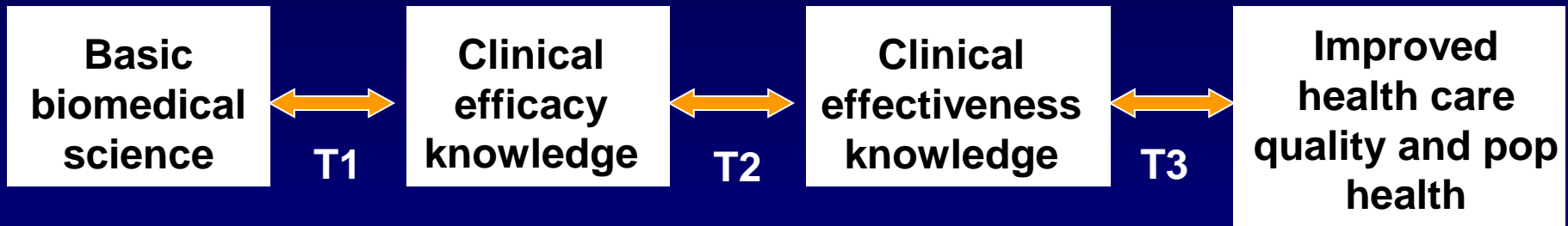


HBV Antiviral Drug Resistance: Prevention and Monitoring in Clinical Practice

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The “3Ts” Road Map to Transform Health Care



**Bench to
clinical trials**

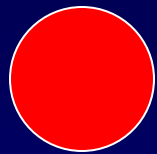
**Patient-specific
evidence of clinical
effectiveness
Identification of the
right treatment for
the right patient at
the right time**

**How to implement
evidenced based
treatment and
intervention in all
settings of care**

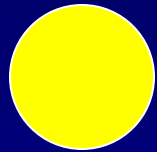
Prevention of HBV Antiviral Drug Resistance

- **Judicious use of antiviral treatment**
 - **Use of most potent drugs that have highest genetic barrier to resistance**
 - **Close monitoring of virologic response and breakthroughs**
 - **Confirmation of genotypic resistance in patients with virologic breakthroughs**
 - **Choice of rescue therapy guided by history of HBV treatment and resistance mutation(s) detected**
 - **Counseling on medication adherence**
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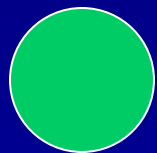
When to Treat?



- Inactive HBV carriers
- Immune tolerance phase, <35



- Immune tolerance phase, >35
- Strong family history of HCC
- Borderline high or fluctuating HBV DNA and ALT



- Hepatic decompensation
- Fulminant hepatitis B
- Severe hepatitis flare
- Cirrhosis and high HBV DNA
- HBeAg+ chronic hepatitis
- HBeAg- chronic hepatitis

Recommendations for HBV Treatment

	HBeAg +		HBeAg -	
	HBV DNA (copies/mL)	ALT	HBV DNA (copies/mL)	ALT
EASL 2009*	$\geq 10^4$	>1 x ULN	$\geq 10^4$	>1 x ULN
APASL 2008#	$\geq 10^5$	>2 x ULN	$\geq 10^4$	>2 x ULN
AASLD 2009#	$\geq 10^5$	>2 x ULN	$\geq 10^5$	>2 x ULN

* Biopsy should be at least Metavir A2 (0-3) or F2 (0-4)

Biopsy if ALT 1-2 x ULN, age >40, treat if moderate-severe inflammation or significant fibrosis

Treatment Indication Should be Based on HBV DNA NOT ALT

- **Positive HBeAg and high serum HBV DNA (>4 log₁₀ copies/mL) had been reported to be associated with increased risk of cirrhosis and HCC**
 - **Moderate inflammation, fibrosis and even cirrhosis can be found in patients with normal ALT**
 - **ALT 0.5-1x ULN is associated with increased risk of hepatic complications vs. those with ALT <0.5x ULN**
-

REVEAL HBV Study

3653 HBsAg+ patients, mean FU 11.4 yr
Mean age 43 yr, 15% HBeAg+, 6% elevated ALT, 2% cirrhosis

HBV DNA Entry	(c/mL) Last FU	No. of Participants	No. of HCC Cases	Adjusted HR (95% CI)
< 4 log	ND	2034	26	1.0
4-5 log	<4 log	256	6	1.3 (0.5 – 3.1)
	4-5 log	161	1	0.4 (0.1 – 3.2)
	≥ 5 log	110	5	2.9 (1.0 – 9.8)
≥ 5 log	< 4 log	146	8	1.9 (0.8 – 4.4)
	4-5 log	120	10	4.3 (2.0 – 9.3)
	≥ 5 log	537	55	5.3 (2.9 – 9.7)

Adjusted for gender, age, smoking, alcohol, HBeAg, cirrhosis & ALT

Liver Disease in Patients with Normal ALT

- 59 patients (44% HBeAg-) with persistently normal ALT and HBV DNA $>4 \log_{10}$ copies/mL
 - 18% Metavir $F_{\geq 2}$, 34% $A_{\geq 2}$
 - Age >40 predictor of significant liver disease
- 21% HBeAg-ve patients with persistently normal ALT and HBV DNA $<5 \log_{10}$ copies/mL had histologically active liver disease
 - Only 29/75 biopsied
 - 6/29 had active disease, max fibrosis score: 1, max HAI: 5
- Significant liver disease may be present in some patients with normal ALT
 - Likelihood low in patients <40 and those with HBV DNA <4 or $5 \log_{10}$ copies/mL

