

Case Study: How to manage patient with HBV Resistant

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Patient case study

- 38 year old Brazilian male
 - Recently arrived in Barcelona
 - Married, no IVDU, no alcohol abuse
 - On treatment for chronic Hepatitis B for the last 4 years
 - He comes in for a second opinion
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Patient history

- He was diagnosed with Chronic Hepatitis B in January 2001 in Sao Paolo
 - Elevated ALT levels
 - HBeAg negative
 - HBV DNA $>10^6$ IU/ml
 - May 2001
 - Asymptomatic
 - ALT 67 IU/mL
 - HBV DNA $>4.6 \times 10^7$ IU/mL
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Further history

- No history of jaundice
 - No exposure to blood or blood products
 - Not an IV drug user
 - Wife HBV vaccinated
 - No children
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Further history

- June 2001
 - Liver Biopsy
 - Chronic active Hepatitis F2 (Ishak Index)
 - July 2001
 - Asymptomatic
 - ALT 45 IU/mL
 - HBV DNA > 5.8×10^4 IU/mL
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What would you do?

- Does he need therapy?



Treatment recommendations for HBeAg-negative patients

2008 EASL Guidelines

Who to treat?

- HBV DNA >2000 IU/mL and/or ALT > ULN and moderate to severe active necroinflammation and/or fibrosis

Indications for treatment should also take into account: age, health status and availability of anti-viral agents

Patient case history

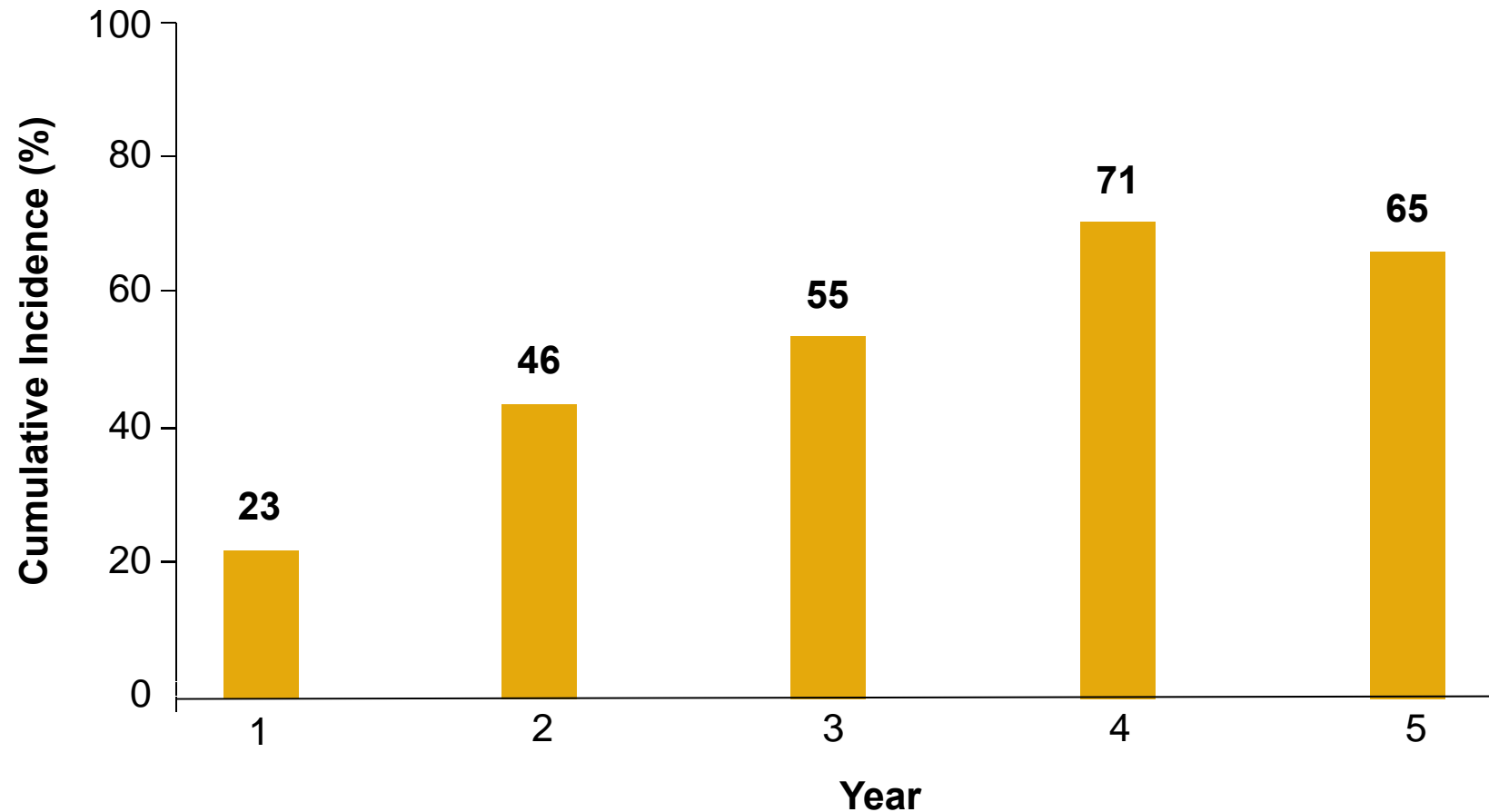
- July 2001
 - He started lamivudine 100mg/day
 - October 2001 (12 weeks of treatment)
 - Normal ALT
 - HBV DNA 10^4 IU/I
 - Good adherence to therapy
 - January 2002 (24 weeks of treatment)
 - ALT 49 UI/mL
 - HBV DNA 10^4 IU/I
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Patient case history

