NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Hepatitis B Case Studies

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No conflicts of interest

NW AETC | echo

Case 1 – Extensive Treatment Experience

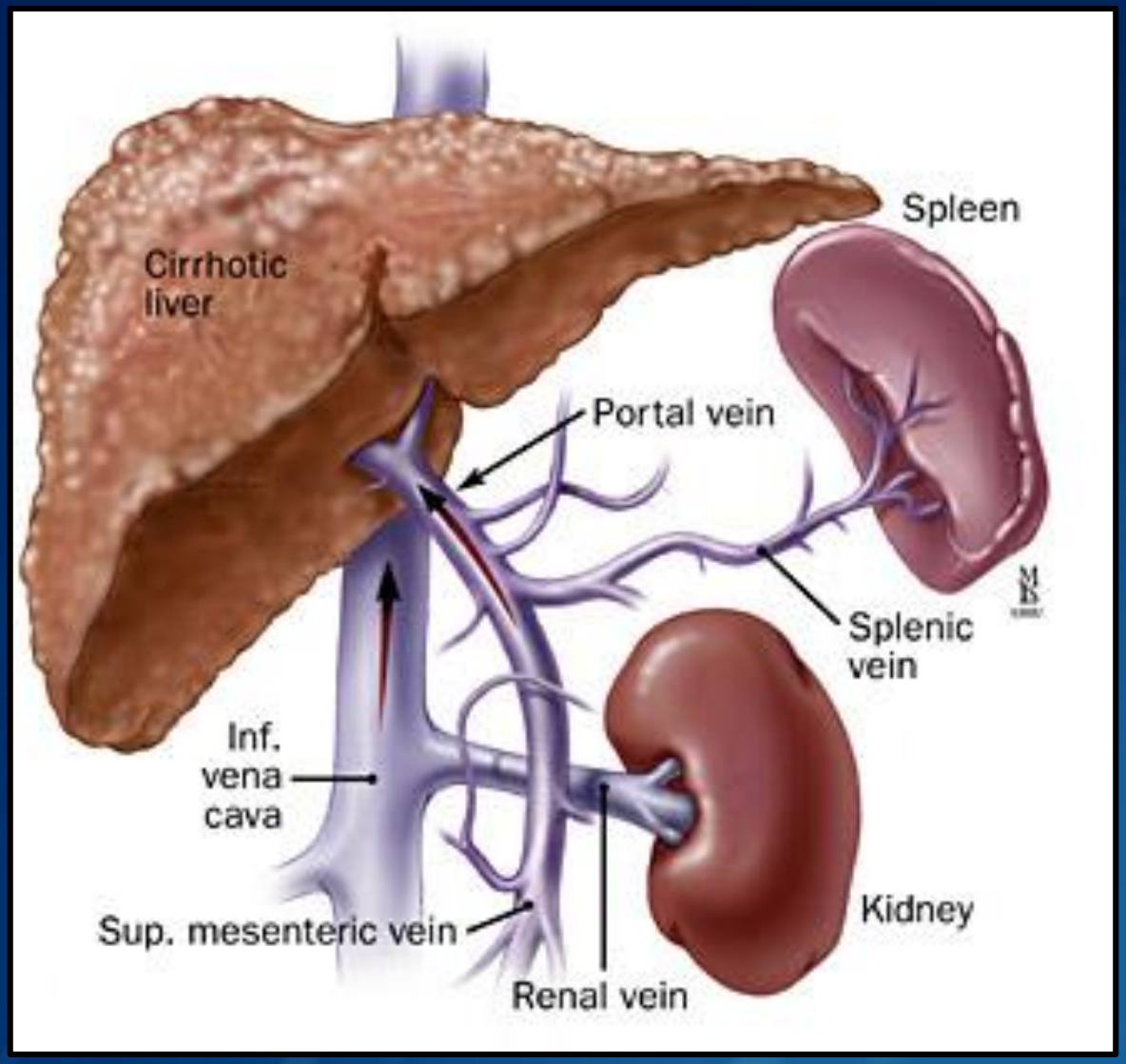
44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection. Diagnosed with both in 1996, risk factor: sex with men & women. Hx major depression.

HIV Hx

- Hx multiple ART regimens including d4T/3TC dual therapy in 1990s
- HIV resistance: Protease mutations - D30N and N88D and RT mutations - M184V, R211K, K70R, L74V, L100I, K103N, and K219E

Chronic HBV Hx

- eAg positive with baseline HBV level of 110 million IU/mL
- Ultrasound: Echogenic liver. In 2004, US showed early hepatofugal flow and mildly enlarged spleen



Source: gi.jhsps.org

Case 1 – Extensive Treatment Experience

44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection, e-Ag positive with high baseline HBV viral level and probable cirrhosis.

- Persistent HBV viremia in 5 $\log_{10}$ IU/mL range on lamivudine/adefovir (along with various antiretroviral agents) for many years