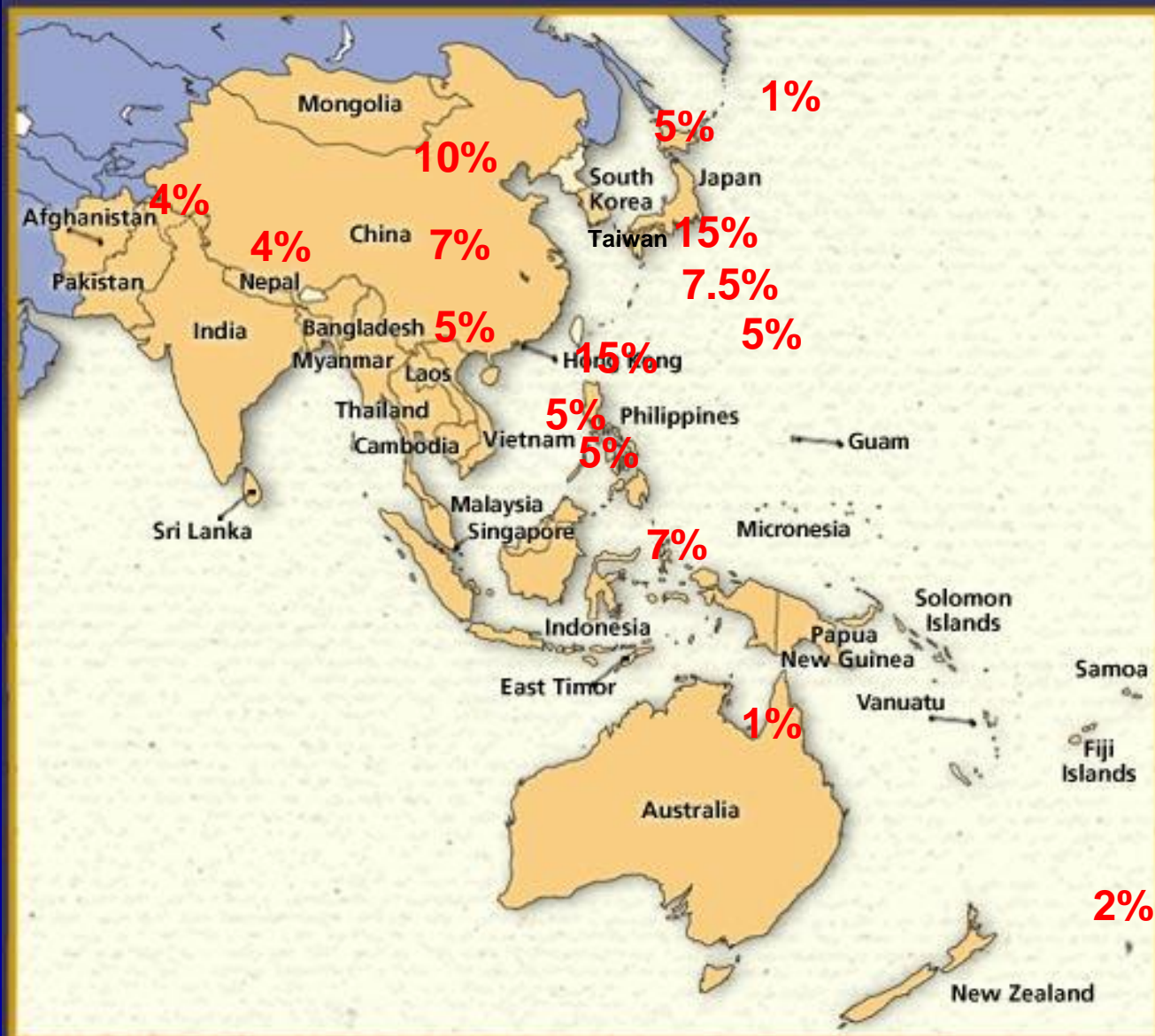
What is Wrong with Liberalizing Treatment?

- **Most patients will require long durations of treatment**
 - HBeAg+ patients ~50% HBeAg seroconversion after 5 yr treatment
 - HBeAg- patients: endpoint unknown, ~5% HBsAg loss after 5 yr treatment
 - **Long durations of treatment**
 - Antiviral drug resistance
 - Costs
 - Adverse events
-

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Prevalence of Chronic HBV Infection in Asian-Pacific Countries



Reimbursement Policies in Asian-Pacific countries

- **Survey sent to experts in 16 countries**
 - **HBV prevalence: median 5%, range 1-15%**
- **15/16 countries have reimbursement policies (none in Philippines)**
 - **Only 4 countries have policies available for all citizens**
 - **8 countries provide full medication coverage for eligible persons**

HBV Medications Approved as First-Line Treatment in Asian-Pacific Countries

- **LAM**
 - LAM only: n=2 (Vietnam and Thailand)
 - LAM as the only NUC: n=1 (New Zealand)
 - LAM no longer used as 1st-line treatment (Hong Kong)
 - **ADV: n=7**
 - **TBV: n=6**
 - **ETV: n=9**
 - **TDF: n=0**
 - **PEG-IFN: n=7, standard IFN only: n=3**
-

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Reimbursement for Monitoring Response to HBV Treatment in Asian-Pacific Countries

- **Yes: n=10**
 - Liver panel: n=10
 - HBV DNA: n=8 (not covered: Hong Kong and Taiwan)
 - Resistance mutation testing: n=1 (New Zealand)
 - **NO: n=5**
-

Monitoring of Virologic Response and Breakthroughs at U of Michigan

- **Standard Protocol**
 - Q 3 month HBV DNA
 - Breakthroughs confirmed by repeat HBV DNA in 1 month and sample collected for genotypic resistance mutation testing
 - Resistance mutation tested by InnoLipa
 - Rescue therapy in patients with breakthroughs that are confirmed and associated with detection of drug resistance mutation
-

Monitoring of Virologic Response and Breakthroughs at U of Michigan

- **Standard Protocol**
 - **Q 3 month HBV DNA**
 - Pre-printed lab requisitions with dates when tests should be performed provided to patients
 - Reminder calls to patients when results not received
 - ~85% adherence
 - ~50% of tests performed in local labs
 - Assays with wide range of LLOD: 30-300 IU/mL
-

Did All of These Patients Have Virologic Breakthrough?

