When to re-treat after stopping NrtI

Marion Peters M.D.

Northwestern University Chicago Il

When to restart NrtI

- Don’t stop NrtIs in those with cirrhosis
- All patients who stop NrtIs should be monitored closely: ALT, HBV DNA and clinical assessment q1-3 for 3mos, q3 mos for 1y at least
- Clinical decompensation or increased bilirubin, INR: restart NrtI
- What about elevated ALT and HBV DNA?
- What about in studies of new drugs: DAAs or immunomodulators?

When to re-start NrtI: EMA FDA

- Stringent Treatment re-initiation criteria for NUC should be predefined in the protocol

Timing of assessment requires:

- Long term f/u of off-treatment responses for Phase IIb/III trials
- May depend on mechanism of action and half-life of the drug

When to re-start NrtI

Agreement

- Liver decompensation
- Treating MD
- Patient request

Similarity

- Very high ALT >10x ULN
- Moderate ALT with HBV DNA
- HBeAg seroreversion

When to re-start Nrtl

*consider re-starting nucs

Study/Co	INR Bili decomp	ALT>ULN + HBV DNA	HBV DNA	ALT	HBeAg seroreversion
Berg JHep	Yes*	>2-5x >20k >12w >5-10x for 4w		ALT >10x*	
Toronto	yes	>5x. >2k	>20k		yes
Assembly Bios	yes	> 3xULN >100k >ULN >2k qmo x3		ALT >10x	
Gilead	yes	ALT>ULN for 8w with *>20k HBeAg+ *>2k HBeAg -		ALT>10x	
JNJ	yes	>5x *>2K confirmed	*>20k conf		yes
Roche	"based on ALT, HBV DNA, LFT values"				

When to restart NrtI

- Close monitoring
- Any evidence of liver dysfunction- immediately- everyone agrees with
  - Elevated bilirubin
  - Elevated INR
  - Development of ascites, encephalopthy
- HBeAg sero-reversion
- All protocols agree on “Treating physician” or patient preference
  - Assembly Bio half restarted Nucs for this reason (EASL 2021)
- Level of HBV DNA and ALT vary

Markers to predict need to restart

- Those with HBV control
  - Reactive HBV specific CD8 higher in those who decreased qHBsAg (PO-430 Asensio)
  - HLA diversity higher in those who did not relapse (Tuefferd PO947)

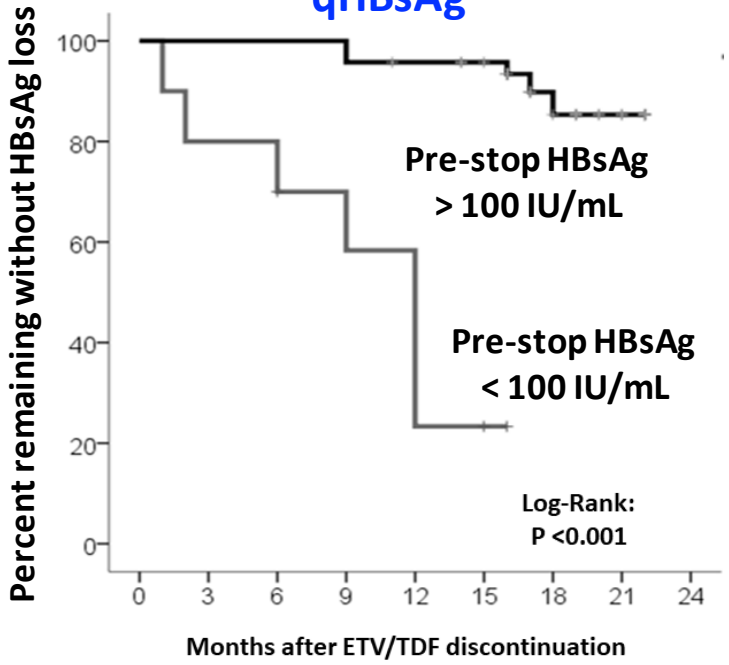
- Relapsers
  - Anti-HBc higher (cut off <325 IU/mL: Cornberg PO-2293)
  - Higher HBcrAg (Sarowar Toronto Stop PO-2269)

Can we predict who will need retreatment?