- July 2002 (1-year on lamivudine)
 - Good compliance
 - ALT 36 IU/mL
 - HBV DNA 10^3 IU/I
- December 2002
 - Good compliance
 - ALT 76 IU/mL
 - HBV DNA 10^5 IU/I

What is the risk of lamivudine resistance?

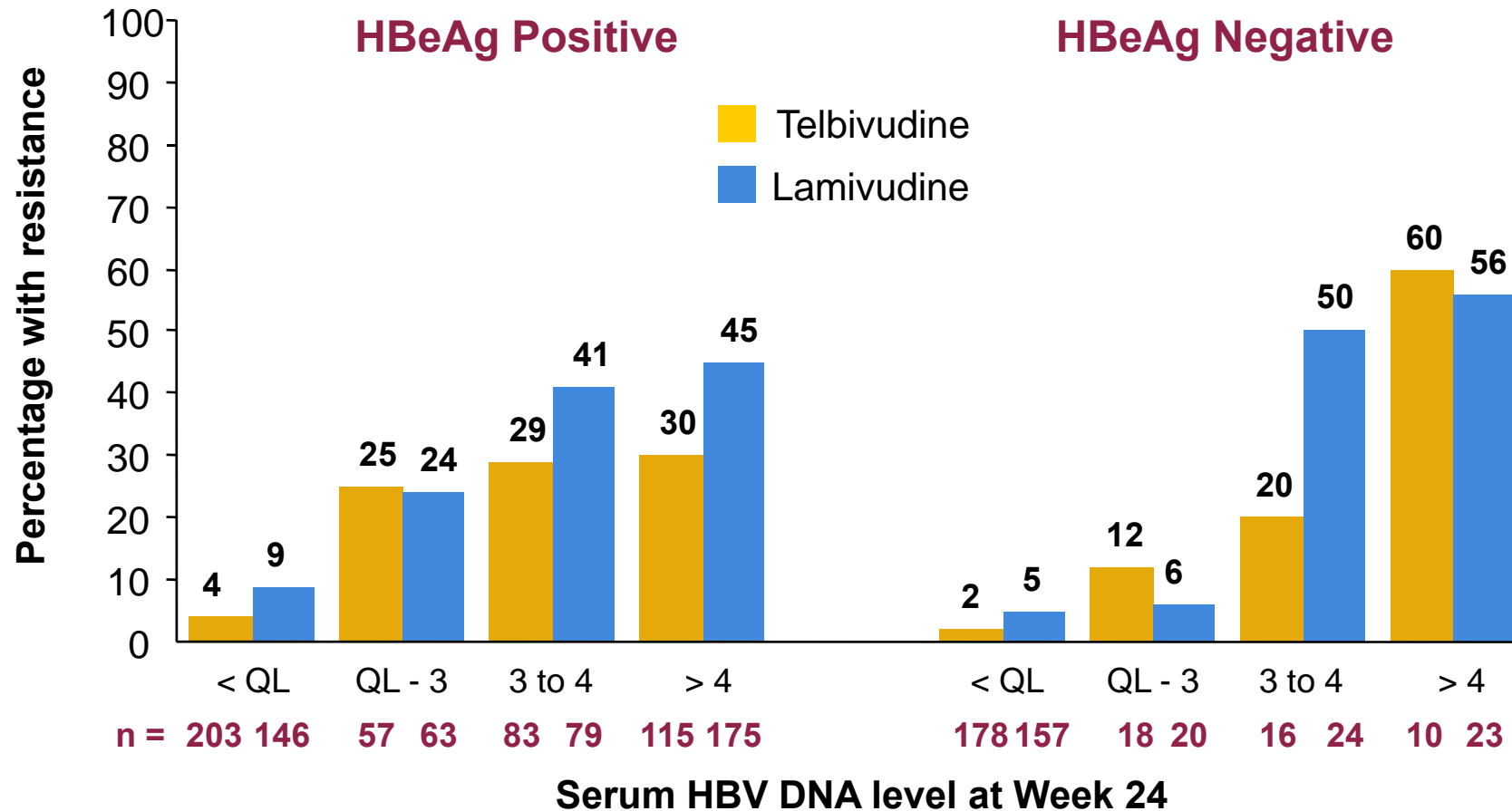
HBV resistance to lamivudine in naïve patients



