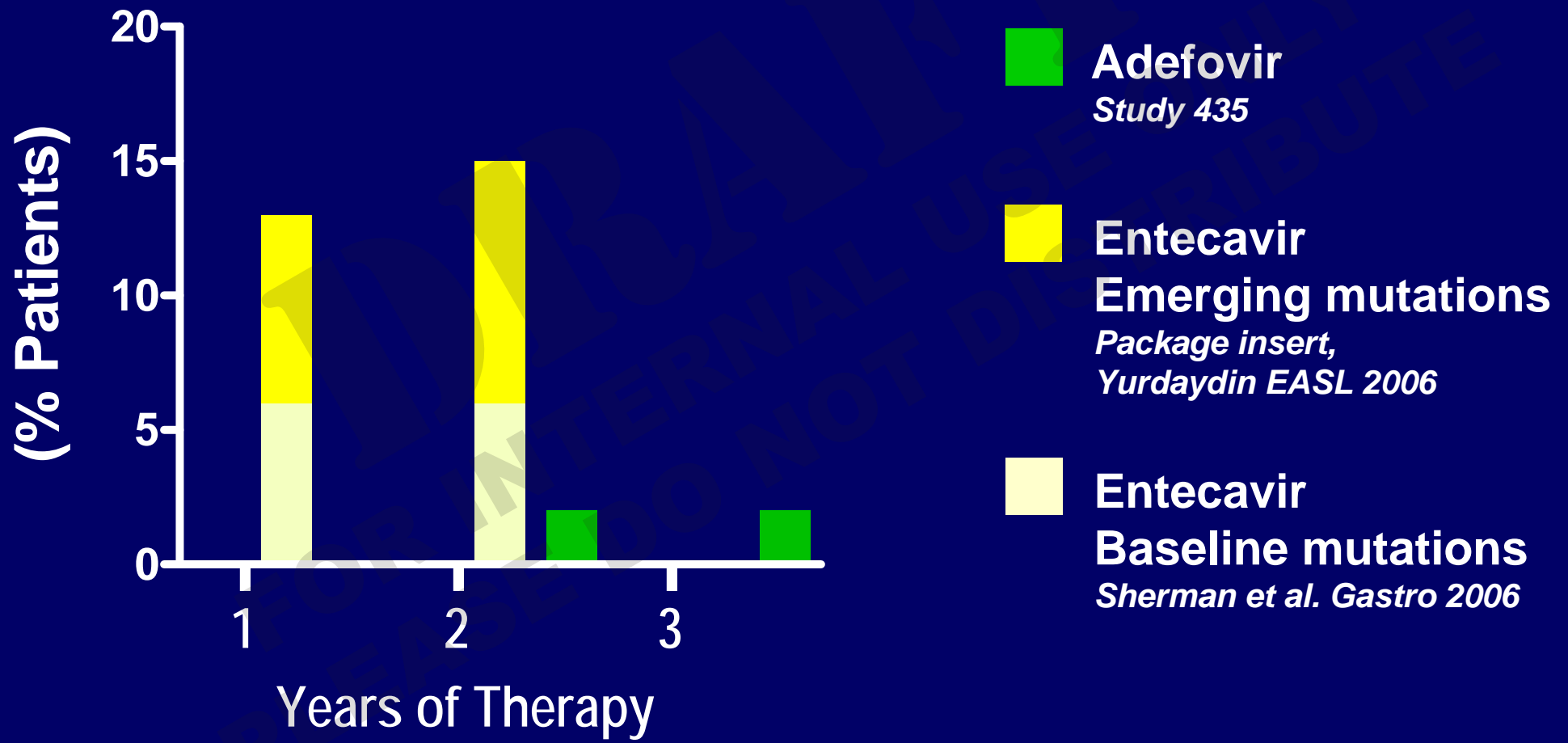
Introduction

- Long-term nucleos(tide) therapy is limited by the emergence of resistance
- Defining resistance profiles of drugs is essential for optimal patient management
- New anti-HBV drugs with structural similarity to ADV or LAM are in advanced clinical development