Serial serum HBV DNA during treatment (IU/mL)

A	8.5 log	2,300	UD <6	15	UD <6
B	7.9 log	3,500	UD <300	97	UD <300
C	9.3 log	6.1 log	4.1 log	2.5 log	3.9 log

Monitoring of Virologic Response and Breakthroughs at U of Michigan

- **Standard Protocol**
 - **Resistance mutation tested by InnoLipa**
 - **Adherence with repeat testing within a month ~70%, within 3 months ~95%**
 - **Sample collection for genotypic resistance mutation testing dependent on patient's return to UMHS, sample collected within 3 months ~90%**
 - **Resistance mutation testing by InnoLipa when free reagents available otherwise by direct sequencing**
-

Monitoring of Virologic Response and Breakthroughs at U of Michigan

- **Standard Protocol**
 - **Rescue therapy in patients with breakthroughs that are confirmed and associated with detection of drug resistance mutation**
 - **41 patients with VBT (HBV DNA >1 log increase from nadir or redetection of HBV DNA after disappearance)**
 - **21 (51%) confirmed VBT on retesting**
 - **13 (32%) genotypic resistance**
-

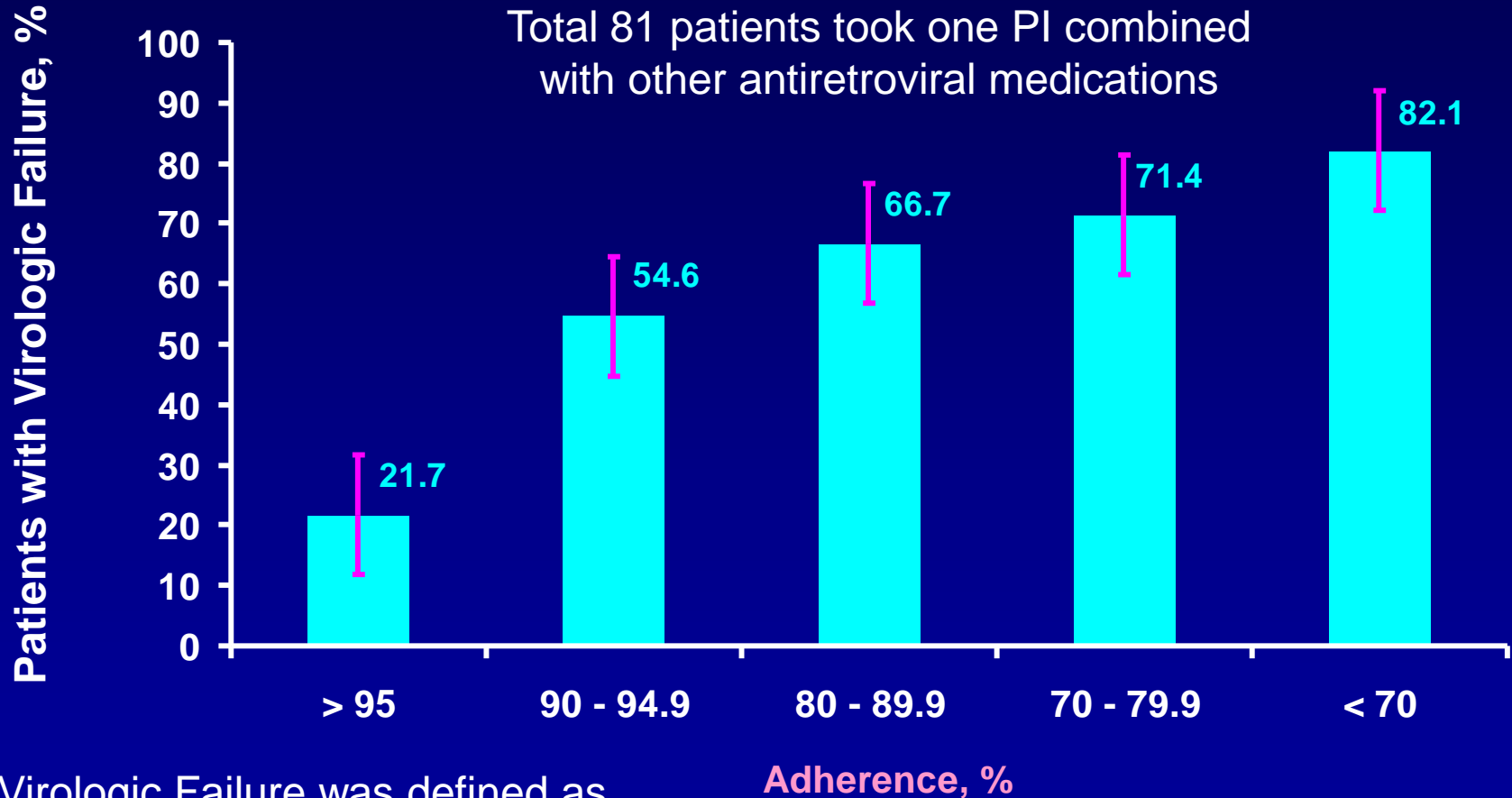
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Virologic Breakthrough and Confirmed Genotypic Resistance in Phase III Clinical Trials of HBV Nucleos(t)ide Analogs – End of Year 1

