

Is Antiviral Drug-resistant HBV a Problem of the Past?

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Approved HBV Treatments

- Interferon alpha 2b (Intron)
- Pegylated interferon alpha 2a (Pegasys)
- Lamivudine (Epivir)
- Adefovir (Hepsera)
- Entecavir (Baraclude)
- Telbivudine (Tyzeka)
- Tenofovir (Viread)

Treatments approved for HIV with activity against HBV

- Emtricitabine (Emtriva)
 - Tenofovir + Emtricitabine (Truvada)
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Antiviral Drug-resistant HBV is Inevitable

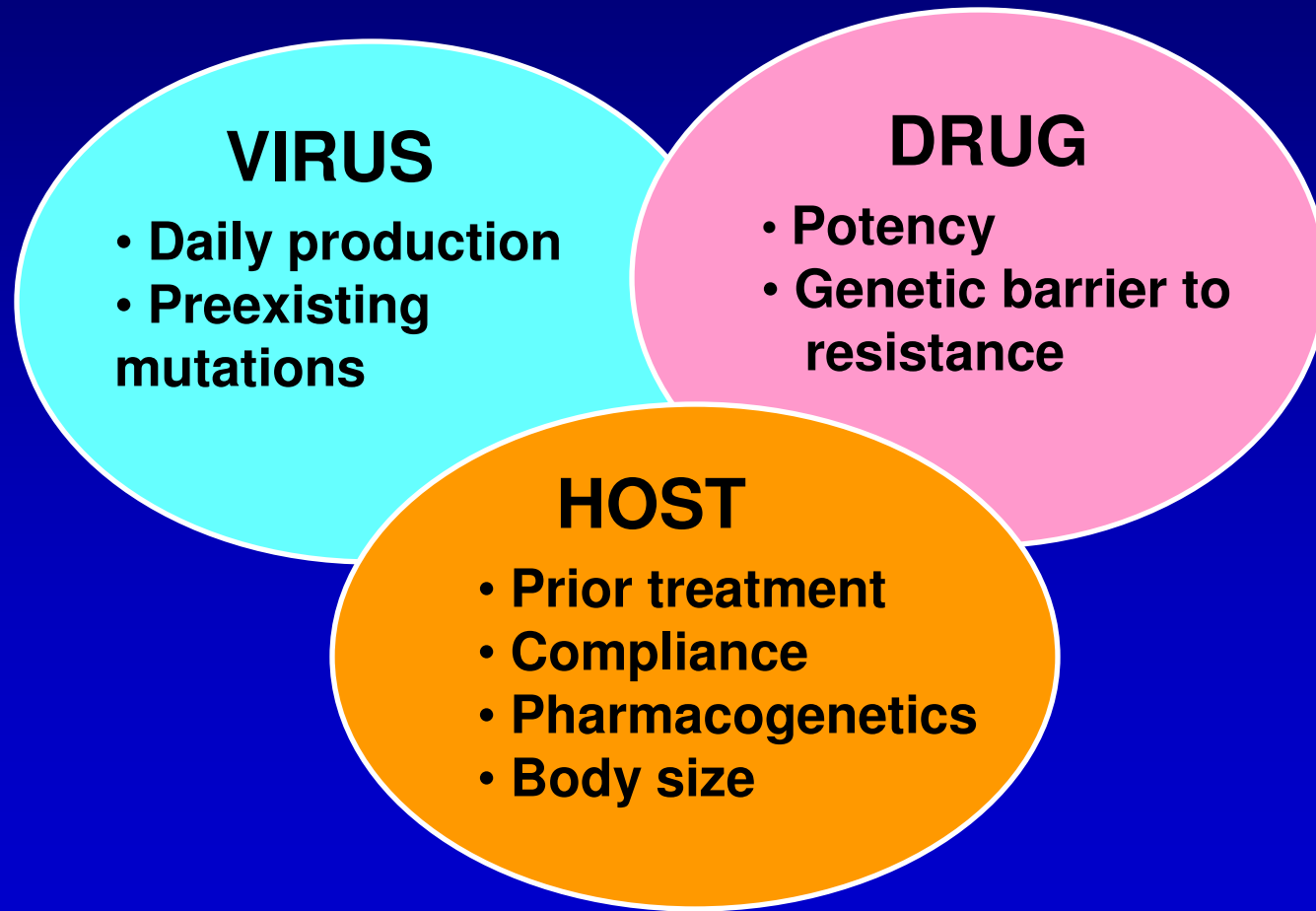
- High rate of HBV replication
 - High error rate in HBV replication – lack of proof reading during reverse transcription of pregenomic RNA to HBV DNA
 - Reservoir of covalently closed circular (ccc) DNA in liver refractory to antiviral therapy → prevents viral clearance
 - Limitations of approved treatments
 - Incomplete virus suppression with some drugs / in some patients
 - Low genetic barrier to resistance with some drugs
 - Realities of life
 - Medication non-compliance
 - Affordability of medications and monitoring
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What Causes Antiviral Drug-resistant HBV Variants to become Dominant?

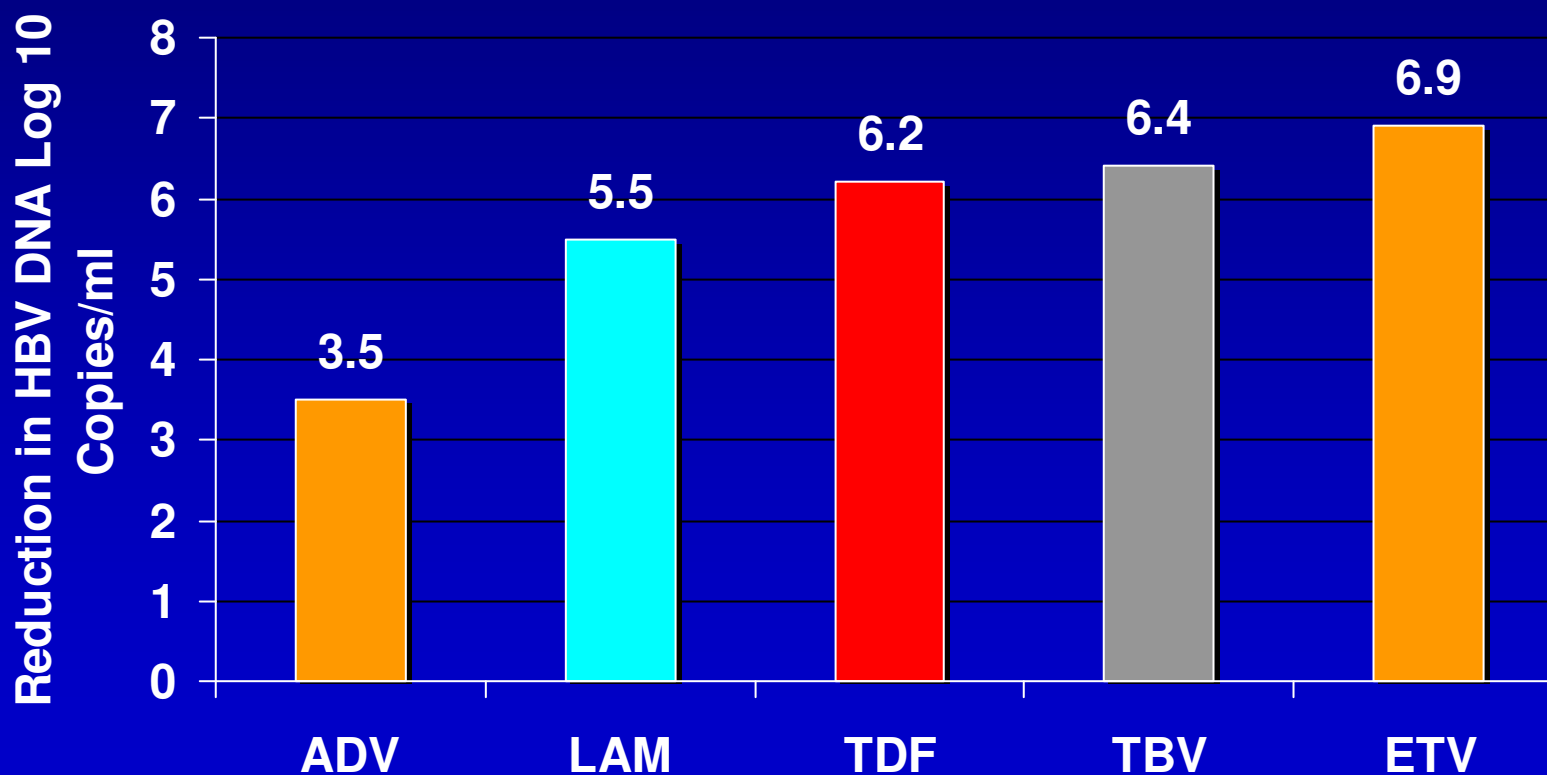
- Antiviral drug-resistant HBV mutations arise spontaneously and are selected during antiviral therapy - survival of the fittest



Factors associated with Antiviral Drug-resistant HBV



Clinical Potency of Approved Nucleos(t)ide Analogs in HBeAg+ CHB at 1 Year



Marcellin P NEJM 2003;348:808; Lai CL NEJM 1998;341:339:61; Dienstag JL NEJM 1999;341:1256; Marcellin P NEJM 2008;359:2442; Lai CL. NEJM 2007;357:2576; Chang TT MEJM 2006;354:1001.