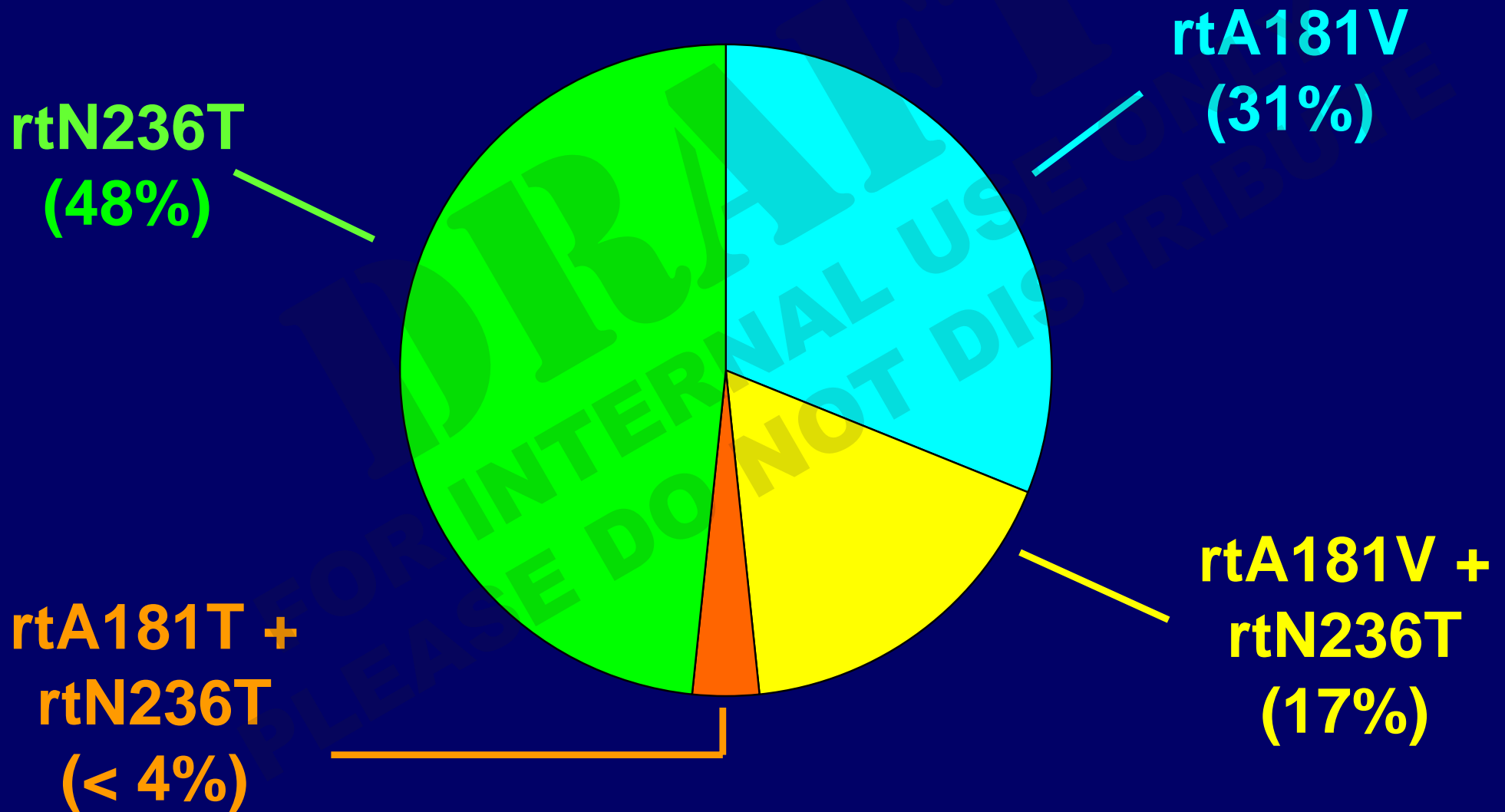
Long-term Genotypic Resistance Rates: Treatment Naive Patients