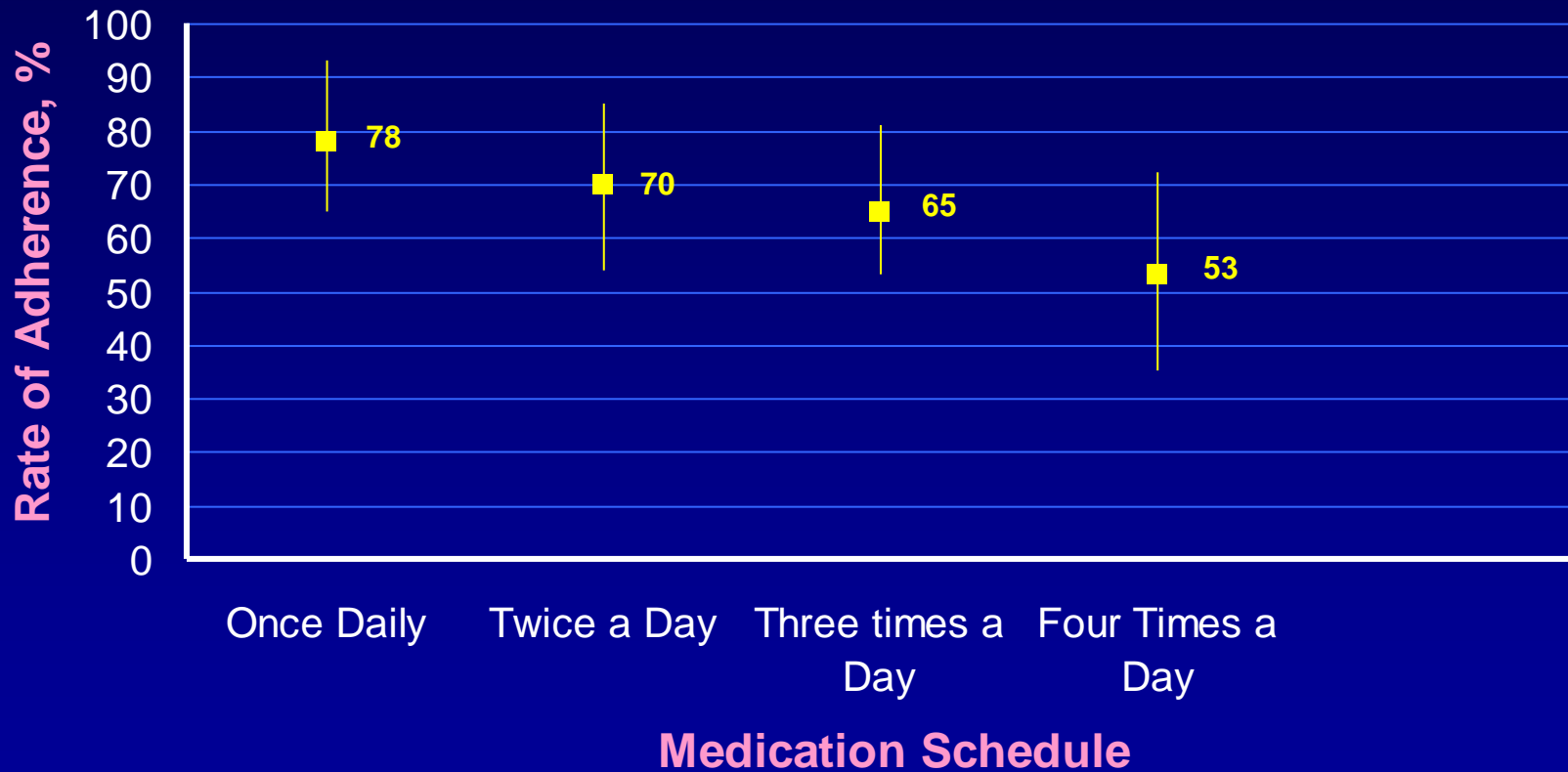
Medication	LAM	ADV	ETV	TBV	TDF
No. of patients	1,355	509	679	680	426
Persistent viremia	34.5%	55.2%	20.5%	26%	8.2%
GR	N/A	N/A	0%	2.6%	0%
Virologic Breakthrough	13.8%	8.2%	1.6%	4.7%	2.3%
GR	10.3%	0.8%	0%	4.1%	0%

Adherence to Protease Inhibitor Therapy and Virologic Failure In Patients with HIV Infection