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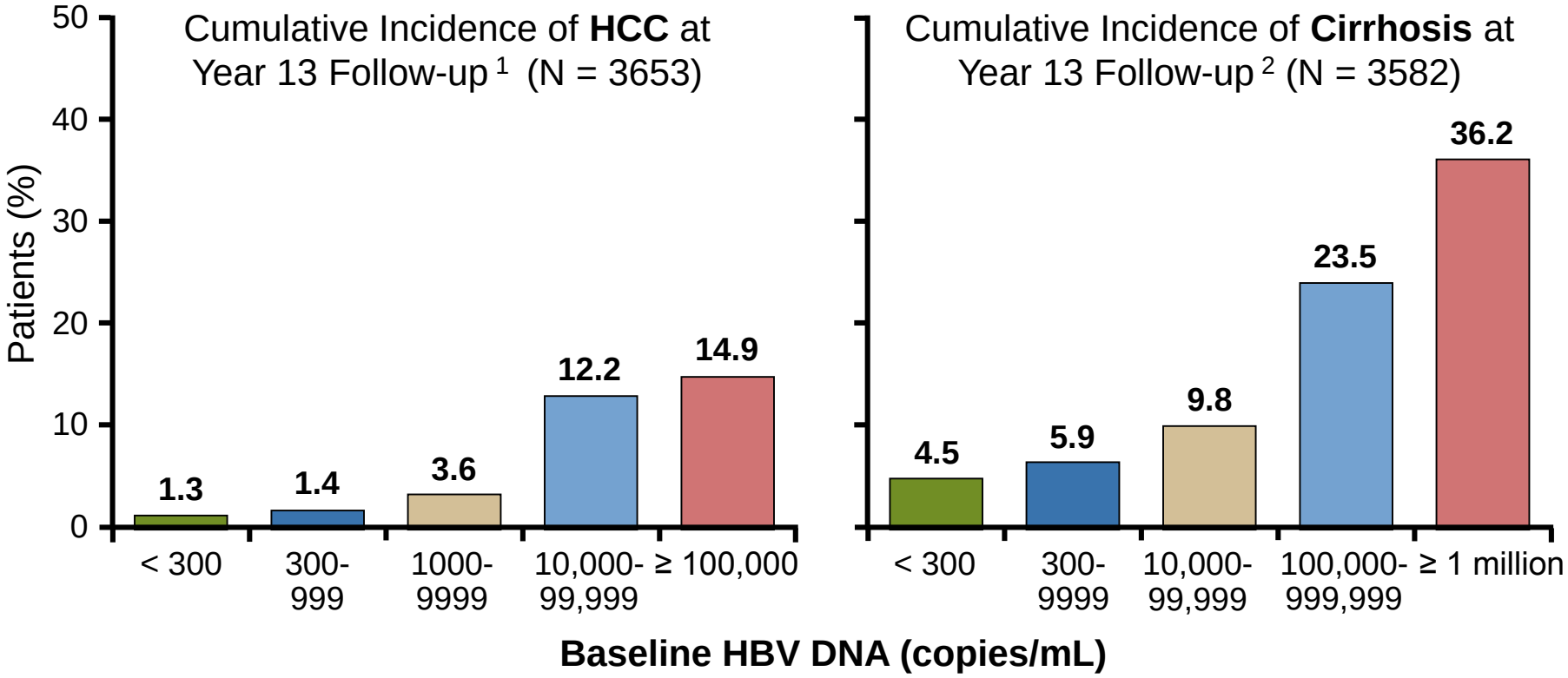
HBV DNA Level Associated With Increased Risk of HCC & Cirrhosis

REVEAL: Long-term follow-up of untreated HBV carriers in Taiwan



1. Chen CJ, et al. JAMA. 2006;295:65-73.
2. Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

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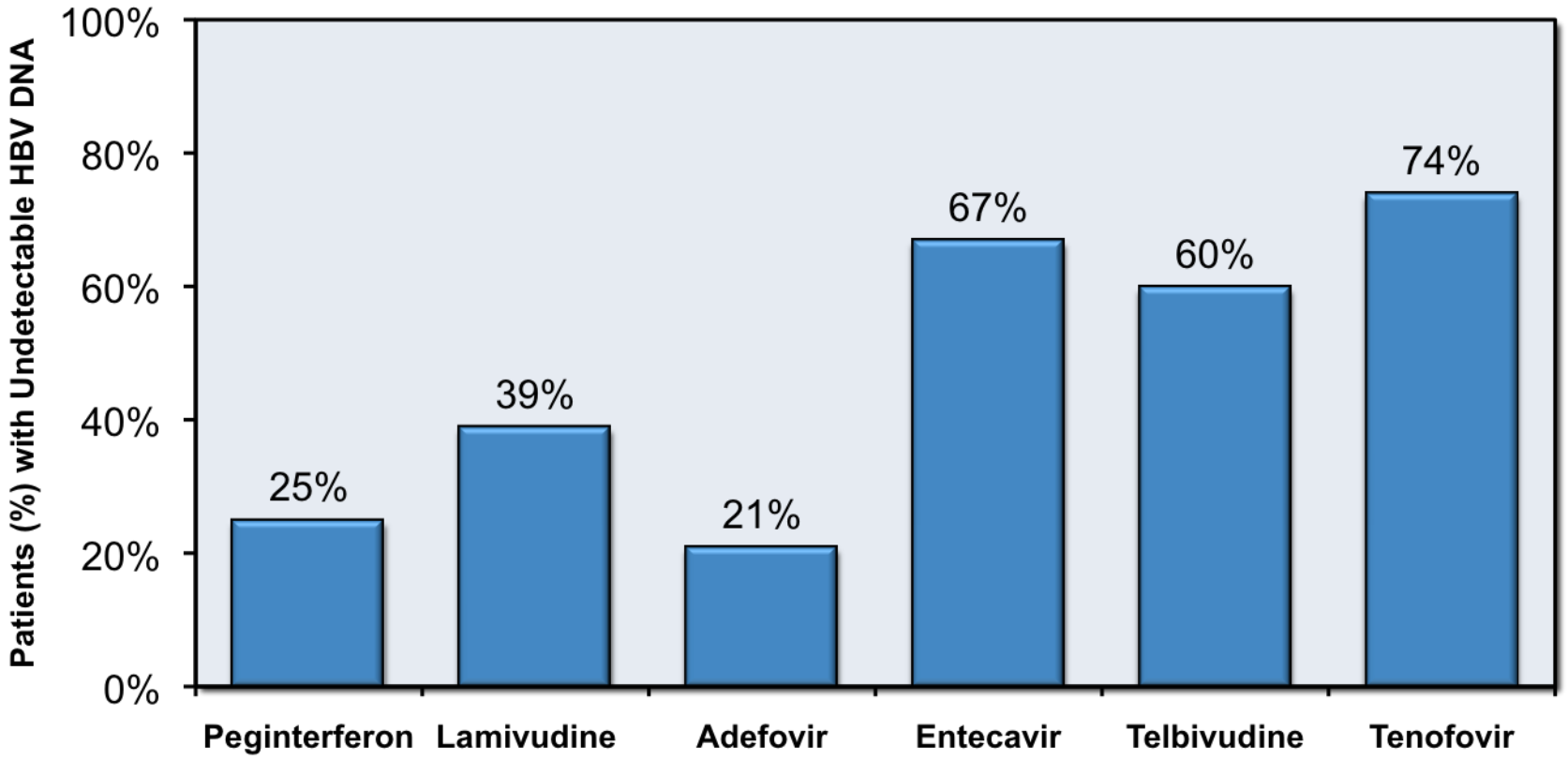
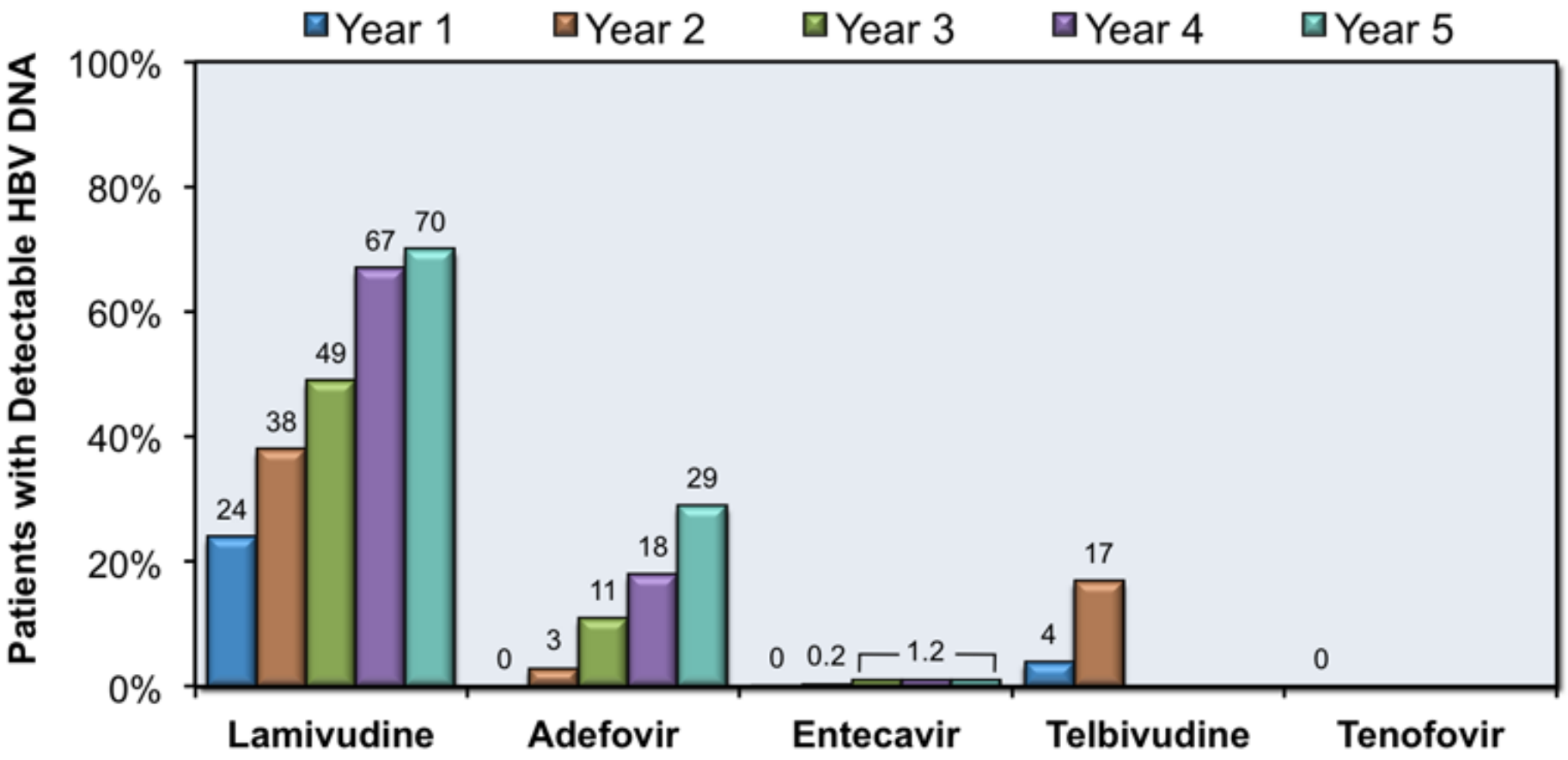
HBV Suppression after 1 Year
HBeAg-positive Patients