Question

- **Has the patient any factors associated with a higher risk of lamivudine resistance?**
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Viral resistance at 2 years vs antiviral effect at Week 24: GLOBE trial



Laboratory

January 2003

- ALT 198 UI/l, AST 186 u/l (< 35 u/l), bilirubin 0.9mg/dl, creatinine 0.8mg/dl HBV DNA 5.2×10^7 UI/L
 - Ultrasound: Liver homogenous.
 - No focal lesions
 - Liver biopsy
 - Mild disease F2
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Investigations

- Anti HIV negative
 - Anti HDV negative
 - Drug compliance
 - HBV drug resistance testing
 - M204V and L180M
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Laboratory

- February 2003
 - Lamivudine was stopped
 - He started with Entecavir 1mg daily
 - HBV DNA 5.2×10^7 UI/L
 - August 2003 (24 weeks)
 - ALT 88 IU/l,
 - HBV DNA 5.2×10^4 IU/L
 - HBeAg negative
 - February 2004
 - ALT 68 IU/l,
 - HBV DNA 2.1×10^3 IU/L
 - He continued with entecavir
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Laboratory

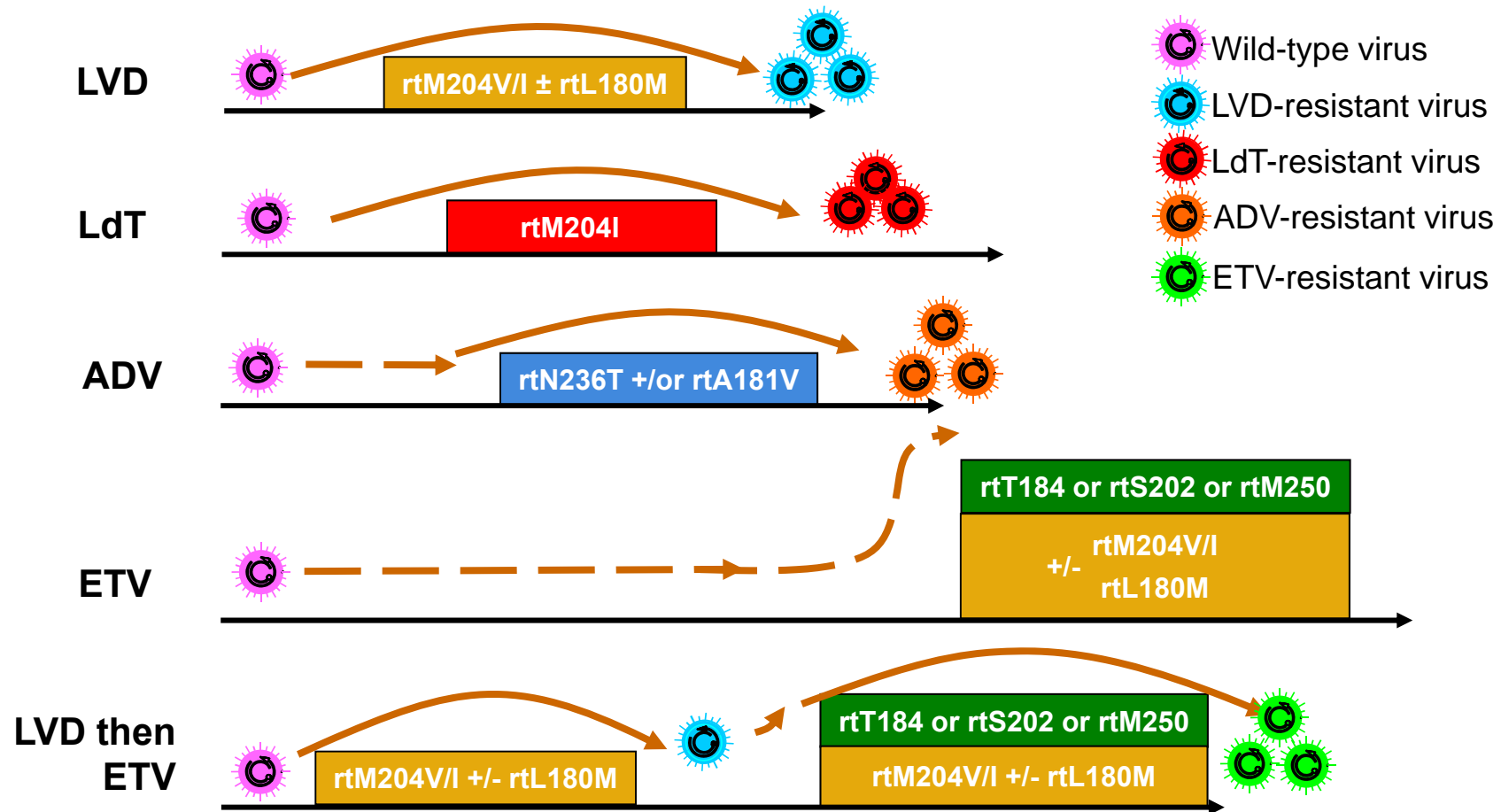
- July 2004
 - ALT 66 IU/l
 - HBV DNA 1×10^3 IU/L
 - December 2004
 - ALT 96 UI/l
 - HBV DNA 1×10^6 IU/L
 - July 2005
 - ALT 99 IU/l
 - HBV DNA 1×10^6 IU/L
 - He asked for a second opinion
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Investigations