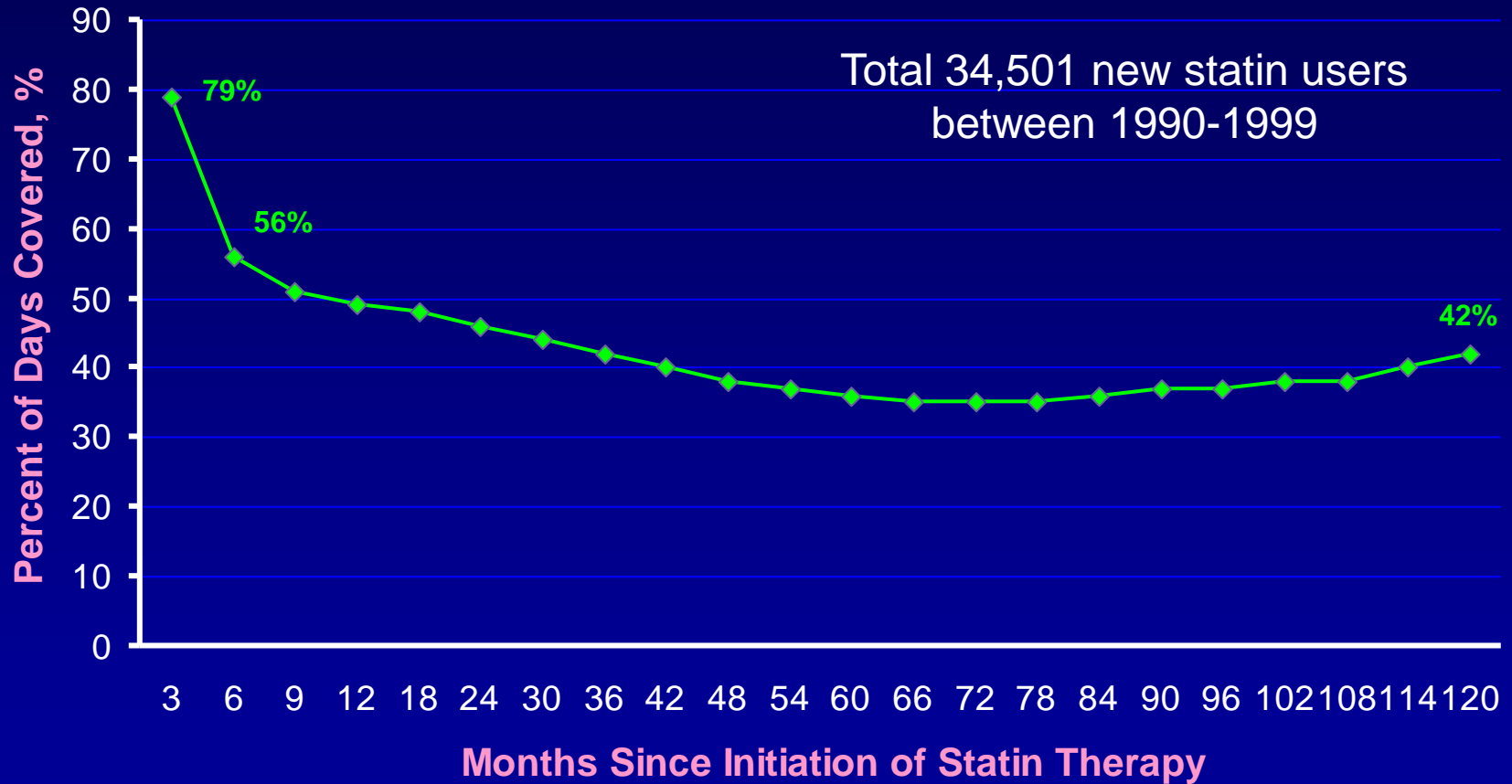


Virologic Failure was defined as HIV RNA level > 400 copies/mL

Adherence to Medication According to Frequency of Dosing



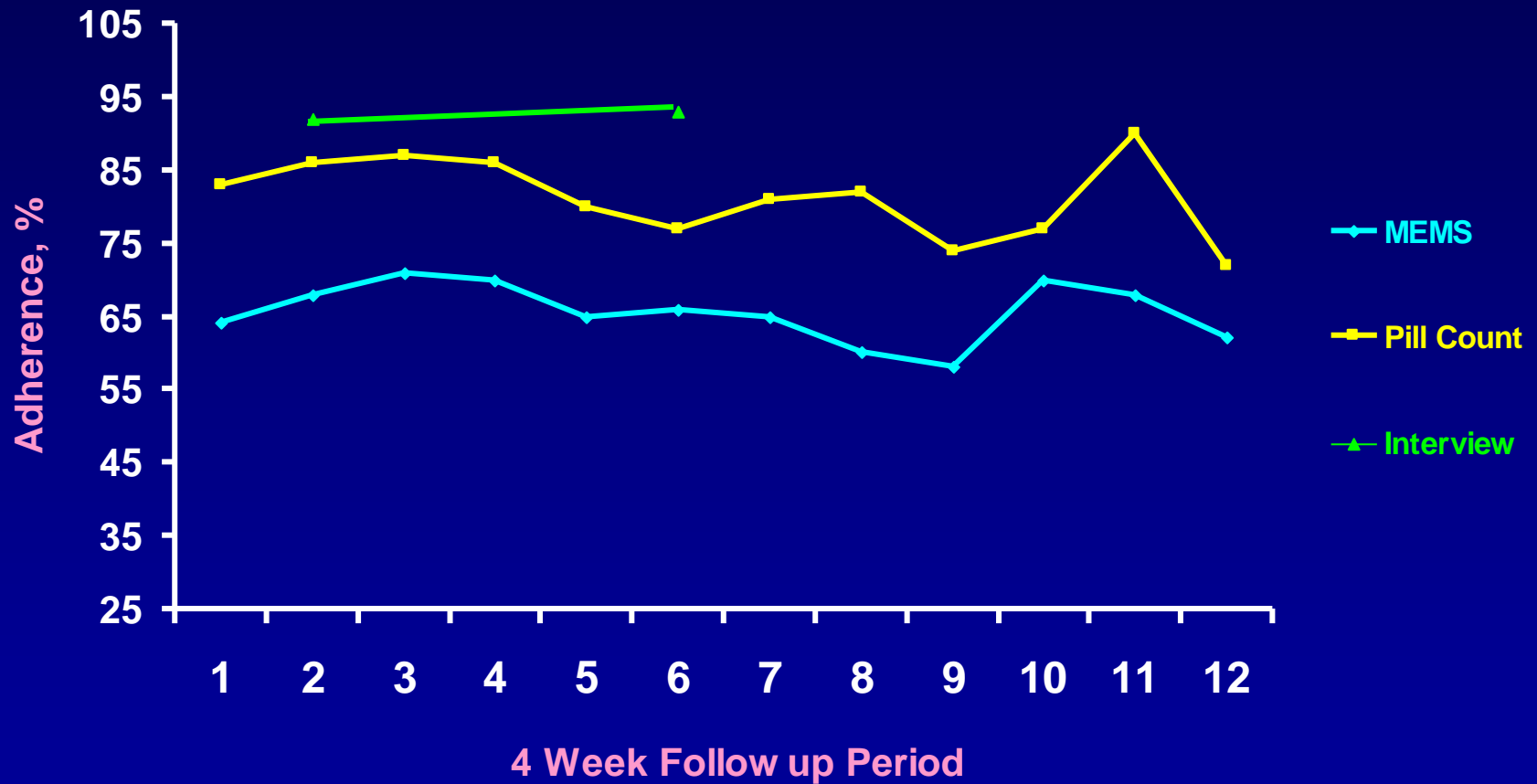
Long-term Adherence to Use of Statin Therapy in Elderly Patients



Methods of Measuring Drug Adherence

Test	Advantages	Disadvantages
Patient Questionnaire/ Self-Reports	Simple, inexpensive, most useful method in the clinical setting	Susceptible to error with increase in interval between visits Potential for inflation
Pill Counts	Objective, quantifiable, and easy to perform	Susceptible to manipulation by patient, impractical outside of clinical trials
Rates of Prescription Refills	Objective, easy to obtain data, large sample	A prescription refill is not equivalent to ingestion of medication
Electronic Medication Monitors	Precise, results easily quantified	Expensive, impractical outside of clinical trials