EASL Hep B Clinical Practice Guidelines 2012

Probability of Virologic Failure



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Case 1 – Extensive Treatment Experience

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- Persistent HBV viremia in 5 $\log_{10}$ range on lamivudine/adefovir (& various ART) for many years until finally
- Switched to ART: Truvada, Kaletra and fosamprenavir in 2007.
- CD4 480 cells/mm^3, HIV suppressed and HBV DNA at nadir 20 IU/mL
- Chemistry panel shows new Cr elevation **1.6**. Serum phophate **2.5**. ALT remain normal. UA: 1+ protein, 1+ glucose (normal serum glucose), no cells or casts.
- What would you do next?

Peginterferon in HIV-HBV Coinfected Patients

Advantages	Disadvantages
• Finite treatment course • No drug resistance • Highly sustainable response* (eAg/Ab conversion) • HBsAg clearance*	• Subcutaneous injection • Frequent adverse effects • Risk of hepatitis flare • Contraindicated in advanced cirrhotics

*Treatment efficacy may be limited/suboptimal in HIV-infected patients, esp. with low CD4 cell counts.

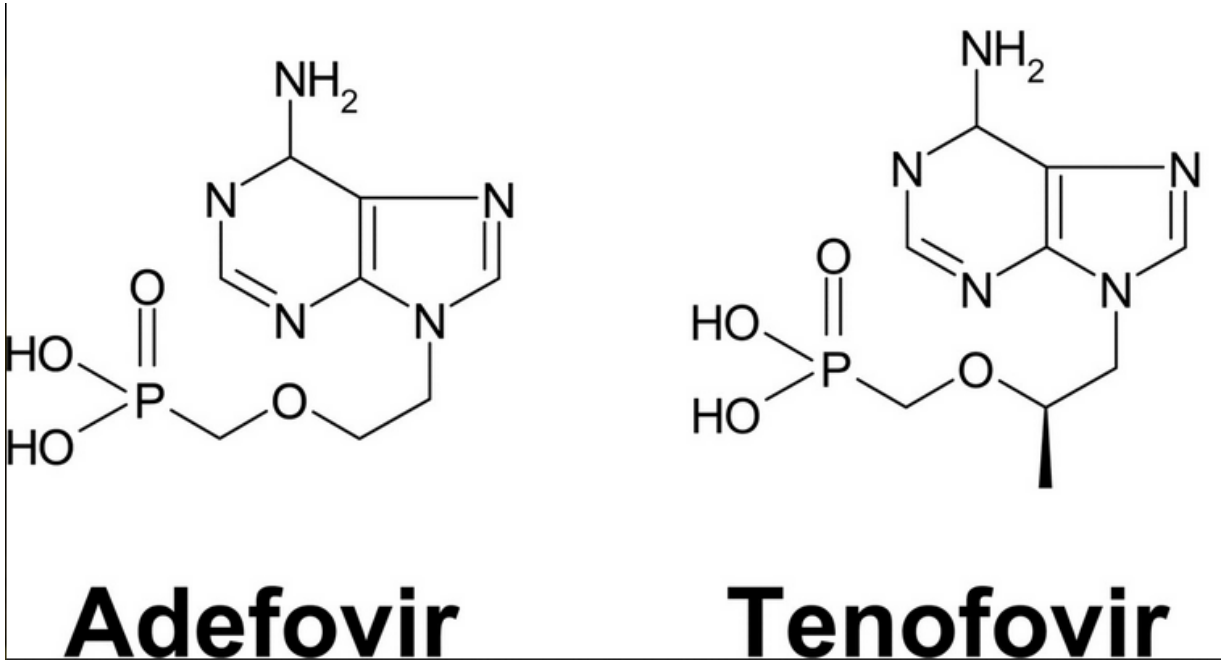
DiMartino, *Gastroenterol* 2002;123:1812-22.

