

Hepatitis B Antiviral Drug Resistance: Navigating the Way Forward

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What Is Antiviral Drug Resistance?

What Causes Antiviral Drug Resistance?

Antiviral drug resistance reflects reduced susceptibility of a virus to the inhibitory effect of a drug

Antiviral drug resistance results from a process of adaptive mutations under therapy

- High replication rates

- Low fidelity of the viral polymerase

- Selective pressure of the drug

- Genetic Barrier of the Virus to Nucleosides Analogues

- Role of replication space (liver turnover)

- Fitness of mutant

Indications of Emergence of Drug-Resistant Virus

Increasing viral load (≥ 1.0 log IU/ml)

Identification of known genotypic markers of drug resistance within viral polymerase:

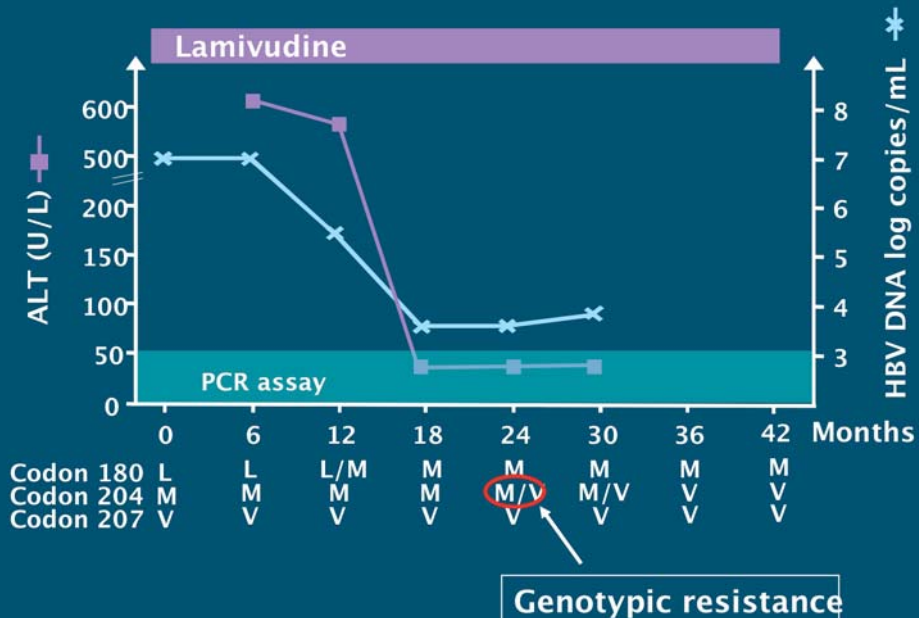
- * primary resistance mutations (rtM204I)
- * secondary resistance mutations (rtL180M with rtM204V)
- * compensatory mutations (rtV173L)