Long-term Resistance Rates: Lamivudine-Resistant Patients



Mutations Among eAg Negative Patients with Virologic Failure During ADV Therapy



Data from Year 5 of study 438; n = 29

Objectives

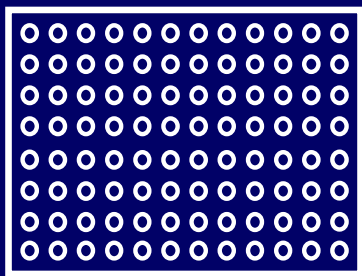
- To quantify in vitro levels of resistance for adefovir-associated mutations
- To quantify in vitro cross-resistance of adefovir-associated mutations to other anti-HBV agents

Methods

- Generated stable cell lines expressing five patterns of adefovir-associated mutations
 - rtN236T
 - rtA181V
 - rtA181V + rtN236T
 - rtA181T + rtN236T
 - rtA181T
- Used previously validated qPCR assay to test drug susceptibility
 - Yang *et al. Antiviral Therapy* 2005 10:625

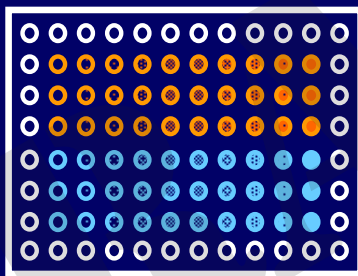
Drug Susceptibility Assay

Seed Cells



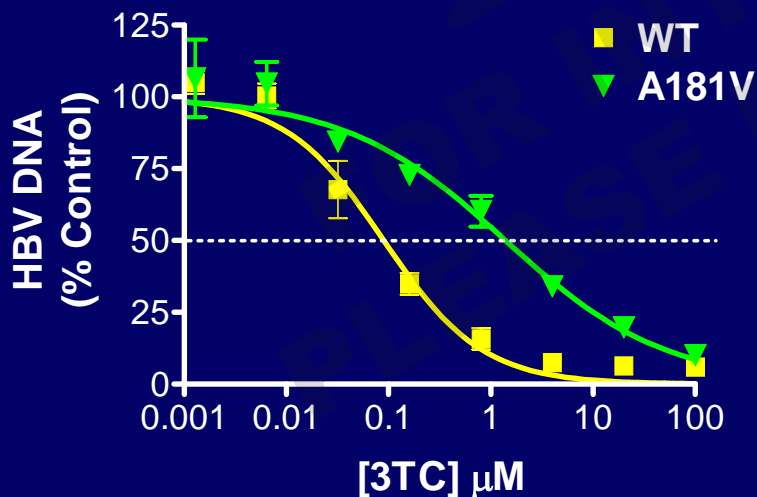
O/N

Add Drugs



1 wk

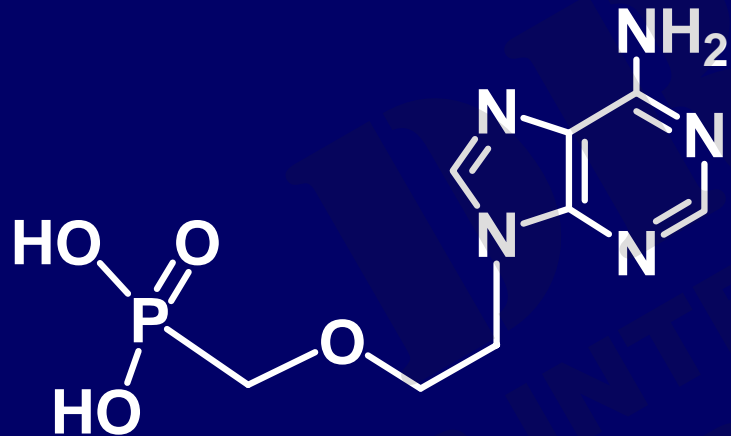
Quantify HBV
TaqMan qPCR



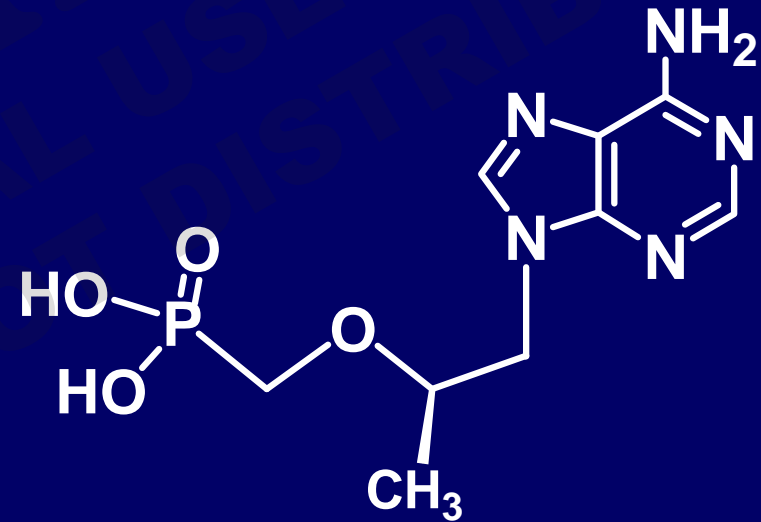
$$\text{Fold Resistance} = \frac{\text{Mutant EC}_{50}}{\text{WT EC}_{50}}$$

Acyclic Nucleotides

Adefovir



Tenofovir



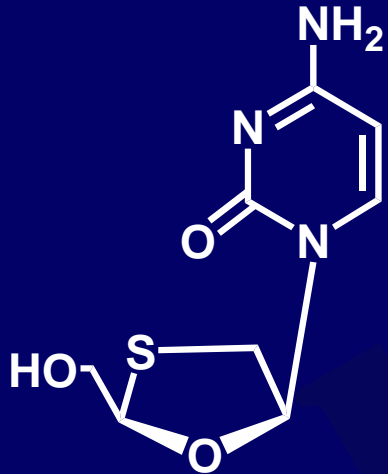
In Vitro Susceptibility Changes

Fold Change in EC₅₀ from WT

	N236T	A181V	A181V+ N236T	A181T+ N236T	A181T	M204I
Adefovir	6.8	4.2	17.4	5.2	1.2	1.8
Tenofovir	4.1	3.0	9.9	2.9	1.2	2.1