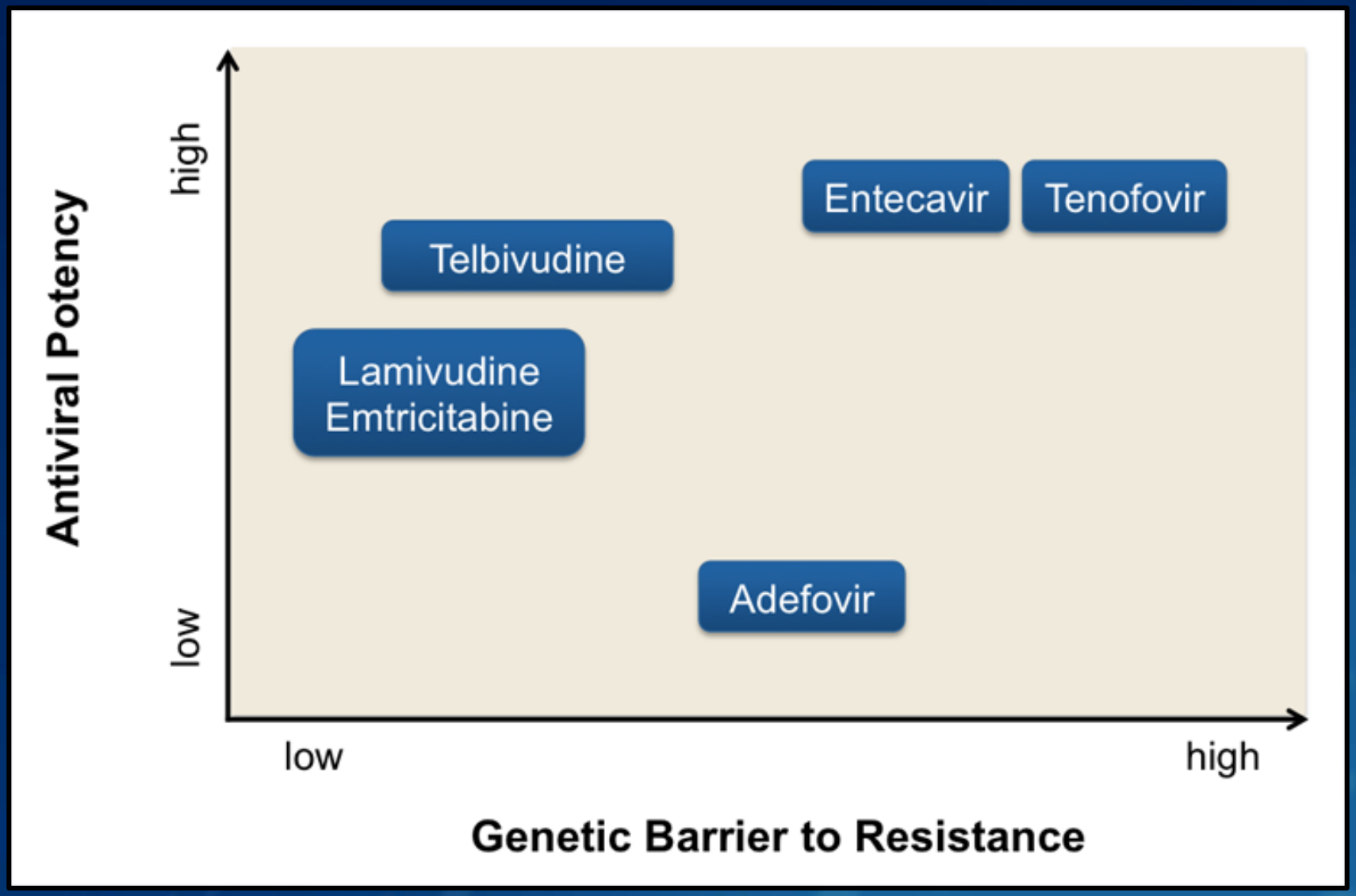
Oral HBV-active Antiviral Agents

Medication	Potency against HBV	Barrier to HBV Resistance	HIV Activity	Selection of HIV Resistance Reported
Lamivudine	**Moderate**	**Low**	**Yes**	**Yes**
Adefovir	Low	Moderate	No[a]	No
Entecavir	High	High	Partial	Yes
Emtricitabine	**Moderate**	**Low**	**Yes**	**Yes**
Telbivudine	High	Low	Partial[b]	No
Tenofovir	**High**	**High**	**Yes**	**Yes**

[a] = anti-HIV activity at higher doses; more potent against HBV
[b] = No in vitro activity observed against HIV, but HIV RNA decline reported

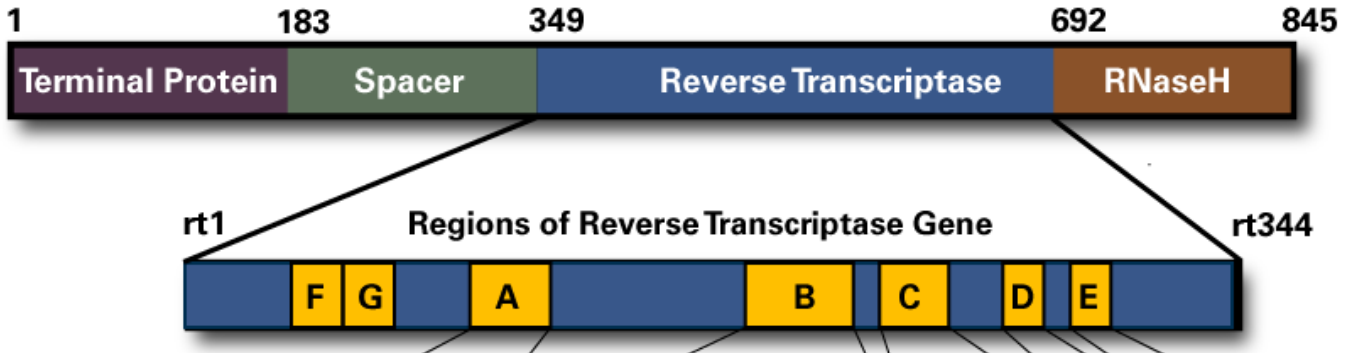
Nucleotide Analogues: Adefovir and Tenofovir