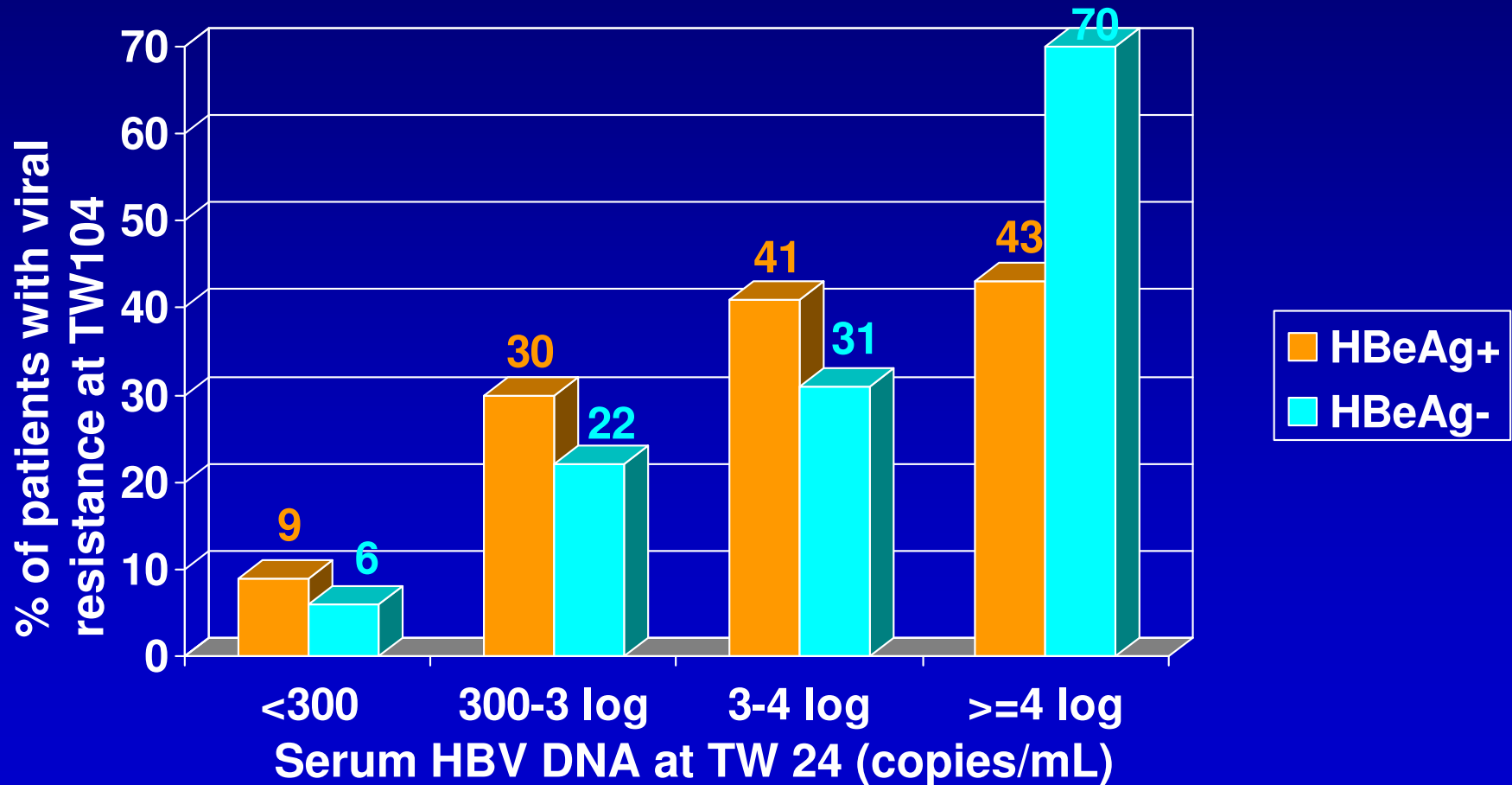
Genetic Barriers to Antiviral Resistance

- No. of amino acid changes required to confer resistance
- Decrease in susceptibility (increase in IC_{50}) caused by the mutations

<u>Nucleosid(t)e analogue</u>	<u>Mutations</u>	<u>Fold-decrease in susceptibility</u>
LAM/TBV	M 204 V/I	> 1,000
ADVDF	A 181 V or N 236 T	3 – 15
ETV	169 or 202	~ 1
	184 or 250	2 – 10
	M 204 V/I + 1 ETV-R	10 – 250
	M 204 V/I + 2 ETV-R	> 500

Suboptimal Viral Response is Associated with Increased Risk of Drug Resistance

Data from Telbivudine Phase III Trial



Viral resistance defined as confirmed genotypic resistance in patients with HBV DNA >5 log₁₀ copies/mL

How Common is Antiviral Drug-resistant HBV?

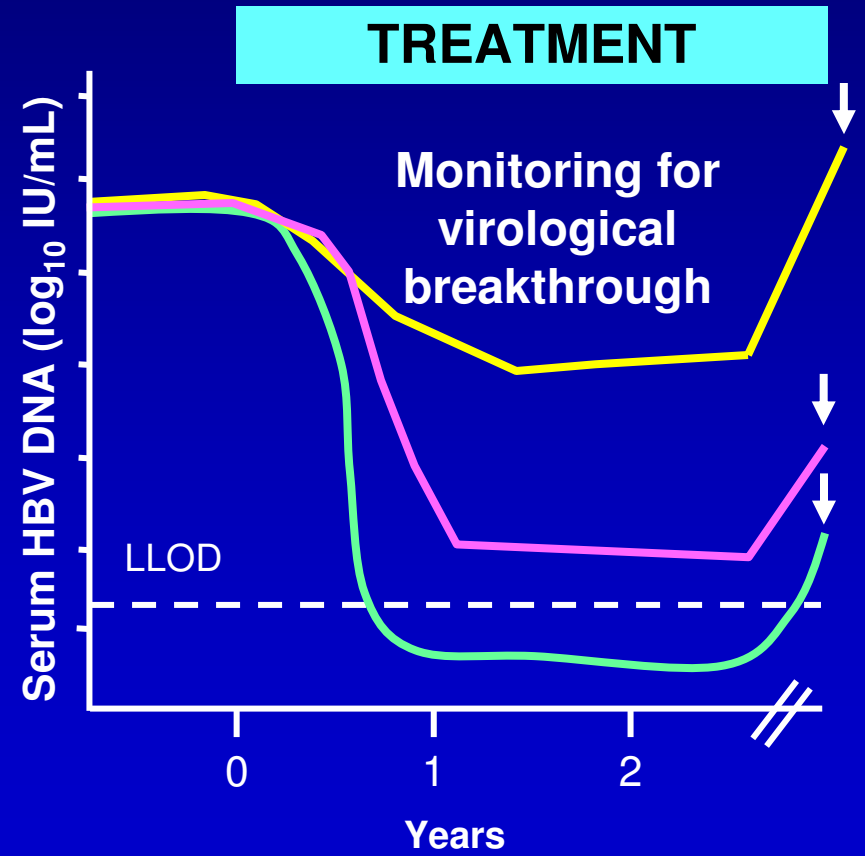
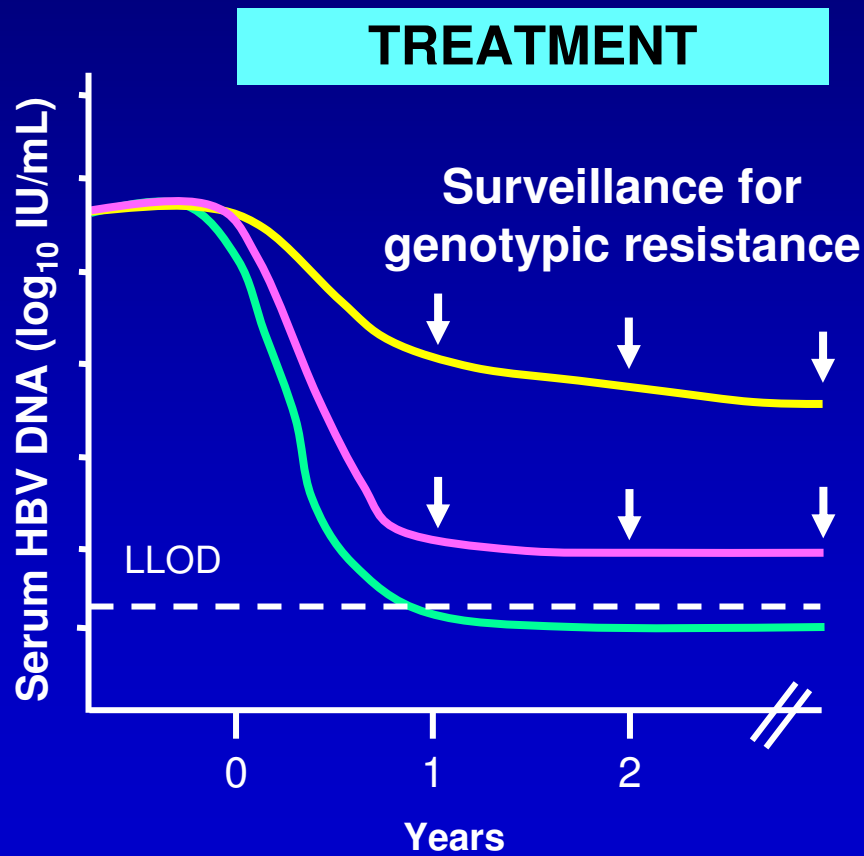
Depends on:

Patient population analyzed

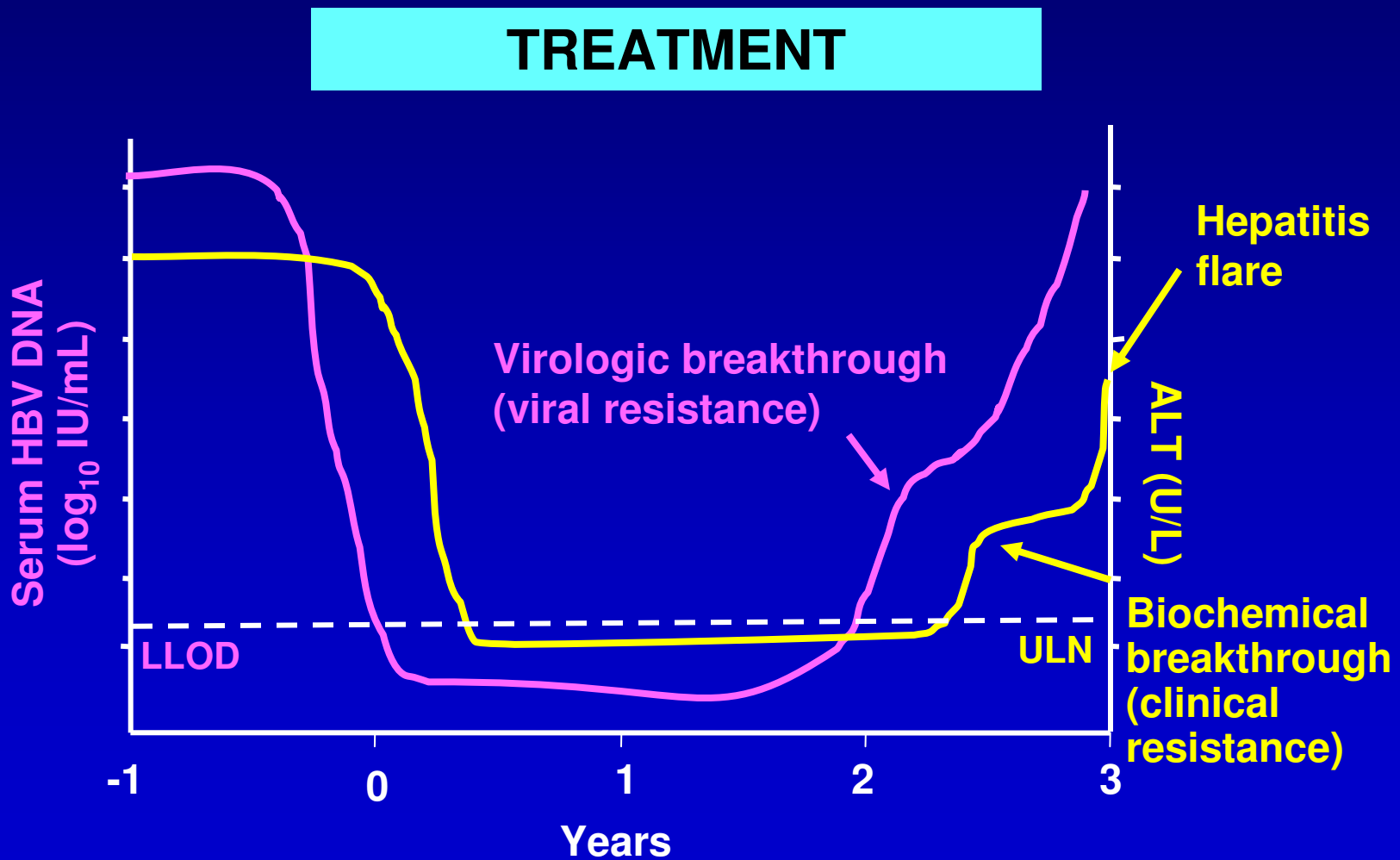
Definition of antiviral resistance

Sensitivity of assay used to detect resistant mutations

Monitoring for Antiviral Resistance

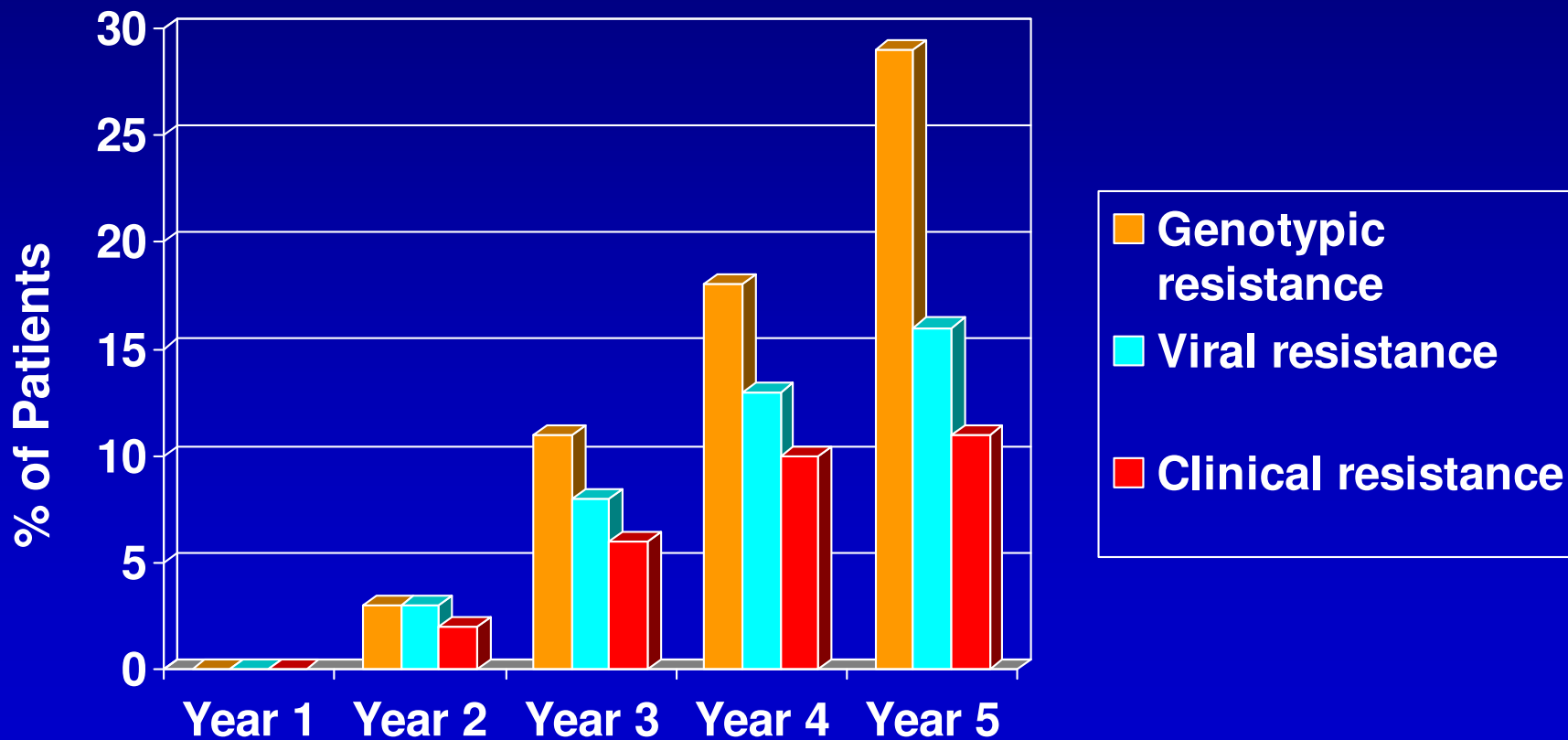


Virological Breakthrough Precedes Biochemical Breakthrough



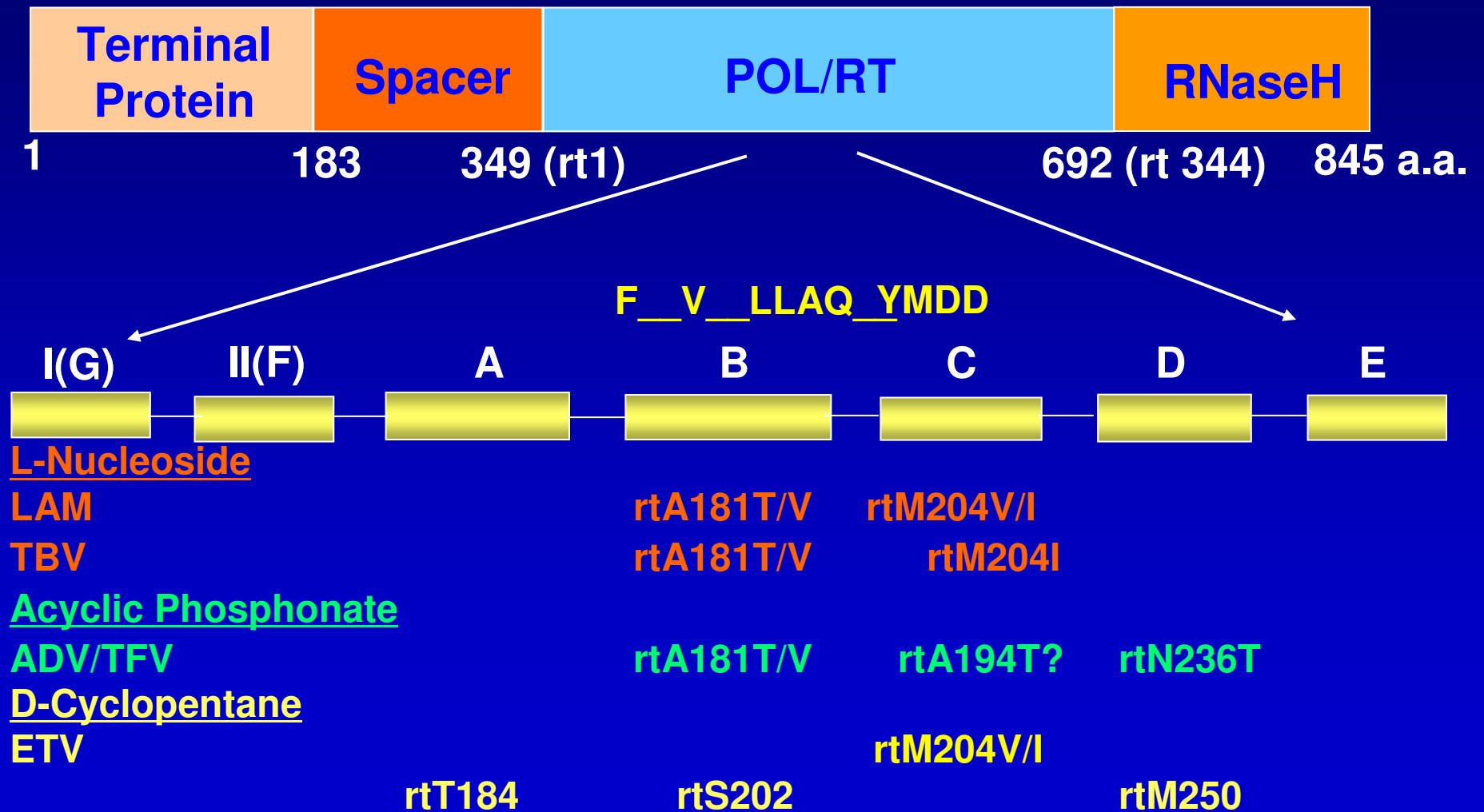
Cumulative Probability of Antiviral Resistance to Adefovir Therapy of HBeAg-negative Patients

Detection of resistant-mutations by direct sequencing



Borroto-Esoda. et al.