- HBV drug resistance testing
 - L180M
 - M204V
 - S202G
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- **What would you do next?**
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Maximising the genetic barrier to resistance



Locarnini S, et al. J Hepato. 2006;44:422-431.

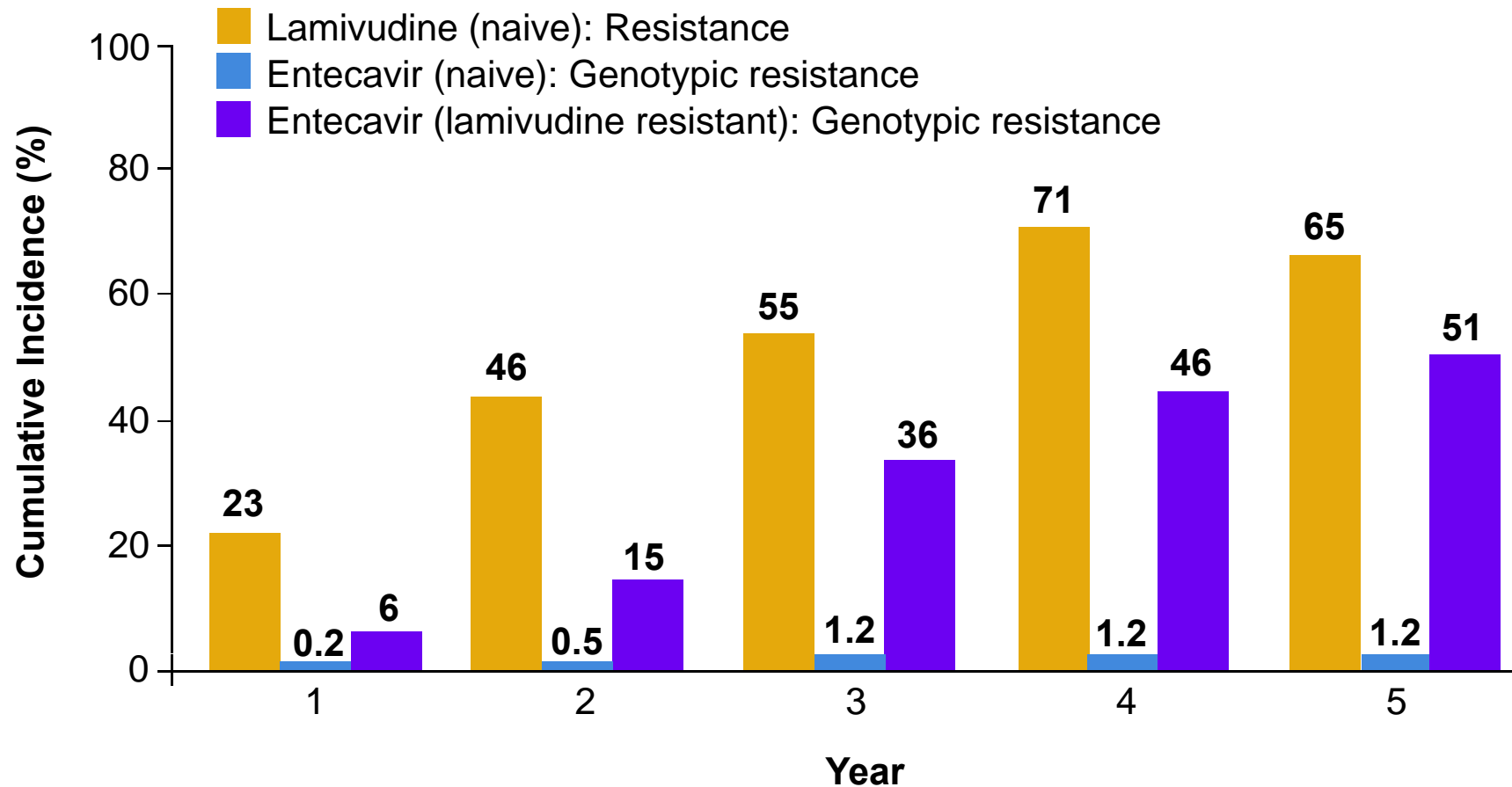
Zeffix® (lamivudine) Summary of Product Characteristics. Glaxo Group Ltd. February 2008.