EASL Hep B Clinical Practice Guidelines 2012

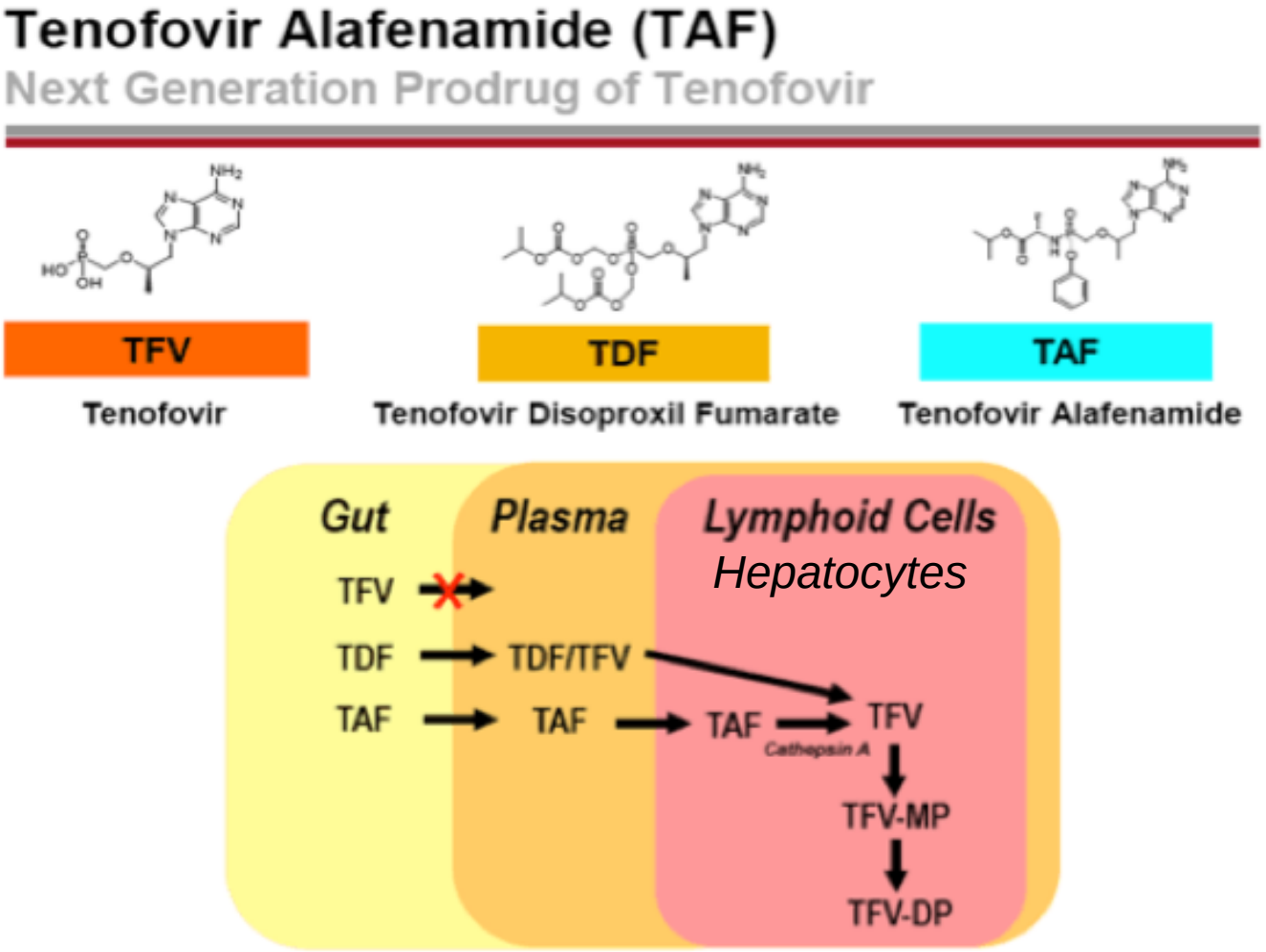
HBV Polymerase Gene



Mutations and Amino Acid Substitutions Associated with Resistance to Nucleoside Analogues

Gene Region	A		B				C		D	E
Baseline Amino Acid Position	80	169	173	180	181	184	202	204	236	250
Baseline Amino Acid	L	I	V	L	A	T	S	M	N	M
Lamivudine Resistance	V/I		L	M	T			V/I/S		
Adefovir Resistance					T/V				T	
Entecavir Resistance		T		M		S/A/I/ L/F/G	G/I	V		V
Telbivudine Resistance								I		

Tenofovir Alafenamide for HBV?