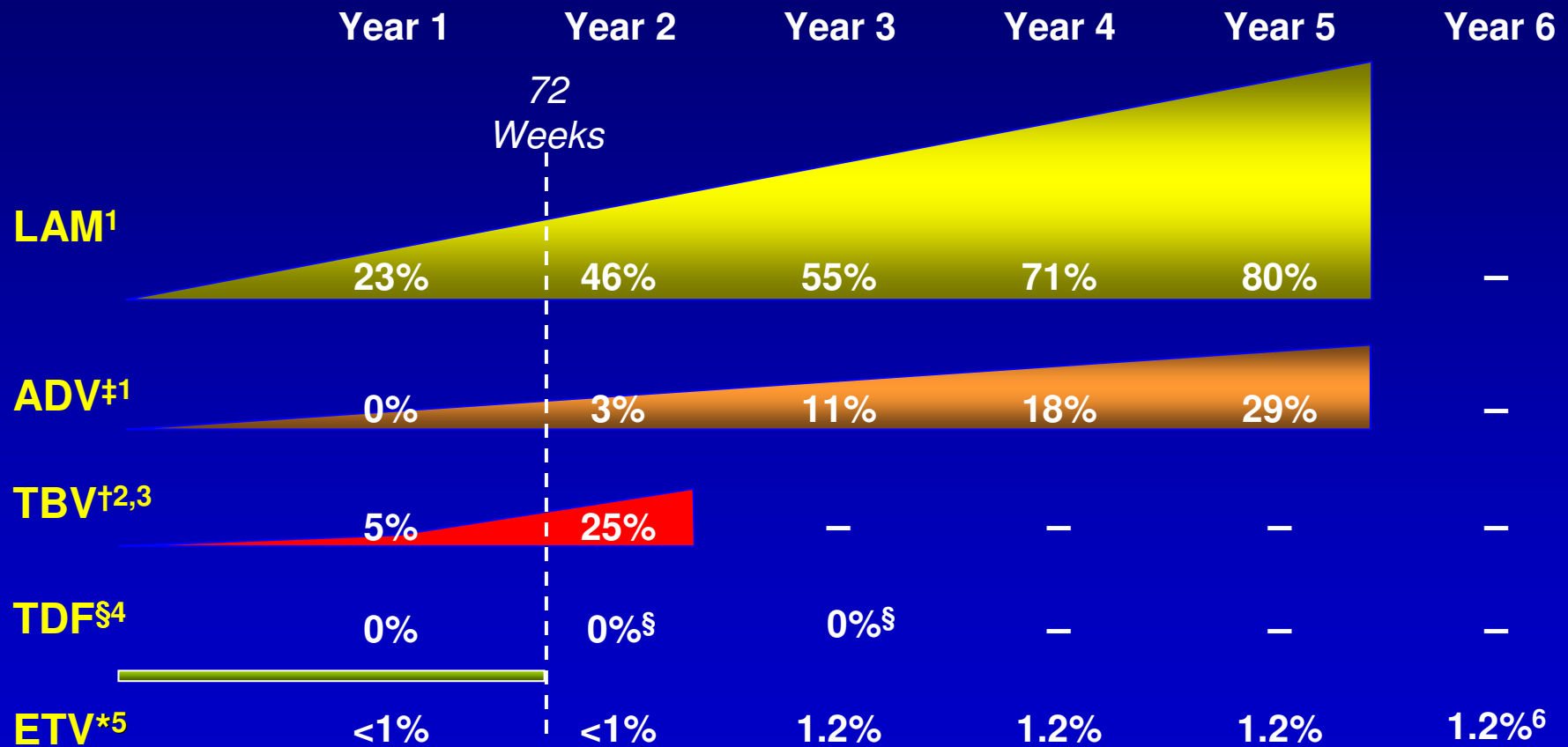
Primary Resistance Substitutions



Assays for Detecting Antiviral Drug-resistant Mutations

Assay	Advantages	Disadvantages
Direct sequencing	Detect all mutations Most useful with new therapies	Least sensitive at detecting minor populations (~20%)
Sequencing of multiple clones	Detect all mutations Sensitivity depends on no. of clones sequenced	Labor intensive
RFLP, Line probe	Sensitive (~5%) Early detection of genotypic resistance	Detect only known mutations
Single genome sequencing, MALDI-TOF mass spectrometry Ultra-deep pyrosequencing	Ultra-sensitive (~0.1%)	Cannot differentiate spontaneous mutations from mutations selected during treatment

Resistance Rates Through 6 Years Among Nucleos(t)ide-Naïve Patients



[§] Patients with HBV DNA \geq 400 copies/mL at Week 72 could add FTC to TDF;

* Cumulative probabilities of resistance taken; [†] Naïve HBeAg (+); [‡] Naïve HBeAg(-); N/A not available.

Is Antiviral Drug-resistant HBV a Problem of the Past in Nucleos(t)ide-naïve Patients?

Very low or no resistance reported, BUT...

- **Entecavir ~1.2% up to 6 yr**
 - A small number of non-responders excluded
 - 1.0 mg dose used from yr 3 onward
 - Data based on 108 patients only
 - **Tenofovir ~0 after 3 yr**
 - Most patients with detectable HBV DNA at wk 72 received additional emtricitabine
 - Data on tenofovir monotherapy beyond 72 wk unknown
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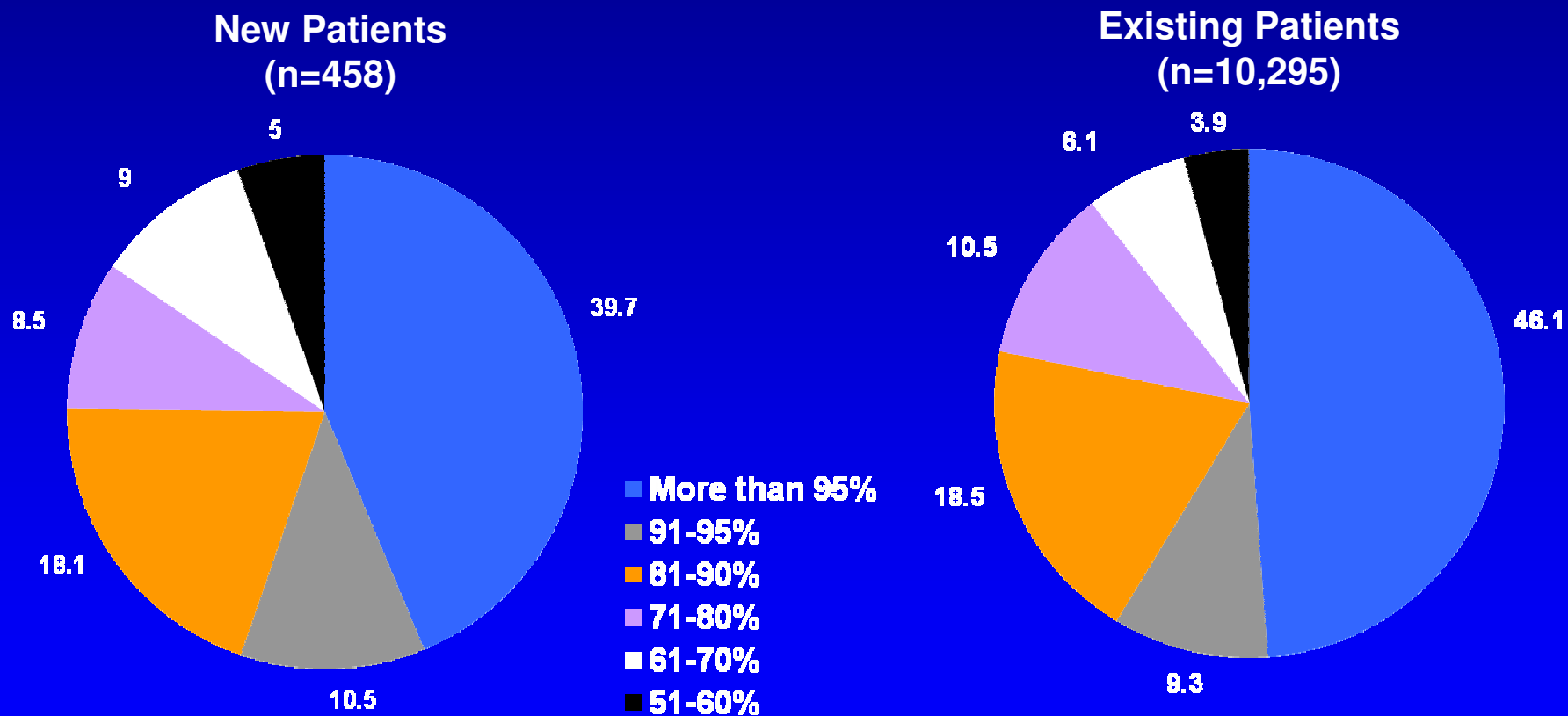
Is Antiviral Drug-resistant HBV a Problem of the Past in Nucleos(t)ide-naïve Patients?