Sebivo® (telbivudine) Summary of Product Characteristics. Novartis Europharm Ltd. June 2007.

Hepsera® (adefovir) Summary of Product Characteristics. Gilead Sciences International Ltd. October 2007.

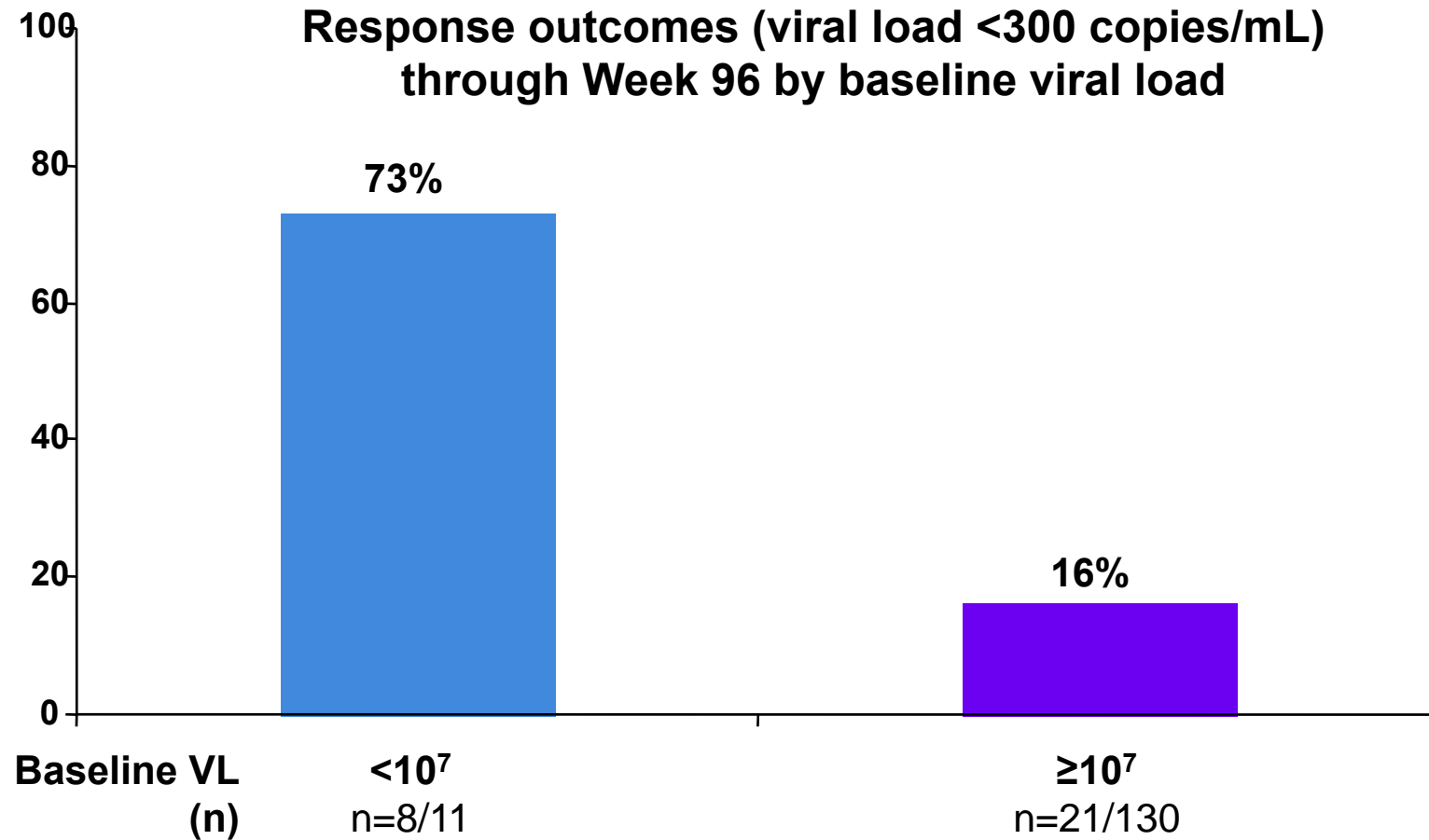
Baraclude® (entecavir) Summary of Product Characteristics. Bristol-Myers Squibb Pharma EEIG. January 2008.