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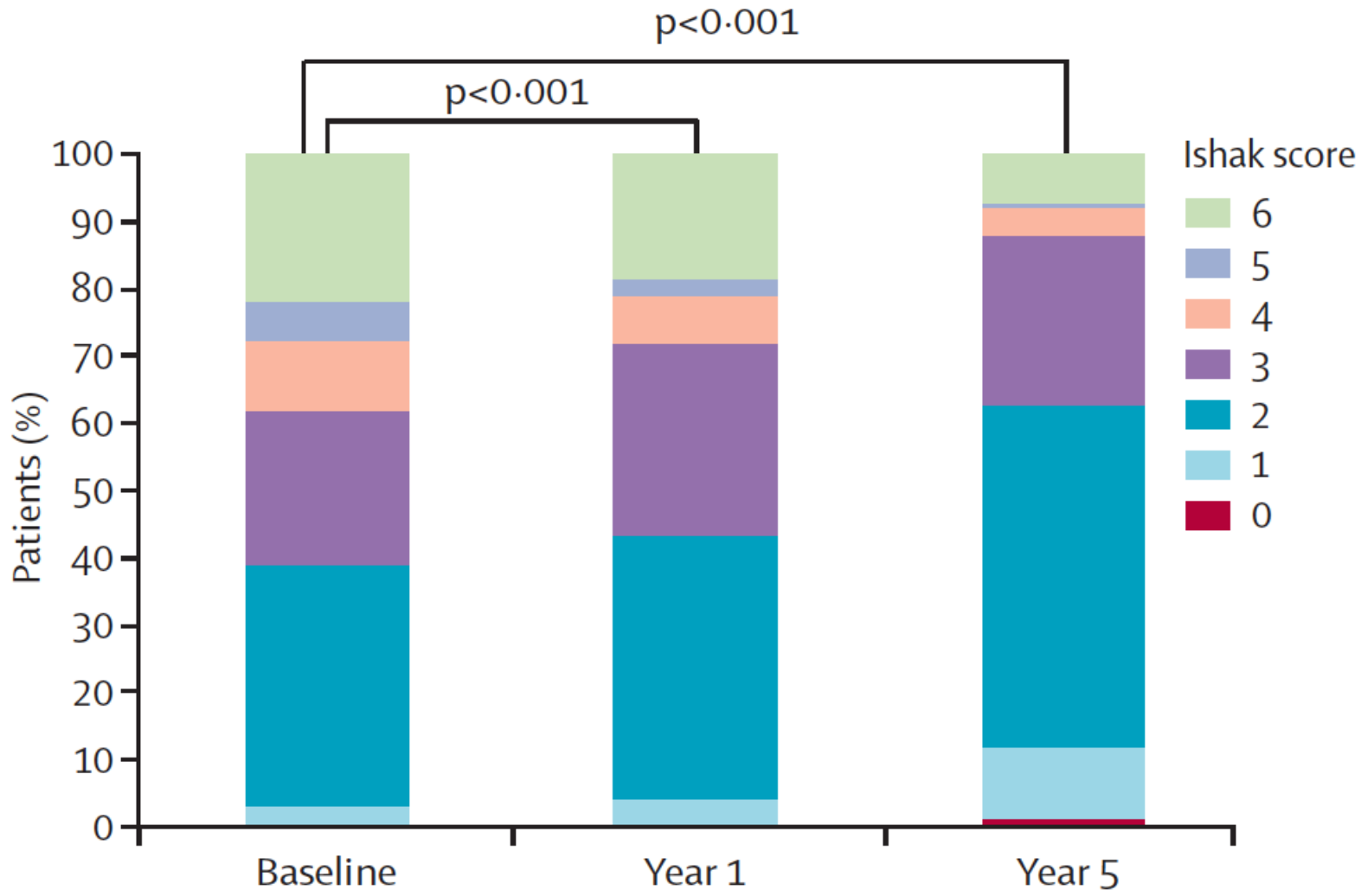
44 yo man with longstanding HIV infection, stage 2 with nadir CD4 220 and chronic hepatitis B infection.

- Persistent HBV viremia in 5 $\log_{10}$ range on lamivudine/adefovir (& various ART) for many years until finally
- CD4 480 cells/mm^3, HIV suppressed and HBV DNA at nadir 20 IU/mL on ART: Truvada, Kaletra and fosamprenavir in 2007.
- Chemistry panel shows new Cr elevation **1.6**. Serum phophate **2.5**. ALT remain normal. UA: 1+ protein, 1+ glucose.
- Tenofovir stopped. Entecavir 1.0 mg daily dose started with continued HBV suppression.
- Ultrasound in 2015: normal-sized spleen, hepatopetal flow & mildly echogenic liver

Regression of Cirrhosis in Patients on Tenofovir



Marcellin, et. al. *Lancet* 2013; 381: 468-75.

Case 2 – Ongoing HBV Viremia on TDF/FTC

47 yo man with stage 3 HIV infection nadir CD4 0 with a history of cryptococcal meningitis in 2007, VZV meningitis in 2008. Seizure disorder and spastic paraparesis 2* HIV myelopathy. Chronic hepatitis B without clinical evidence of cirrhosis.

- 2009 – started on Truvada (TDF/FTC), abacavir, darunavir, raltegravir
- 2009-2010 – Still HBV viremic to 5-7 $\log_{10}$ IU/mL range in background of HIV suppression

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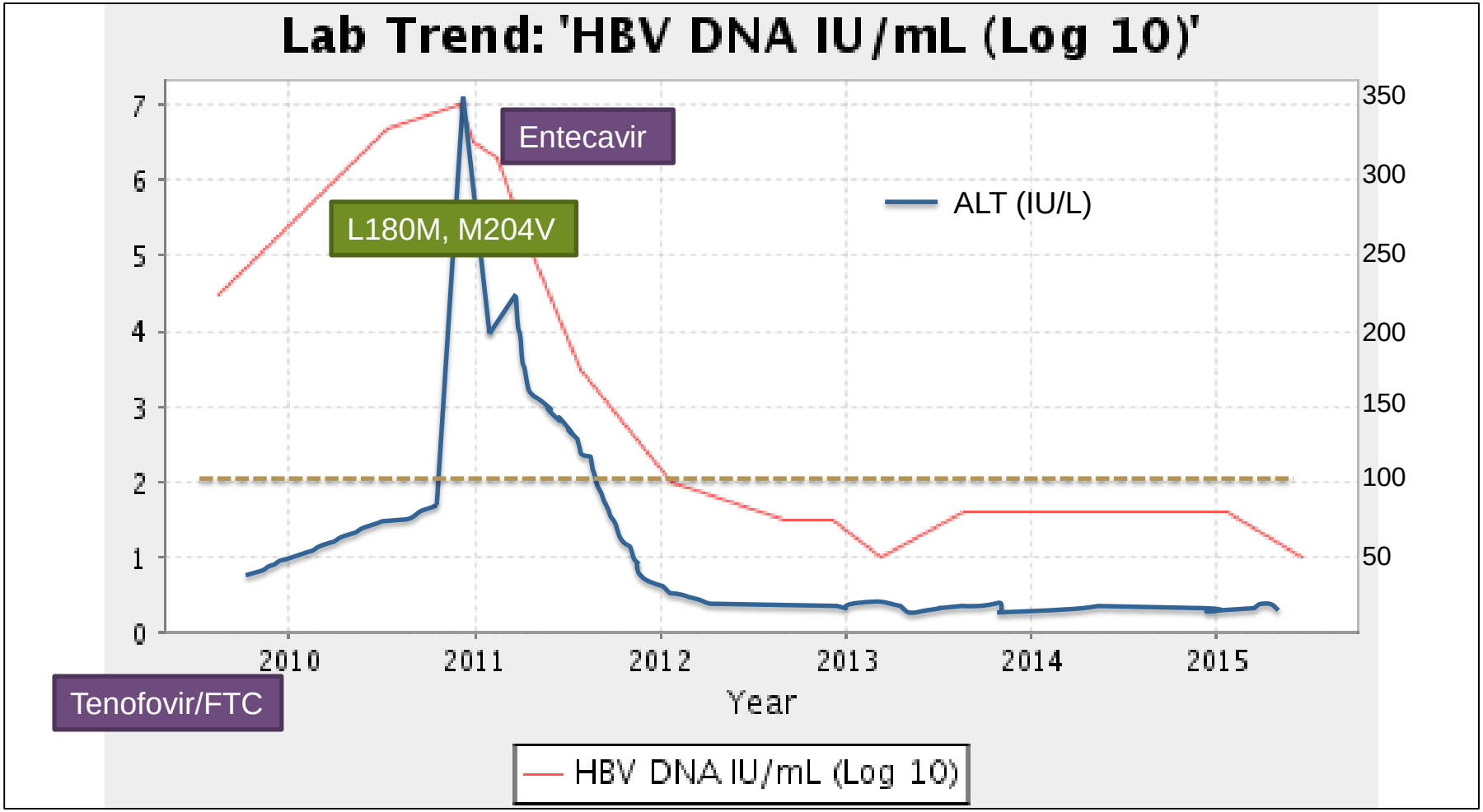