- **Data based on small number of patients in phase III trials, adherence in clinical practice likely lower**
 - **Tenofovir not available in most Asian countries**
 - **Entecavir >10 times the cost of lamivudine, adefovir or telbivudine and not covered by health ministries in many countries**
 - **Lamivudine and adefovir remain the 1st line drug in most countries endemic for HBV**
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Adherence to HBV Nucleos(t)ide Analogs in Clinical Practice

- Pharmacy claims data base in the U.S.
 - 3 cohorts of CHB patients receiving LAM, ADV, ETV or TDF (2009 cohort only) in Jan 2007, 2008 and 2009 followed for 1 year
 - New patients = patients started on treatment in Jan of that year
 - Existing patients = patients who had been on treatment in the prior year
 - Adherence = % of days during that year in which patient had medications
 - E.g. existing patient who had 11 refills of 30 day supply in the calendar year would have adherence of $(11 \times 30 / 365) \times 100 = 90\%$
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Adherence to HBV Nucleos(t)ide Analogs: Analysis of pharmacy claims database in 3 cohorts of patients treated in the US in 2007, 2008 and 2009



Not All Virologic Breakthroughs Are Caused by Antiviral Resistance Mutations

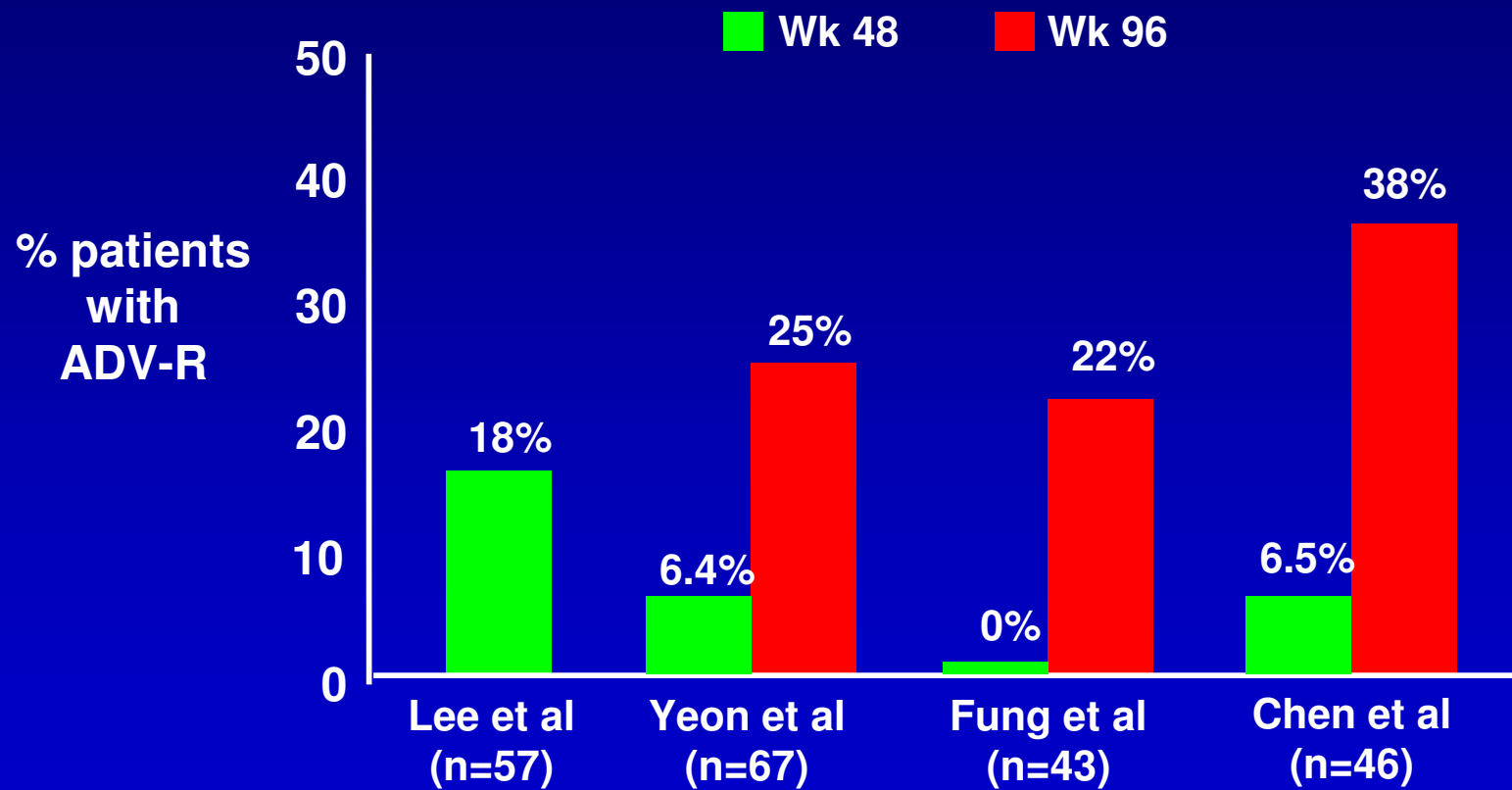
- 148 CHB patients receiving NUC >1 year
- 39 (26%) had >1 virologic breakthrough (VBT)
 - 15 (38%) VBT not confirmed on retesting 1-3 mo later
 - 13 (33%) no evidence of genotypic resistance (GR) by direct sequencing and line probe assay
- 10 patients with VBT but no confirmed VBT / GR continued on same medications
 - HBV DNA decreased in all 10 and became undetectable in 9

Cross Resistance Analysis

(*in vitro* studies)

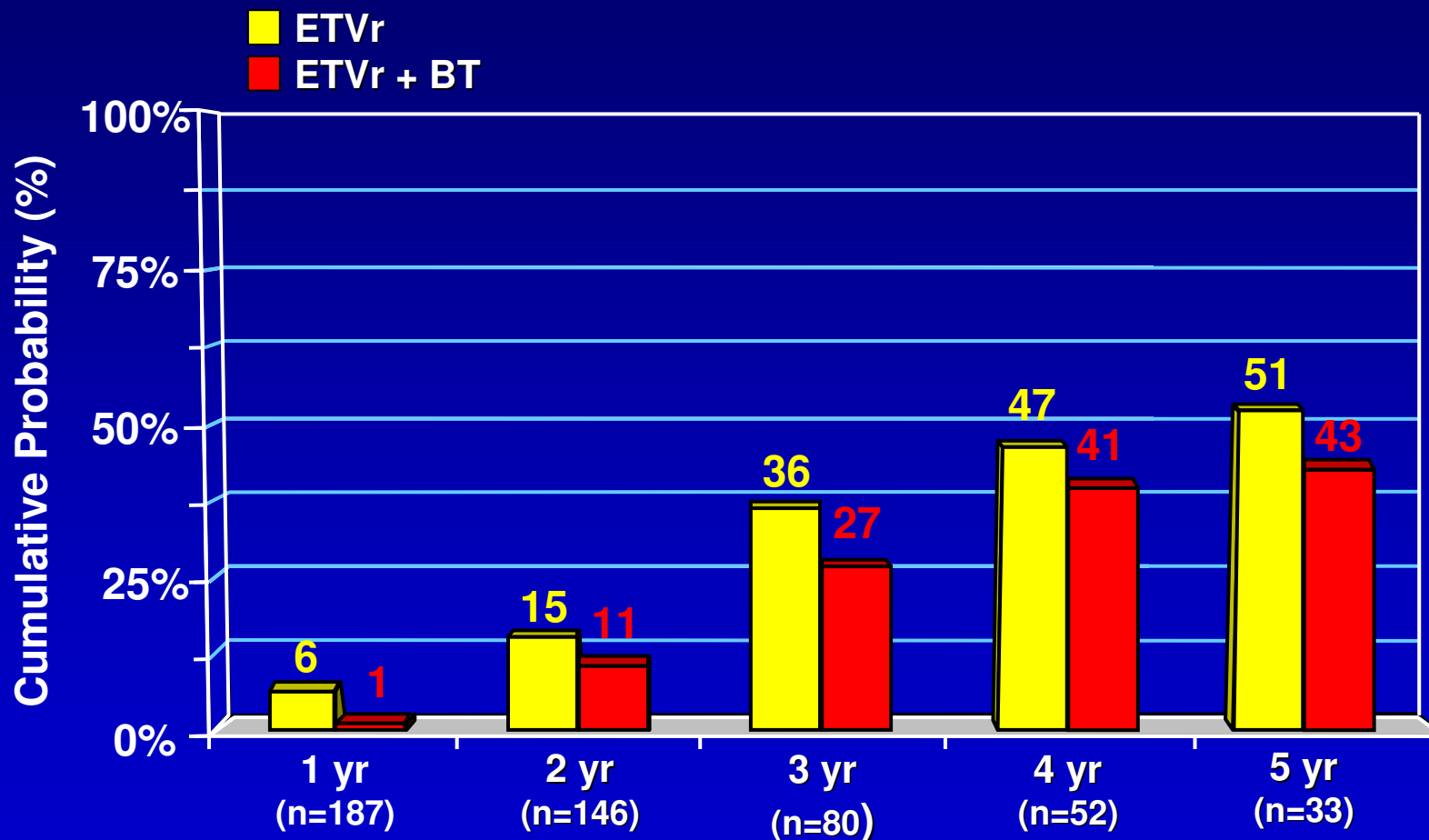
Resistantce mutations	M204V/I	N236T	A181V/T	T184, S202, M250
Drugs with marked decrease in activity	<ul style="list-style-type: none"> ▪ Lamivudine ▪ Emtricitabine ▪ Telbivudine 	<ul style="list-style-type: none"> • Adefovir 	<ul style="list-style-type: none"> • Adefovir • Lamivudine 	<ul style="list-style-type: none"> • Entecavir
Drugs with some decrease in activity	<ul style="list-style-type: none"> ▪ Entecavir 	<ul style="list-style-type: none"> • Tenofovir 	<ul style="list-style-type: none"> ▪ Entecavir ▪ Telbivudine ▪ Emtricitabine ▪ Tenofovir 	
Drugs remaining fully active	<ul style="list-style-type: none"> ▪ Adefovir ▪ Tenofovir 	<ul style="list-style-type: none"> • Lamivudine • Emtricitabine • Telbivudine • Entecavir 		<ul style="list-style-type: none"> • Adefovir • Tenofovir