HBV resistance to entecavir affected by previous resistance to lamivudine



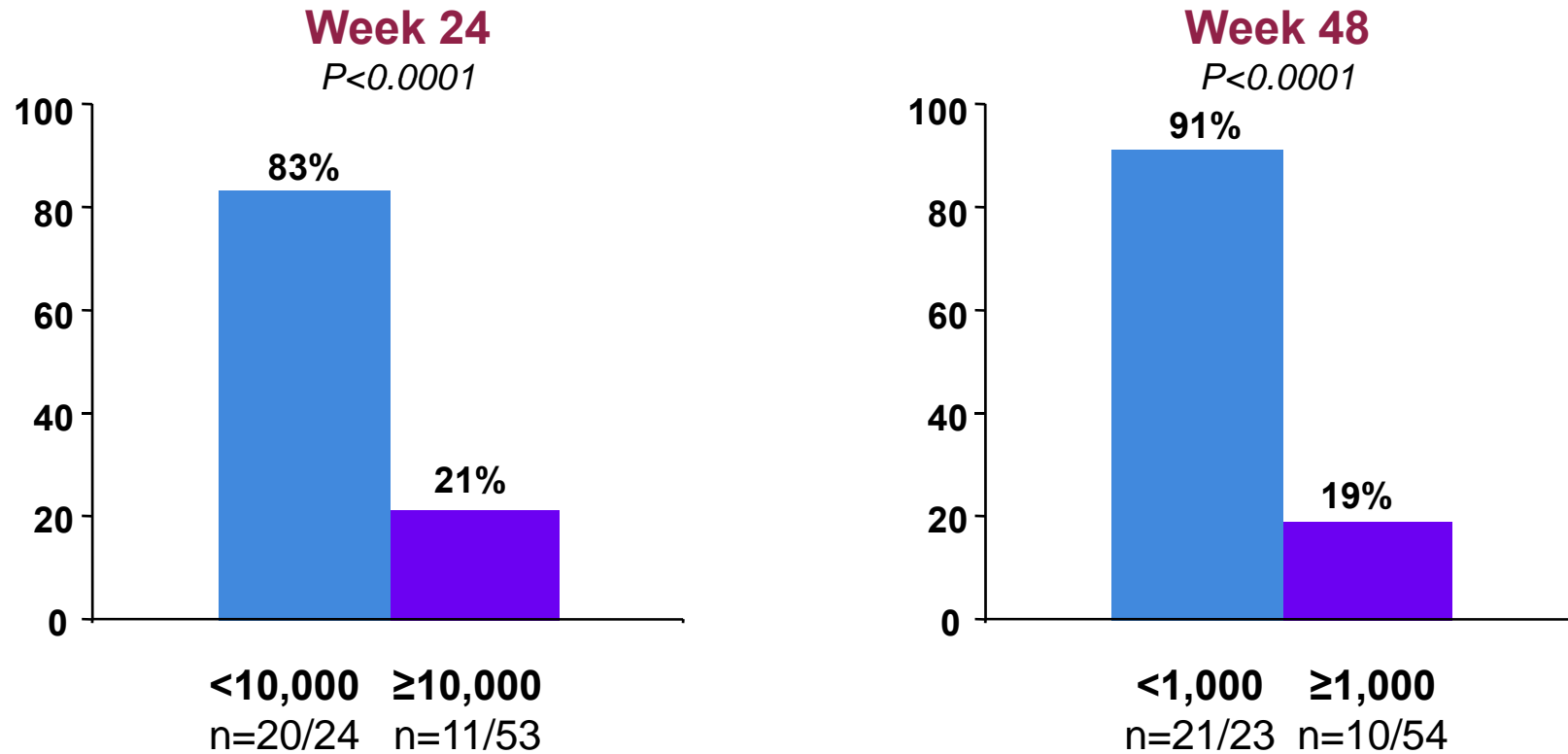
Colonna RJ, et al. EASL 2007. Abstract 781. Lai CL, et al. Clin Infect Dis. 2003;36:687-696.
Lok AS, et al. Gastroenterology. 2003;125:1714-1722.
Tenney DJ et al. Hepatol Int 2008; 2 (Suppl. 3): S302-S303 (abstract PL02)