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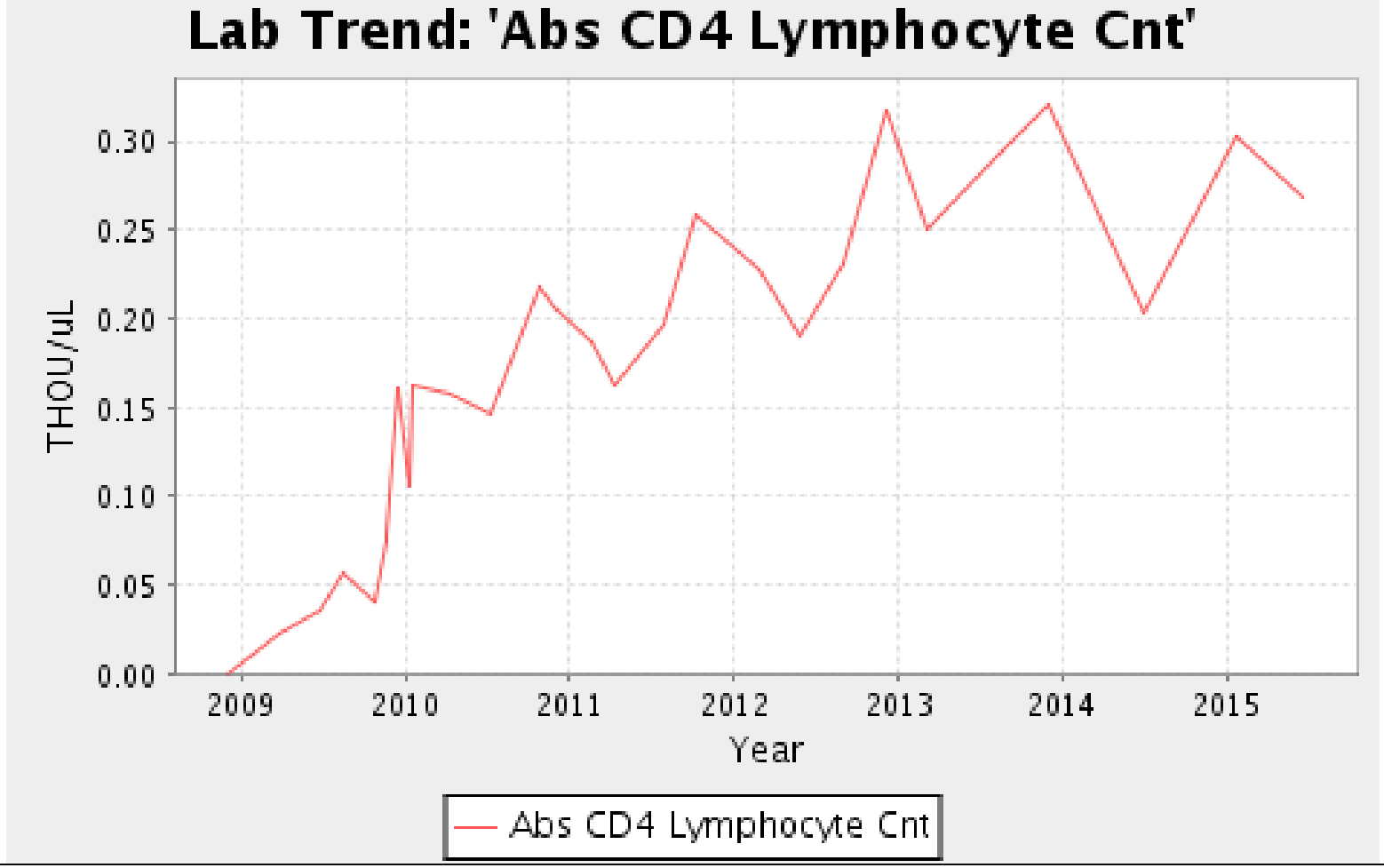
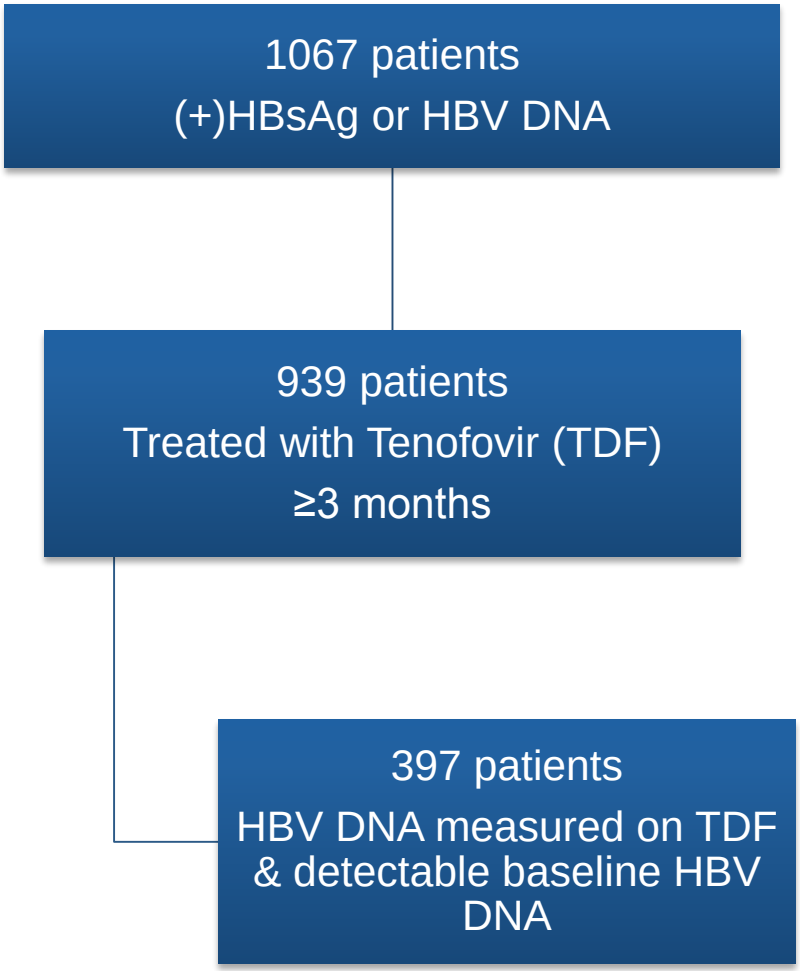