High Rate of Adefovir Resistance among Patients with Lamivudine Resistance Receiving Adefovir Monotherapy



Fung et al, J Hepatol 2006, Yeon et al, Gut 2006; Lee et al, Hepatology 2006; Chen et al, Antiviral Therapy 2006

High Rate of Entecavir Resistance in Lamivudine-Refractory HBeAg+ Patients



- 72/187 (39%) achieved HBV DNA < 300 cp/mL;
- 3/72 (4%) had subsequent genotypic ETV resistance

Antiviral-Drug Resistant HBV Remains a Problem in Nucleos(t)ide-experienced Patients

- LAM resistance → ADV monotherapy ~20% ADV resistance after 2 yr
 - LAM resistance → ETV 1.0 mg dose ~50% ETV resistance after 5 yr
 - ADV resistance → TDF partial virus suppression, persistence of ADV-resistance mutations
 - LAM resistance → Switch to ADV monotherapy → ADV resistance → Add LAM → Multi-drug resistance HBV
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How to Prevent HBV Antiviral Drug Resistance?

- **Judicious use of antiviral treatment**
 - **Use potent drugs that have high genetic barrier to resistance**
 - **Initiate treatment with combination therapy?**
 - **Close monitoring of virologic response and breakthroughs**
 - **Modify treatment in patients with suboptimal viral suppression**
 - **Counseling on medication adherence**
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Which Should be the Initial Oral Drug?

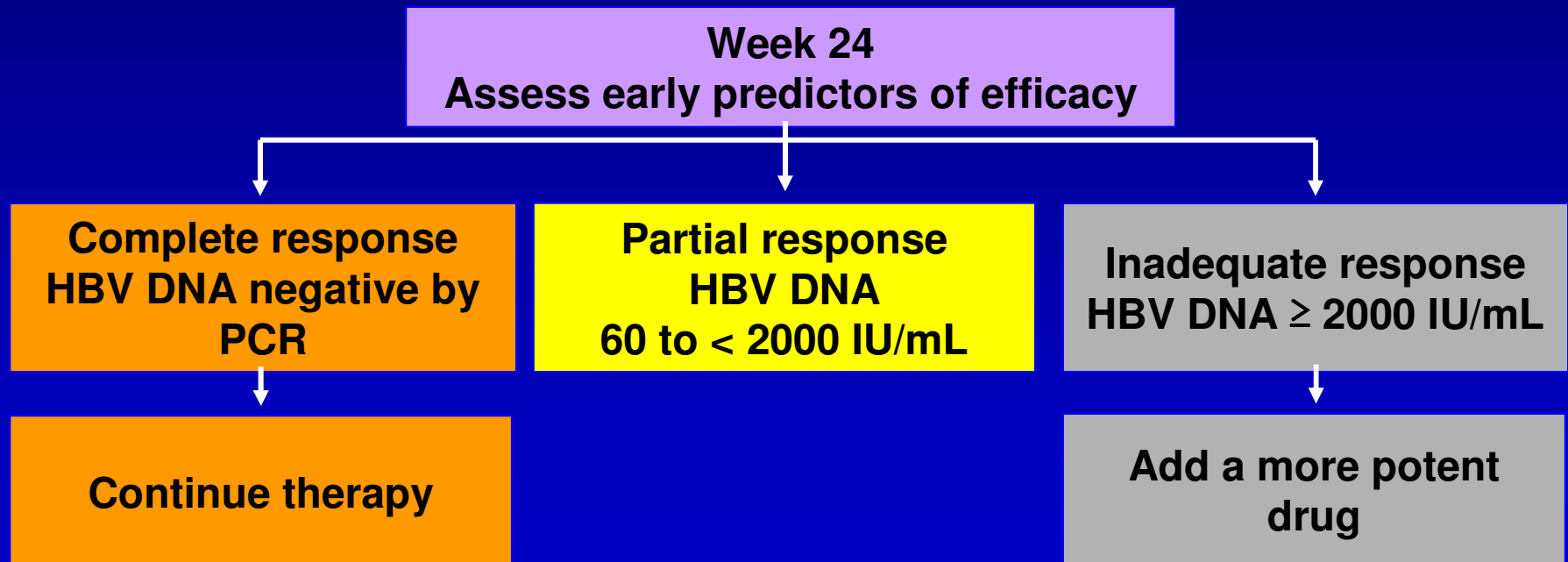
	LAM	ADV	ETV	TBV	TDF
Antiviral activity	++	+	+++	+++	+++
Safety	+++	++	+++	++	++
Risk of drug resistance	++++	++	+	+++	+

LAM = lamivudine, ADV = adefovir, ETV = entecavir, TBV= telbivudine, TDF = tenofovir

Can *De Novo* Combination Therapy Prevent Antiviral Resistance?

- **Combination therapy involving antiviral drugs with low genetic barrier to resistance**
 - Reduces but not completely prevent resistance
 - PegIFN + LAM: 1 yr resistance 1-4%
 - LAM + ADV: 2 yr resistance 15%
 - LAM + TBV: 1 yr resistance 10%
 - **Combination therapy involving antiviral drugs with high genetic barrier to resistance**
 - Will complete prevention of antiviral resistance be possible?
 - How to prove that combination therapy is superior?
 - To demonstrate decrease in resistance from 1% to 0% will require >1,000 patients in each treatment arm
 - Will this strategy be cost-effective?
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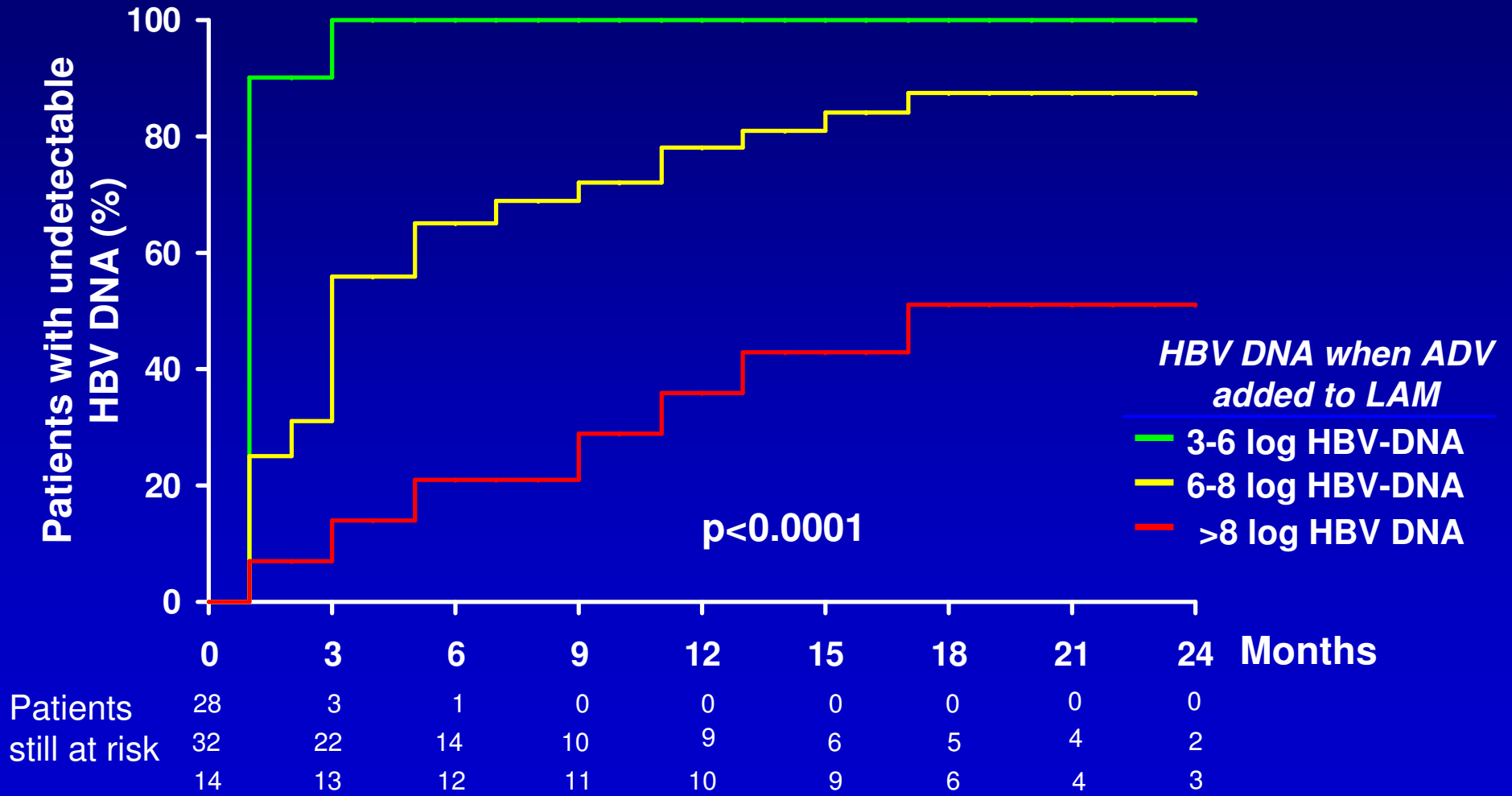
Management Roadmap According to Week 24 Virologic Response