Cyclic Nucleoside Analogs

Lamivudine



Emtricitabine



Entecavir



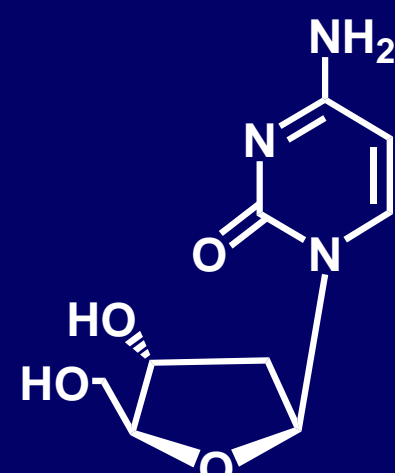
Telbivudine



Clevudine



Torcitabine



In Vitro Susceptibility Changes

Fold Change in EC₅₀ from WT

	N236T	A181V	A181V + N236T	A181T + N236T	A181T	M204I
ETV	1.9	12.1	18.9	2.8	7.8	471
3TC	10.7	14.1	34.0	34.6	10.4	>1000
FTC	12.5	14.7	73.4	47.3	12.4	>2000
L-dT	2.9	>24	>37	19.9	15.5	>322
L-dC	2.1	87	>270	101	126	>180
L-FMAU	8.2	>164	>175	>175	87.7	>1600

In Vitro ADV Cross-resistance Summary (I)

- **A181T is not resistant to adefovir or tenofovir**
- **Tenofovir is more active than adefovir against ADV-associated mutants**
- **Entecavir and tenofovir are likely active clinically against ADV-associated mutations**
 - Villeneuve *et al.* *Hepatology* 2005 42:588A.
 - Fung *et al.* *J Hepatol* 2005 43:937-43.
 - Ratziu *et al.* *Comp Hepatol* 2006 5:1

In Vitro ADV Cross-resistance Summary (II)

- **A181V/T shows reduced susceptibility to all L-nucleosides**
 - lamivudine, emtricitabine may retain sufficient activity for clinical efficacy
 - clevudine, telbivudine, torcitabine lose substantial activity
- **Further clinical studies necessary for establishing in vitro cutoffs**

Acknowledgements

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