Increasing serum ALT levels

Clinical deterioration

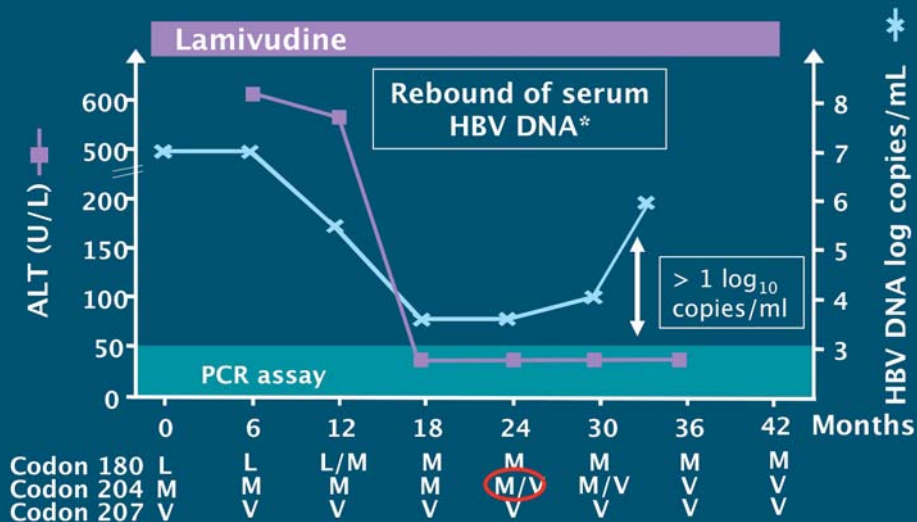
Dynamics of Resistance Emergence

Genotypic Resistance

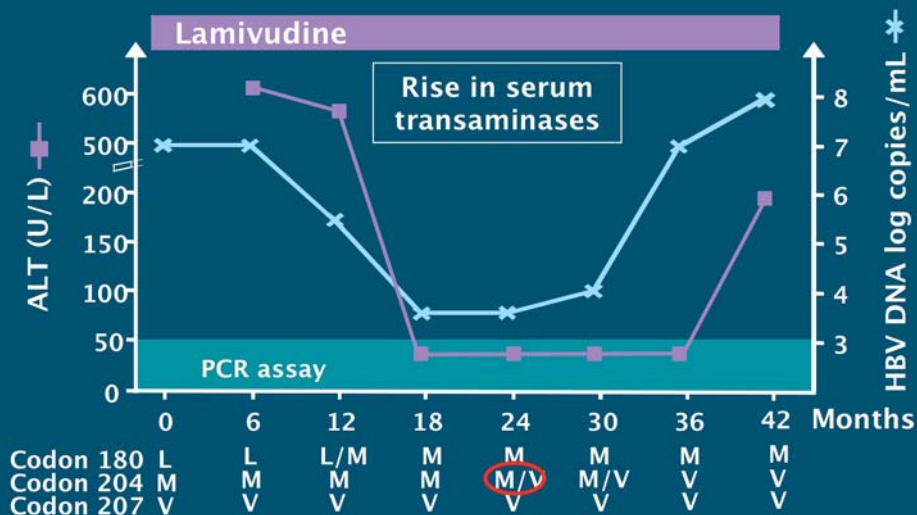


Dynamics of Resistance Emergence

Virologic Breakthrough



Dynamics of Resistance Emergence Clinical Breakthrough



Worsening of liver disease

Resistance to Antiviral Therapy can Compromise Treatment Goals

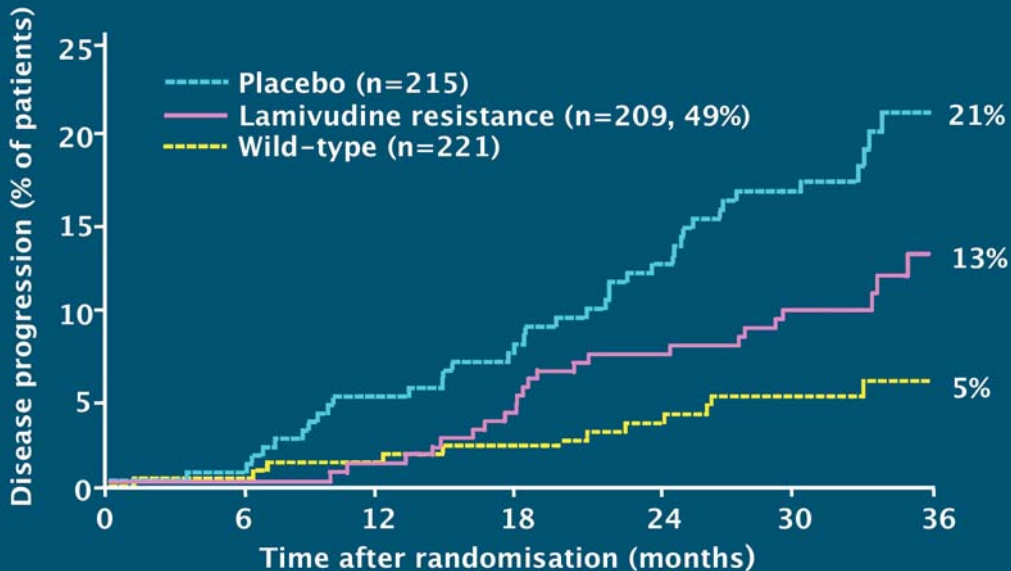
Development of resistance has a negative impact on CHB therapy:

- Virological breakthrough¹
- ALT elevation or ALT flares^{1,2}
- Decreased HBeAg seroconversion³
- Resistant variants may be archived (cccDNA)⁴
- Resistant viruses may escape vaccination⁵
- This may lead to progression of liver disease⁶
 - Hepatic decompensation
 - Hepatocellular carcinoma

Limits Future Treatment Options

1. Lok ASF, et al. *Hepatology* 2007;45:507-39. 2. Fung S & Lok A. *Antivir Ther.* 2004;9:1013-26. 3. Leung NWY, *Hepatology*. 2001;33:1527-1532. 4. Zoulim F, et al. *Antiviral Res.* 2004;64:1-15. 5. Sheldon J & Soriano V. *J Antimicrob Chemotherapy* 2008;4:766-8. 6. Pawlotsky JM, et al. *Gastroenterology* 2008;134:405-15.

Antiviral Effect on Disease Progression* is Reduced when Resistance Develops



Disease progression, defined by the first occurrence of any of the following: an increase of at least 2 points in the Child-Pugh score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding gastric or esophageal varices, the development of hepatocellular carcinoma, or death related to liver disease.

Adapted from 1. Liaw Y-F, et al. *N Engl J. Med.* 2004;351:1521-31. 2. Liaw Y-F, et al. *Semin Liver Dis.* 2005;25 (Suppl 1):40-7.