Adherence to HIV Protease Inhibitor Therapy Assessed by 3 Different Methods



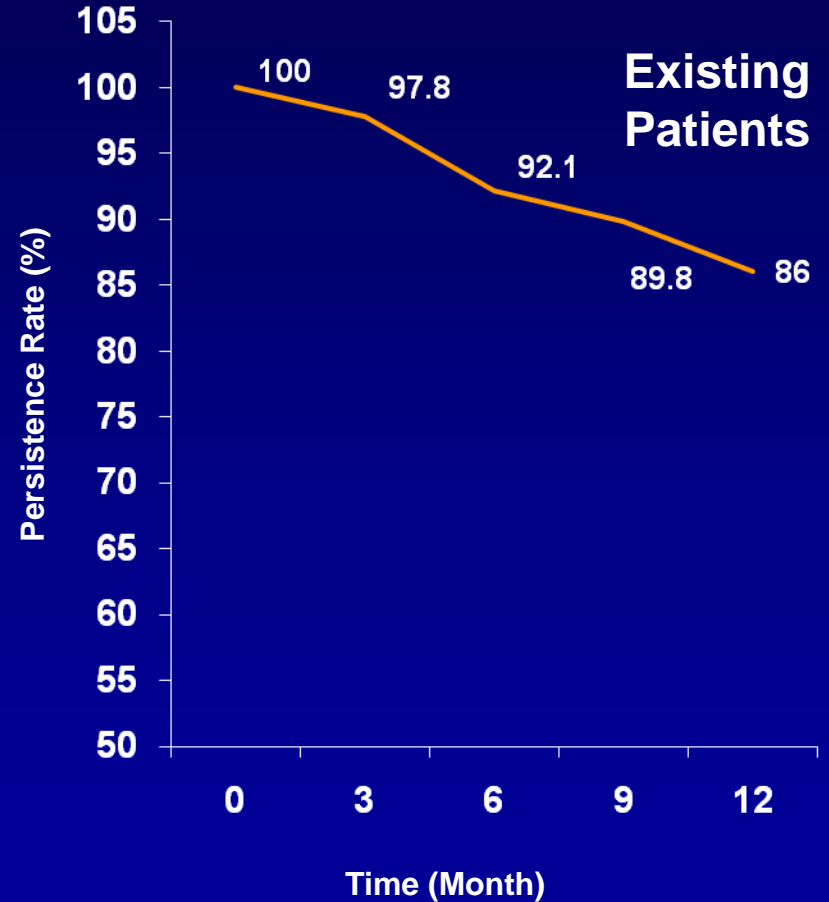
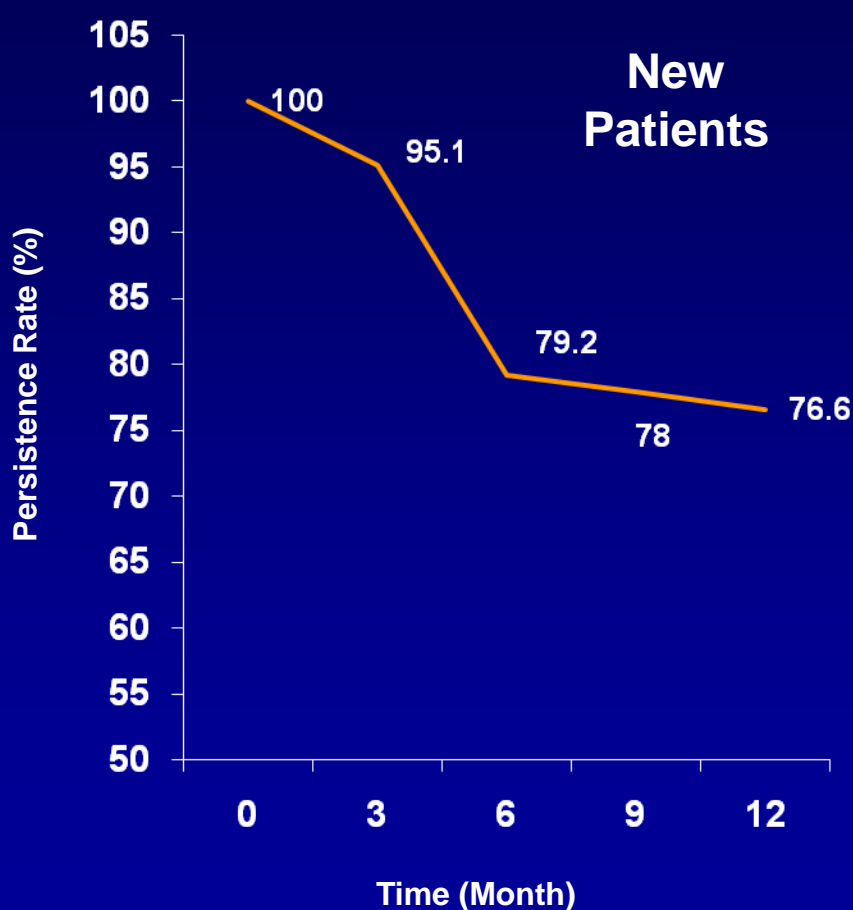
Persistence and Adherence to HBV Nucleos(t)ide Analog Treatment

- **Pharmacy claims data of 2 cohorts of patients receiving LAM, ADV or ETV in Jan 2007 and Jan 2008 analyzed**
 - **New patients defined as those with no pharmacy claims for these medications during the preceding 18 months**
 - **Persistence was defined as continuing acquisition of the medication (by pharmacy refill data) during a 12-month period**
 - **Adherence was defined as the percent of days in which patients had medication during the period in which the medication was prescribed**
-

RESULTS

- **Data were available for 7,784 CHB patients from USA**
 - 2007: 3,695 patients
 - 2008: 4,089 patients
- **Persistence**
 - The persistence rate of patients in the combined 2007 and 2008 cohorts was $85.5 \pm 3.1\%$
 - Existing patients had higher persistence rates than new patients
 - Persistence rates decreased during the course of the year, with the most rapid decrease between month 3 and 6