ETV in LVD-refractory patients: predictors of success



ETV in LVD-refractory patients: predictors of success

Response outcomes (viral load <300 copies/mL)
through Week 96 by viral load



Laboratory

- July 2005
 - Entecavir was stopped
 - Tenofovir 300mg/day
 - October 2005
 - ALT 97 IU/l
 - HBV DNA 2.1×10^3
 - March 2006
 - ALT normal
 - HBV DNA undetectable
 - September 2006 until now
 - He continued with tenofovir
 - Normal ALT and HBV DNA undetectable
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What would you do?

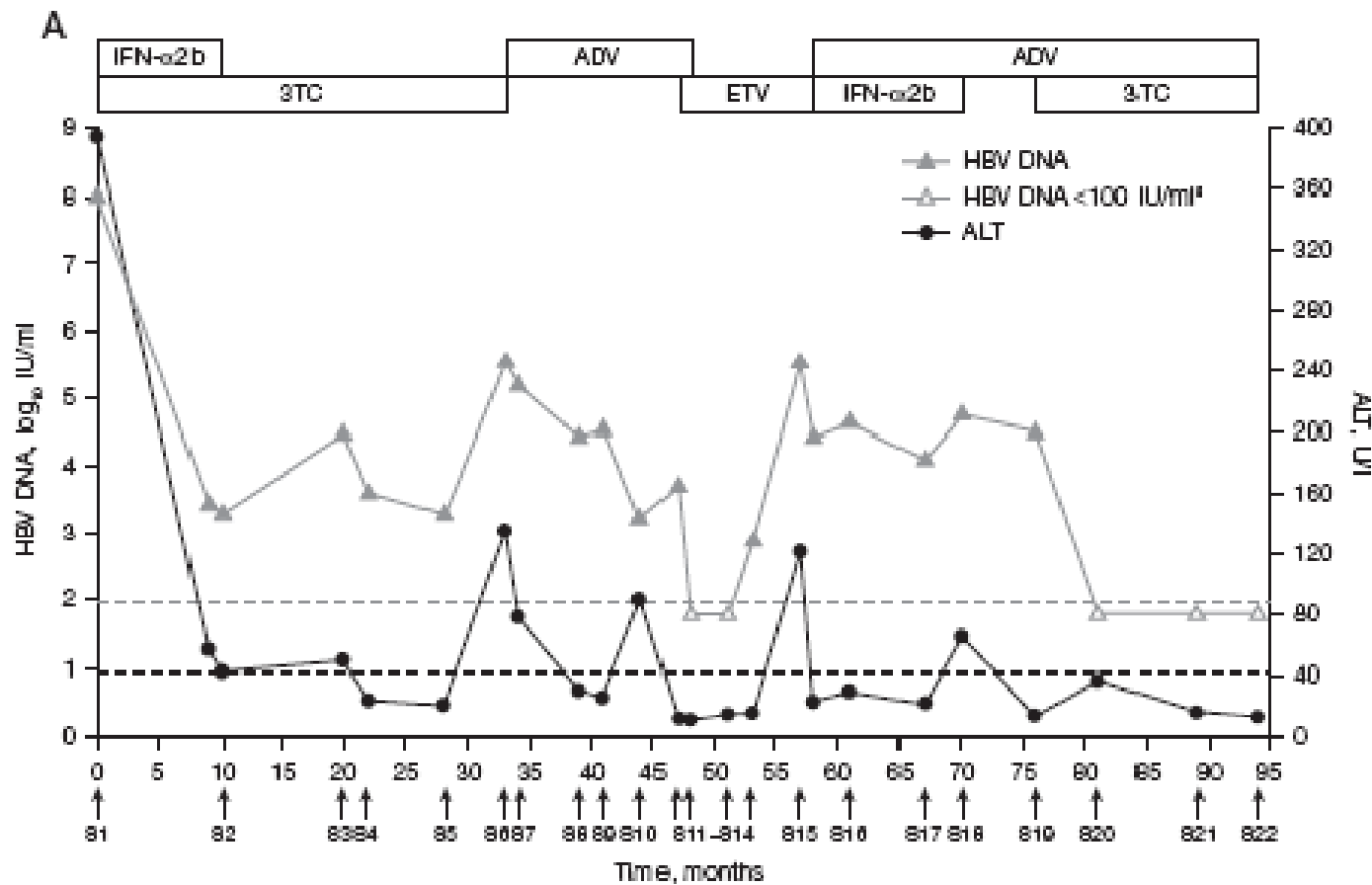
- **How to treat HBV entecavir resistance?**
 - **Which drugs?**
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Cross-resistance data for the most frequent variants