Chronic HBV in the CNICS Cohort



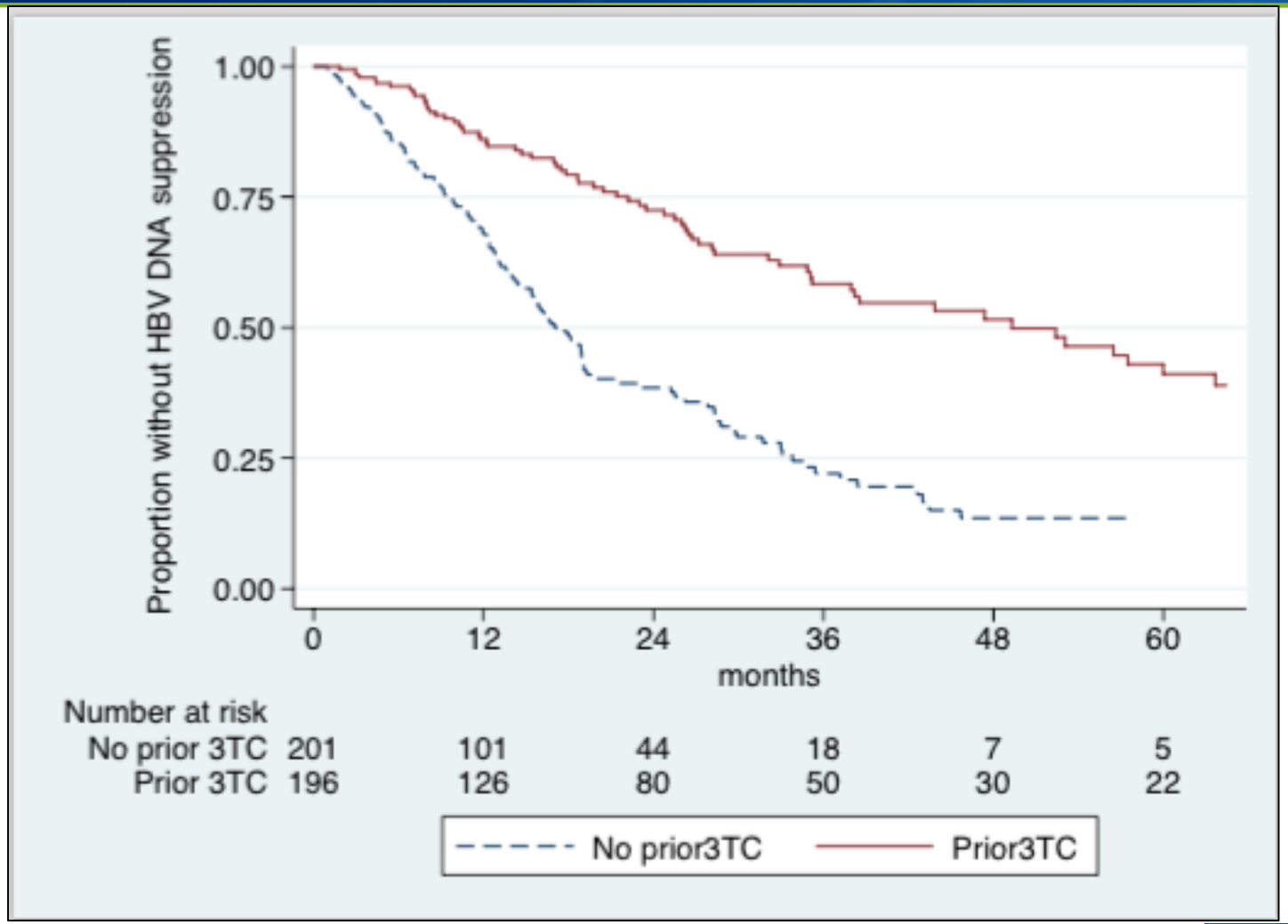
Kim, *JAIDS* 2014; 66:96-101.

Risk Factors for Delayed HBV Suppression

Variable	Adjusted Hazard Ratio (95% CI)	P
3TC exposure	**0.60 (0.42-0.85)**	**<0.01**
Age >40 yrs	1.08 (0.81-1.43)	0.62
Nadir CD4, cells/mm^3 (ref: ≥500)		
350-499	0.58 (0.33-1.01)	0.06
200-249	0.55 (0.32-0.93)	0.03
<200	**0.53 (0.31-0.88)**	**0.02**
HBV DNA level >10,000 IU/mL	**0.34 (0.22-0.53)**	**<0.01**
Race (ref: white)		
Black	0.78 (0.56-1.08)	0.14
Other	1.21 (0.60-2.45)	0.61
Serum ALT >80 U/L	**1.56 (1.14-2.15)**	**0.01**

Kim, *JAIDS* 2014; 66:96-101.

Delayed HBV DNA Suppression on Tenofovir



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Dual Therapy for HBV: TDF + ETV or FTC

- Probably not worth the cost & additional drug exposure in HBV mono-infected patients who are treatment-naive.
- Dual* therapy may be considered in patients who are:
  - Treatment-experienced esp if HBV viremic on prior therapy
  - Cirrhotic
  - HIV-co-infected (esp. if lamivudine-experienced)
  - Transplant patients

*NOTE: It remains unclear if dual therapy should be TDF/FTC vs TDF/ETV

Lok, *Gastroenterol* 2012;143:619.
Petersen, *J Hepatol* 2012;56:520.

Take Home Points

- Avoid lamivudine or emtricitabine monotherapy for your HIV-HBV co-infected patients
- Adefovir is not potent. Know the limitations of these antivirals.
- Peginterferon is not 1st-line standard of care in HIV-HBV
- HBV viral suppression can be delayed out to 2 or more years in some HIV-HBV patients.
  - Some of this may not be due to drug but to lack of immune clearance
  - Not everyone needs entecavir