

Hepatitis B Antiviral Drug Resistance: Navigating the Way Forward

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Managing Antiviral Drug Resistance

Cross-Resistance

- Resistance to drug(s) to which a virus has never been exposed
- Resistance-associated mutations selected by drugs may diminish the antiviral activity of other drugs¹:
 - ***this should be considered before any antiviral drug is prescribed***
- Cross-resistance tends to be more common for compounds sharing structural properties²
- Any change in therapy, typically combination or add-on strategies, should be made using drugs that lack cross-resistance with the failing agent¹

Common Pathways of Antiviral Resistance in CHB: Cross-Resistance

Pathway	Resistance Substitutions	Antiviral Agent	Cross Resistance Profile			
			L-NA	ADV	TDF	ETV
L-Nucleoside (L-NA)	rtM204V/I	Lamivudine (LMV) Emtricitabine (FTC) Telbivudine (LdT)	R	S	S	I
Acyclic Phosphonate	rtN236T	Adefovir (ADV) Tenofovir (TDF)	S	R	I	S
"Shared"	rtA181T	L-Nucleoside Acyclic Phosphonate	R	R	I	S
Naïve Entecavir Resistance	rtL180M+rtM204V with one of rtT184, S202 or M250	Entecavir (ETV)	R	S	S	R
Multi Drug Resistance	Complex patterns e.g. rtA181T+rtI239V+ rtN236T+rtM250L	Multi-Drug	* consult reference laboratory * Role of IFN- α			

R = Resistance; S = Sensitive; I = Intermediate

Viral Mutational Pathways: rtM204V/I



LAMIVUDINE

not effective

TELBIVUDINE

not effective



ENTECAVIR

higher dose needed
Reduced sensitivity



rtM204V/I



ADEFOVIR

effective

TENOFOVIR

effective



Viral Mutational Pathways: rtA181T/V



ADEFOVIR

not effective

LAMIVUDINE

not effective

TELBIVUDINE

not effective



TENOFOVIR

Reduced sensitivity



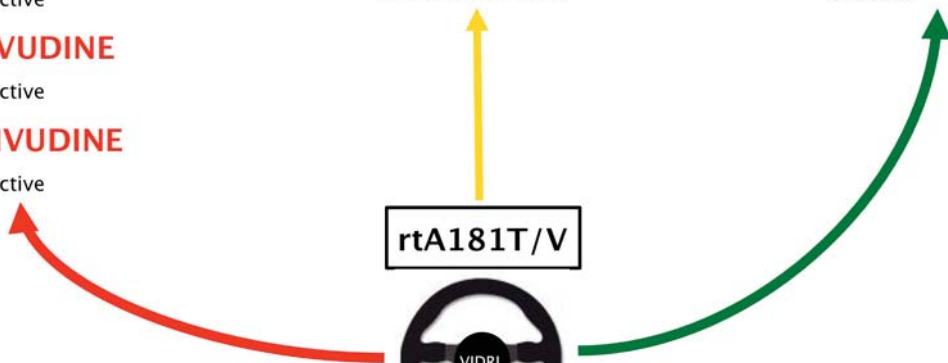
ENTECAVIR

effective

rtA181T/V



VIDRL



Viral Mutational Pathways: rtL180M+rtM204V+ T184* or S202* or M250*



ENTECAVIR

not effective

LAMIVUDINE

not effective

TELBIVUDINE

not effective

rtL180M+rtM204V
+
T184* or S202* or
M250*



ADEFOVIR

effective

TENOFOVIR

effective

* other aa changes

Viral Mutational Pathways: rtN236T



ADEFOVIR

not effective



TENOFOVIR

Reduced sensitivity



LAMIVUDINE

effective

TELBIVUDINE

effective

ENTECAVIR

effective

rtN236T



Viral Mutational Pathways: rtN236T+rtA181T/V



ADEFOVIR

not effective

TENOFOVIR

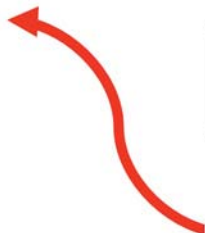
not effective

LAMIVUDINE

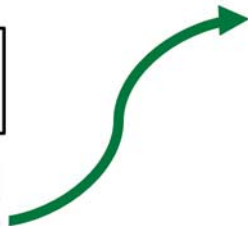
not effective

TELBIVUDINE

not effective



rtN236T +
rtA181T/V



ENTECAVIR

effective

What to do on First Virological Breakthrough/Partial Virological Response

CHECK IF PATIENT COMPLIANT

- Repeat HBV DNA testing in a timely manner to confirm VL breakthrough
- If confirmed [HBV VL \geq 1.0 log IU/ml] THEN perform HBV POL SEQUENCING