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild-type	S	S	S	S	S
M204I	R	R	I/R	S	S
L180M + M204V	R	R	I	S	S
A180T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

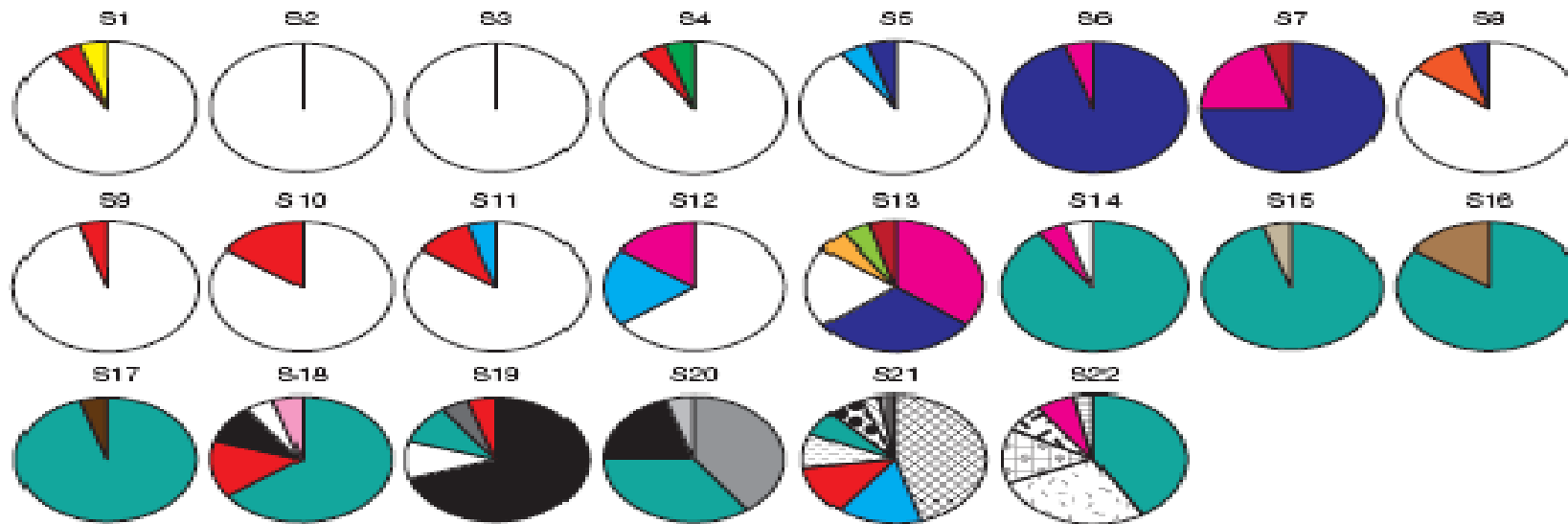
Green = sensitive Purple = resistant

Evolution and Suppression of HBV strains with MDR to LMV, ADV and ETV in a patient with CHB



Evolution and Suppression of HBV strains with MDR to LMV, ADV and ETV in a patient with CHB

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Efficacy of Tenofovir Monotherapy for HBV Patients After Failure of NAs

- 131 Patients with NAs Failure treated with Tenofovir
 - LMV N=18
 - ADV N=8
 - Sequential or Combination of LMV and ADV N=102
 - Entecavir N=3
- Mean Tenofovir duration of 23 mo (range, 6-60)
- 1 Case rtL180M, rtM204V, and rtS202G.
- Complete Response to Tenofovir HBV DNA < 400 copies/mL after 12 weeks

Guidelines for the Management of Antiviral-Resistant HBV

Resistance	Recommendations
LAM	Add ADV or TDF Switch to TDF/FTC* Switch to ETV (LAM-R predisposes to ETV-R)
ADV	Add LAM Switch to TDF/FTC* Switch to or add ETV
ETV	Switch to or add ADV or TDF
Telbivudine	Add ADV or TDF Switch to TDF/FTC* Switch to ETV (LdT-R predisposes to ETV-R)

Case study conclusions

- The best treatment for HBV drug resistance is prevention
 - Treat only those patients who need therapy
 - Use potent antivirals for first line therapy
 - Monitor HBV DNA
 - Adjust therapy in case of incomplete virologic response
 - Promote drug adherence
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