Problems with the Proposed Roadmap

- **Based on data of drugs with low genetic barrier to resistance**
 - **For patients receiving lamivudine or telbivudine, response at week 24 associated with lower but not 0% drug resistance at week 48**
 - **~50% of HBeAg+ patients would be considered as having partial or inadequate response at week 24**
 - **For patients receiving entecavir or tenofovir, continued treatment in patients with incomplete response at week 24 associated with very low rate of drug resistance after 3-5 years treatment**
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Adefovir is More Effective when Added at the First Sign of Lamivudine Breakthrough



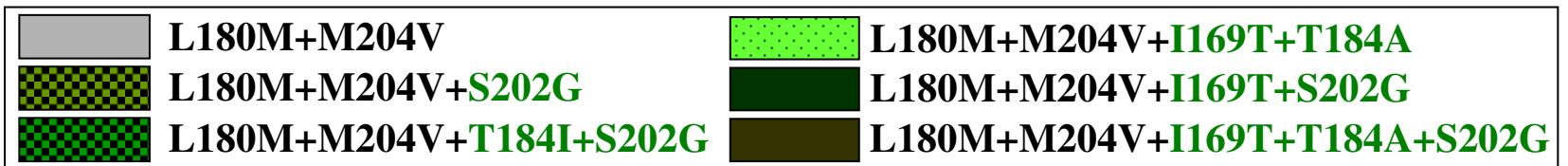
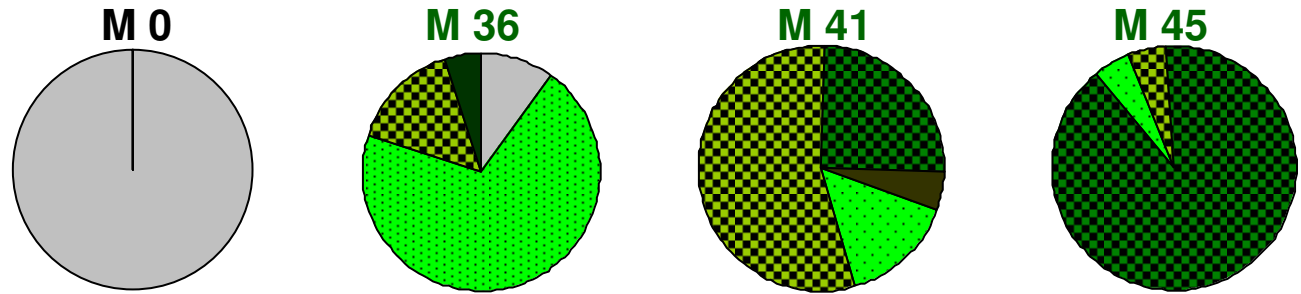
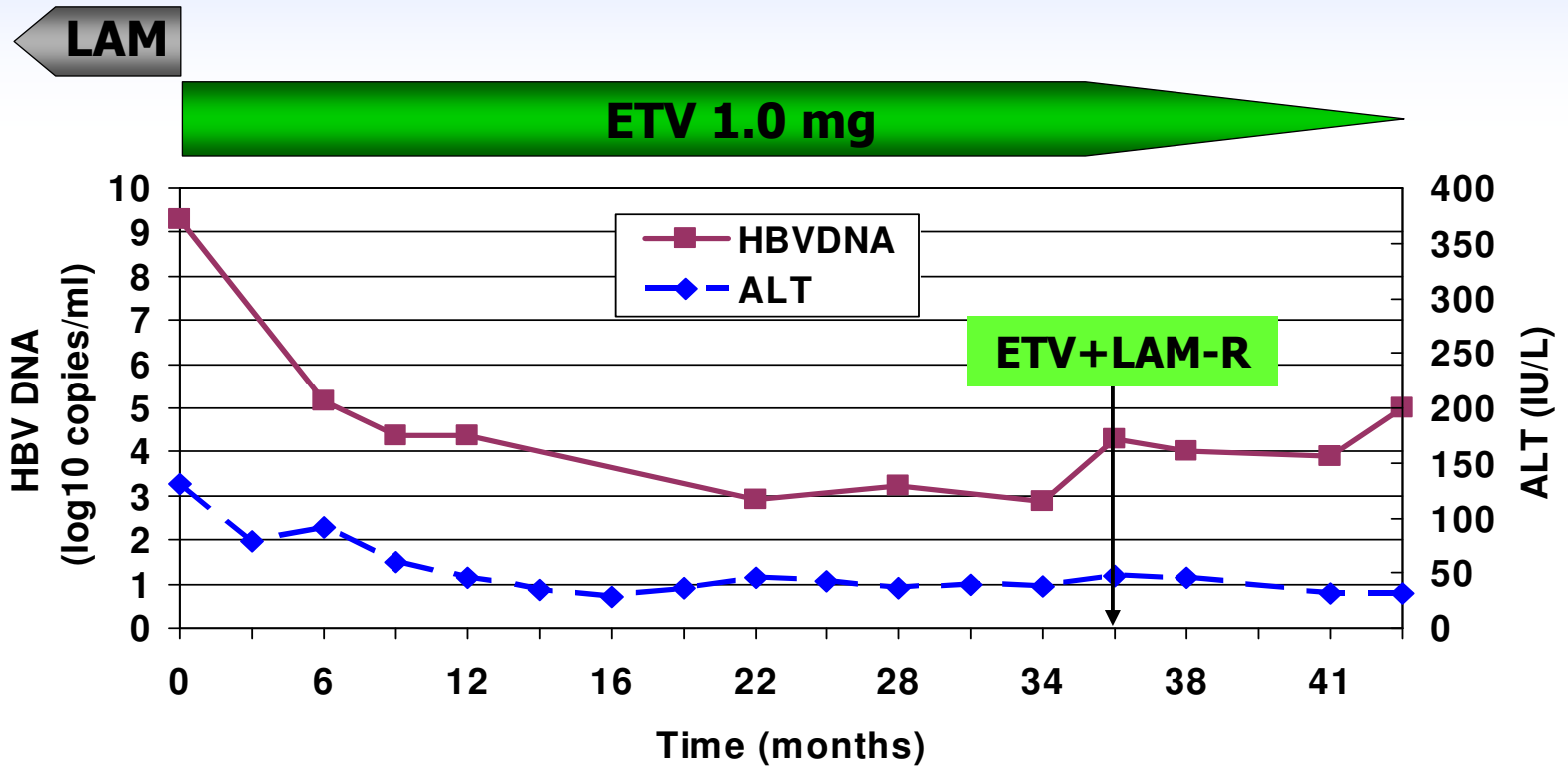
Rescue Therapy Options for Antiviral Drug-resistance HBV

Type of resistance	Preferred rescue therapy	Other options
Lamivudine or Telbivudine	<ul style="list-style-type: none"> • Tenofovir – add / switch 	<ul style="list-style-type: none"> • Add adefovir • Switch to tenofovir + emtricitabine • Switch to entecavir (not preferred)
Adefovir	<ul style="list-style-type: none"> • Entecavir – add / switch 	<ul style="list-style-type: none"> • Switch to tenofovir + emtricitabine • Add lamivudine or telbivudine (not preferred if prior lamivudine resistance) • Switch to tenofovir (not preferred, partial cross-resistance)
Entecavir	<ul style="list-style-type: none"> • Tenofovir – add / switch 	<ul style="list-style-type: none"> • Add adefovir