Persistence to HBV Nucleos(t)ide Analogs

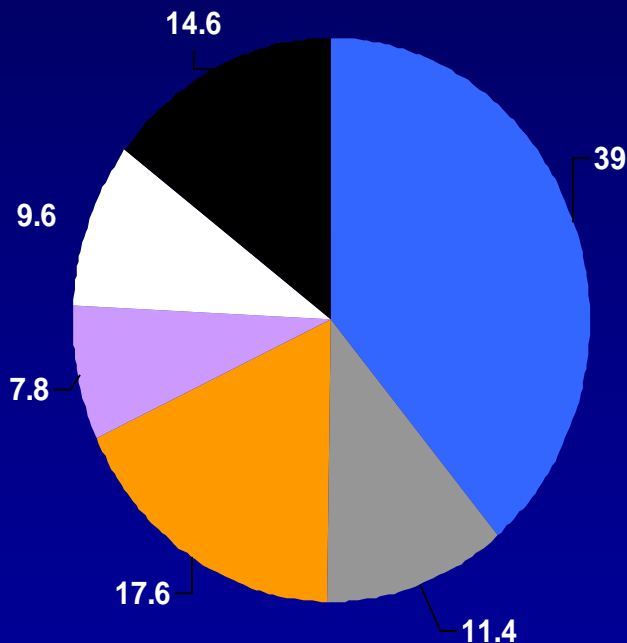


RESULTS

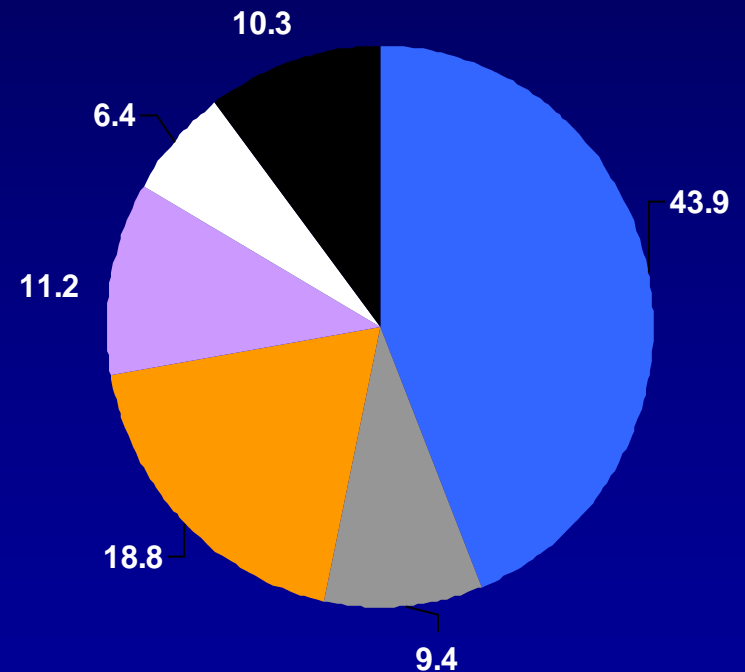
- **Adherence**
 - Overall adherence rate for the combined 2007 and 2008 cohorts was $86.7 \pm 18.9\%$
 - Existing patients had higher adherence rate than new patients ($86.9 \pm 18.7\%$ vs. $84.1 \pm 21.8\%$, $p=0.02$)
 - Factors associated with good adherence (adherence rate $>90\%$) for the 2008 cohort
 - Existing patients vs. new patients, $p=0.02$
 - Patients older than 45 years, $p=0.001$
 - Receipt of ADV or ETV (vs. LAM), $p<0.001$

Adherence to HBV Medications in The Combined 2007 and 2008 USA Cohorts

New Patients (N=387)



Existing Patients (N=7,170)