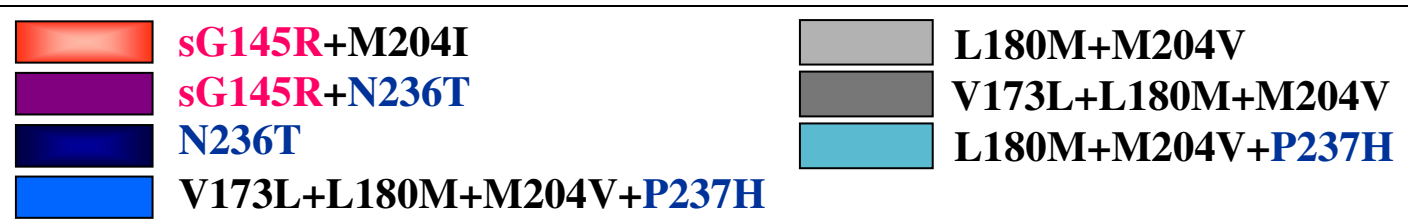
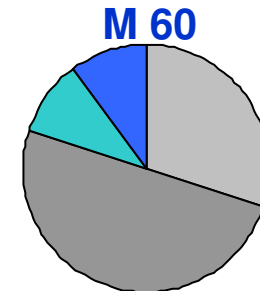
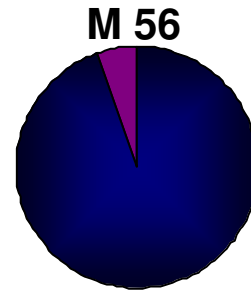
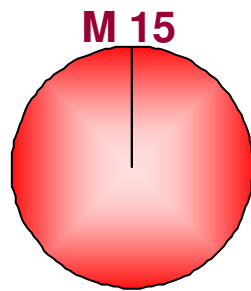
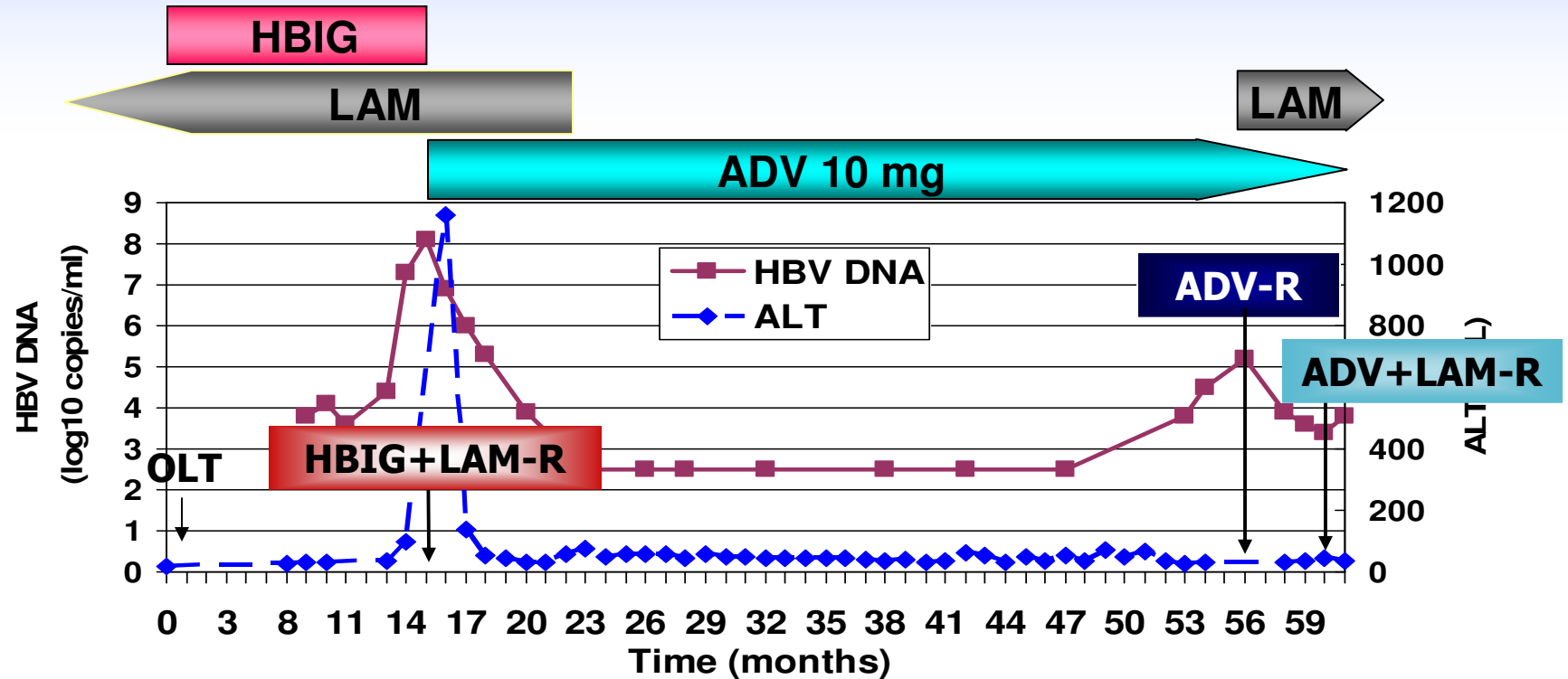
Is Antiviral-resistant HBV a Problem of the Past?

- Diminishing problem but not gone
 - Nucleos(t)ide-naïve patients – rare if drugs of high genetic barrier used and patient adherent to medications
 - Nucleos(t)ide-experienced patients – still a problem particularly if suboptimal rescue therapy used, risk of multi-drug resistance
 - More attention to medication adherence is needed
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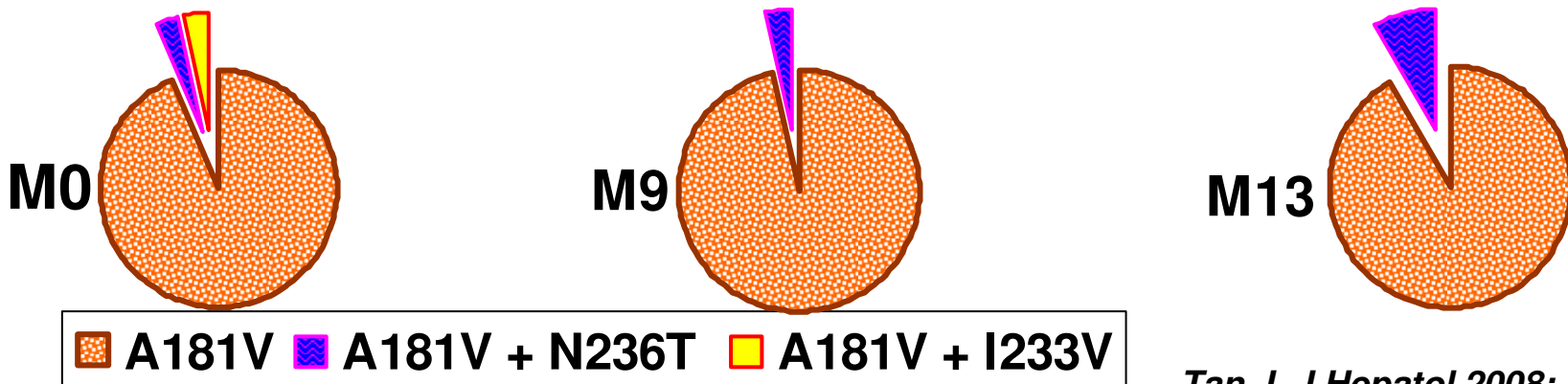
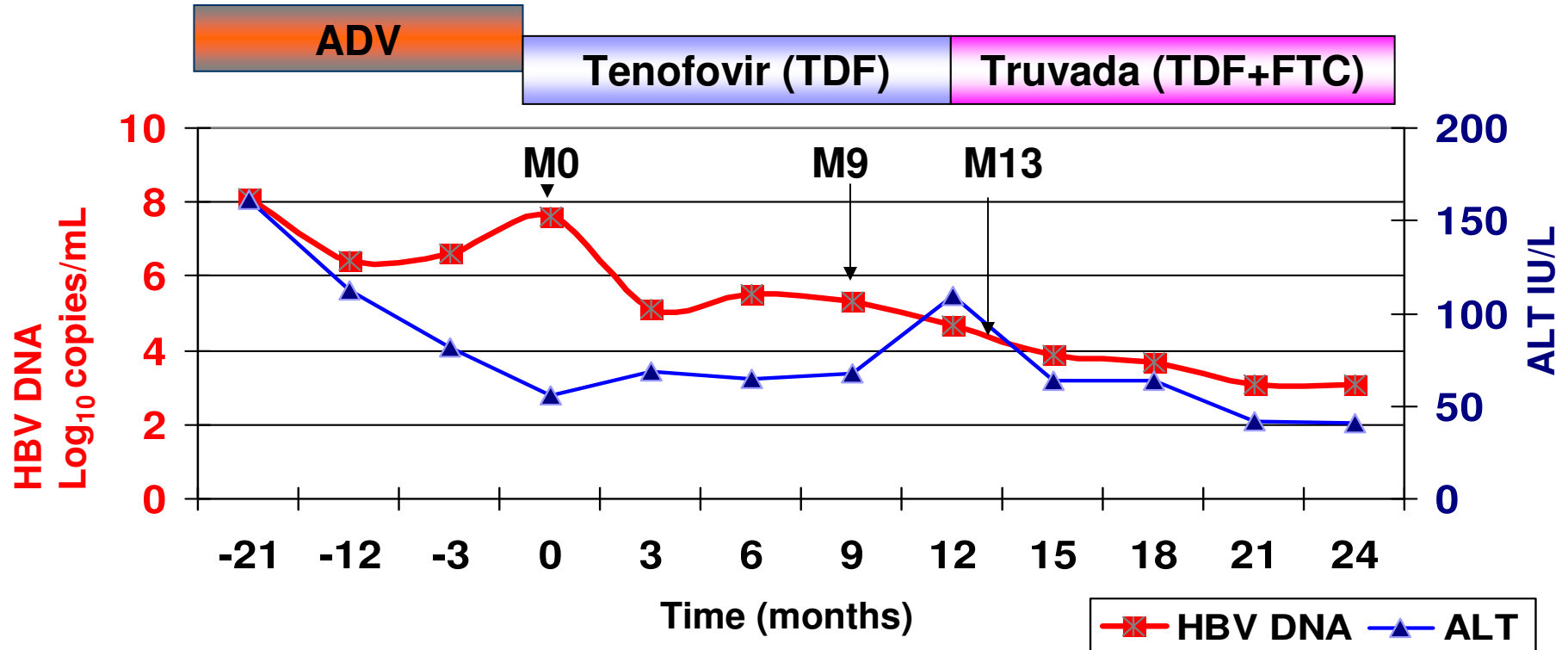
LAM+ETV Resistance



LAM+HBIG, LAM+ADV Resistance



Tenofovir alone does not adequately suppress adefovir-R HBV



Monitoring viral response and resistance

- **Monitoring of serum HBV DNA**
 - Sensitive assay, preferably real-time PCR, lower limit of detection ~30 IU/mL
 - Same assay
 - Baseline, then every 3 months
 - To detect lack of initial response → modify treatment
 - To detect early breakthrough → rescue therapy more effective when serum HBV DNA is low
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