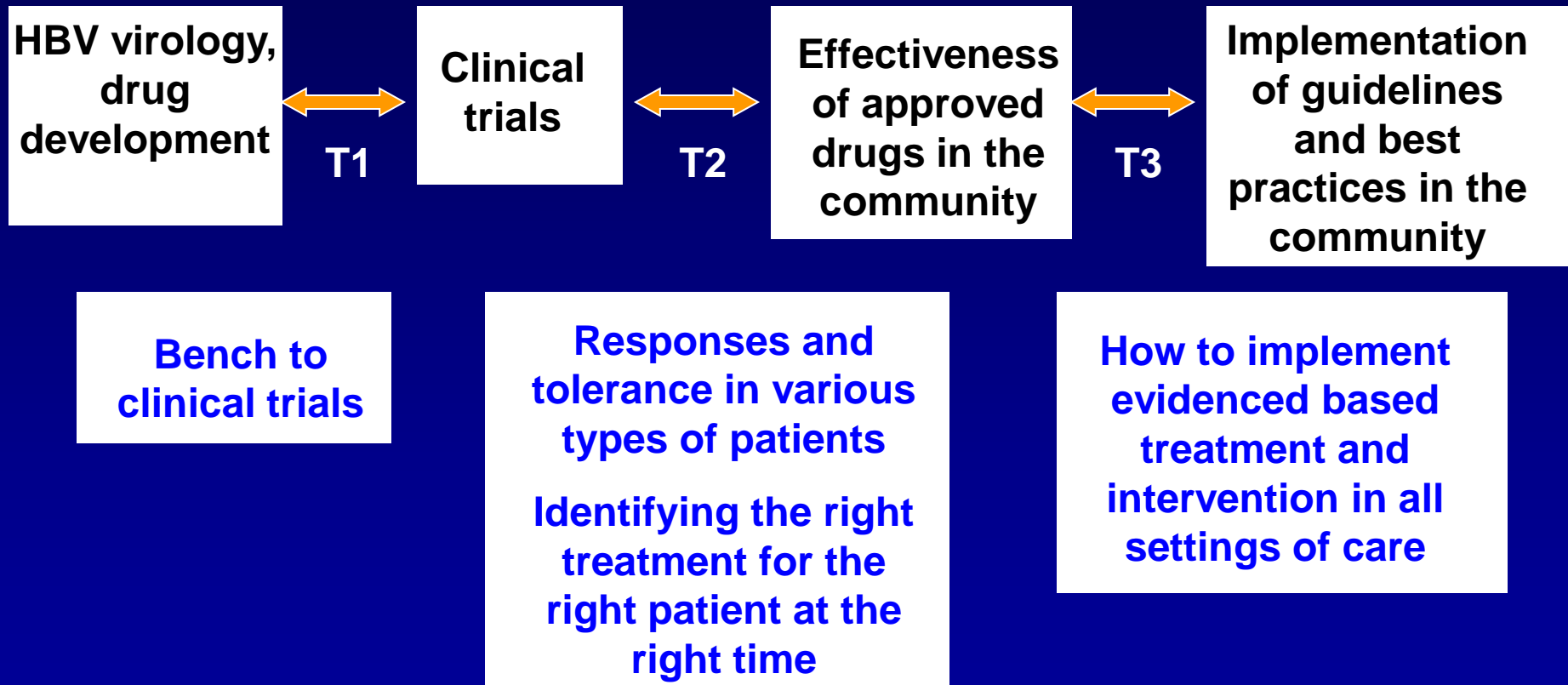


Note: Missing Data – 187 Patients

Prevention and Monitoring of HBV Antiviral Drug Resistance in Clinical Practice

- Choice of medication may be limited by socio-economic factors
 - Same assay to monitor HBV DNA rarely possible
 - Not all “blips” in HBV DNA reflect virologic breakthrough
 - Not all virologic breakthroughs are due to drug resistance
 - More studies on adherence to HBV nucleos(t)ide analog and its impact on response and drug resistance are needed
-

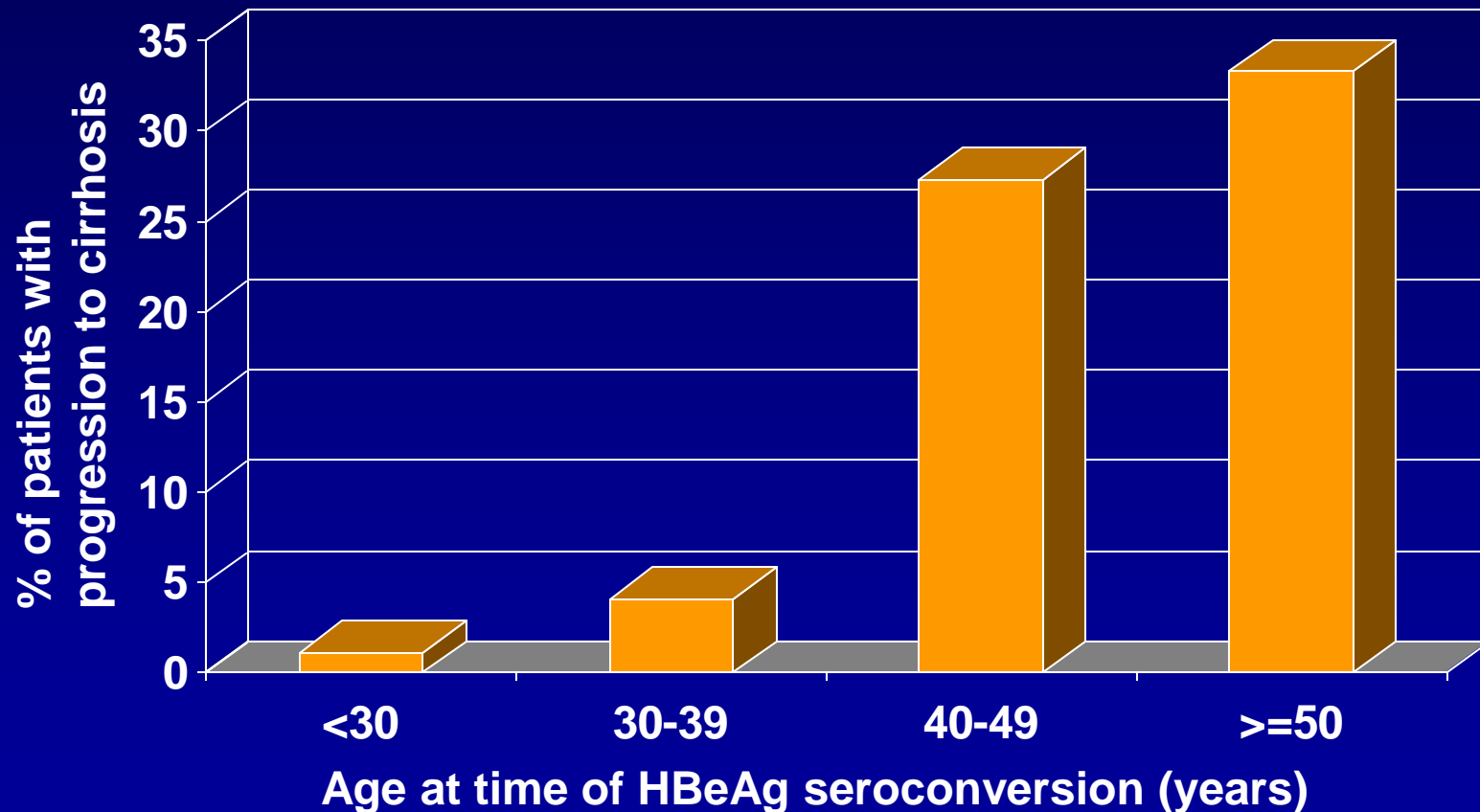
Improving Accessibility and Effectiveness of HBV Treatment



Limitations of Study

- **Cannot correlate adherence data with virologic response or breakthroughs**
- **Detailed analysis of factors associated with adherence not possible**
- **Patients switched to medications other than the 3 study drugs not captured**

Persistence of HBeAg is Associated with Significantly Higher Risk of Progression to Cirrhosis



Criteria for Treatment Reimbursement

- Based on doctor's opinion: n=8
- Based on specific criteria: n=7
 - ALT: n=7 (>2x ULN in 5)
 - HBV DNA: n=4
 - Histology: n=3

Reimbursement for Rescue Therapy

- **Rescue therapy reimbursed: n=13**
 - Not reimbursed: Vietnam and Indonesia
- **Rescue therapies covered**
 - Adefovir: n=13
 - Entecavir: n=8
 - Tenofovir: n=0