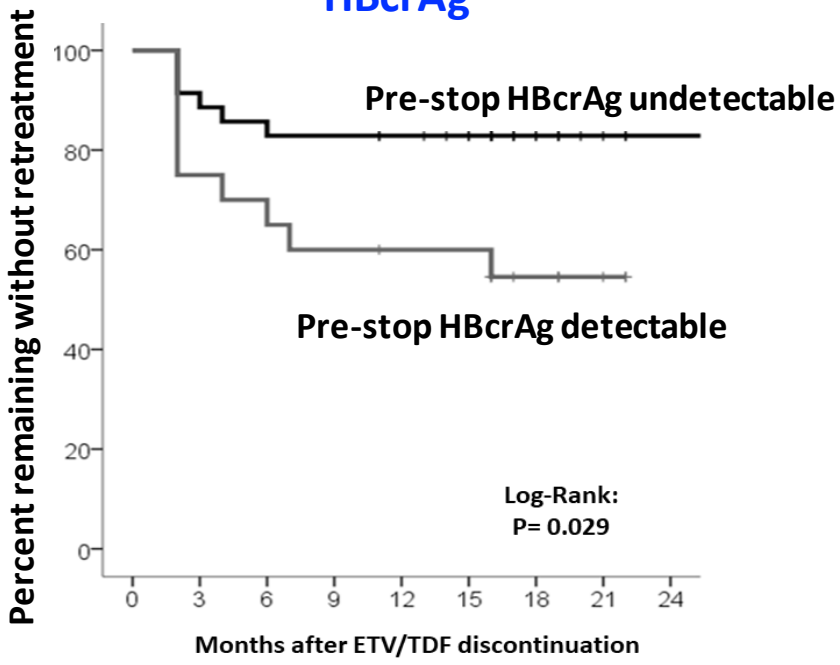
Prospective RCTs of stopping long-term NA therapy

DARING-B (n=60)

qHBsAg

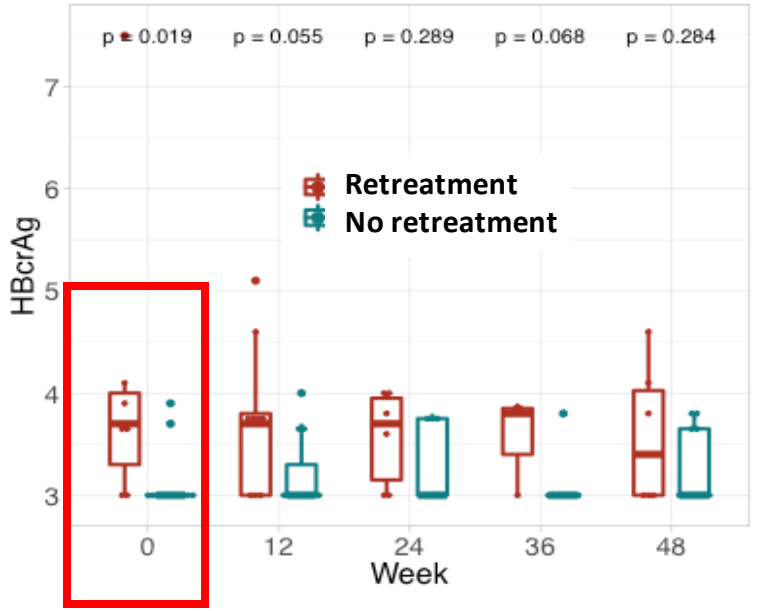


HBcrAg



FINITE Study (n=40)

HBcrAg



- Multiple small studies showing **undetectable HBcrAg** and/or low **qHBsAg** at the **time of stopping** = lower risk of relapse & increased chance of HBsAg loss
- Need more data but could be promising predictive tools

Papatheodoridis, Abst 408, Van Bommel et al, Abst 458D, Hsu YC et al, Abst 0397, Seto et al, Abst 0417 EASL 2020

Sarowar
EASL 2021
PO-2269
Toronto STOP nucs

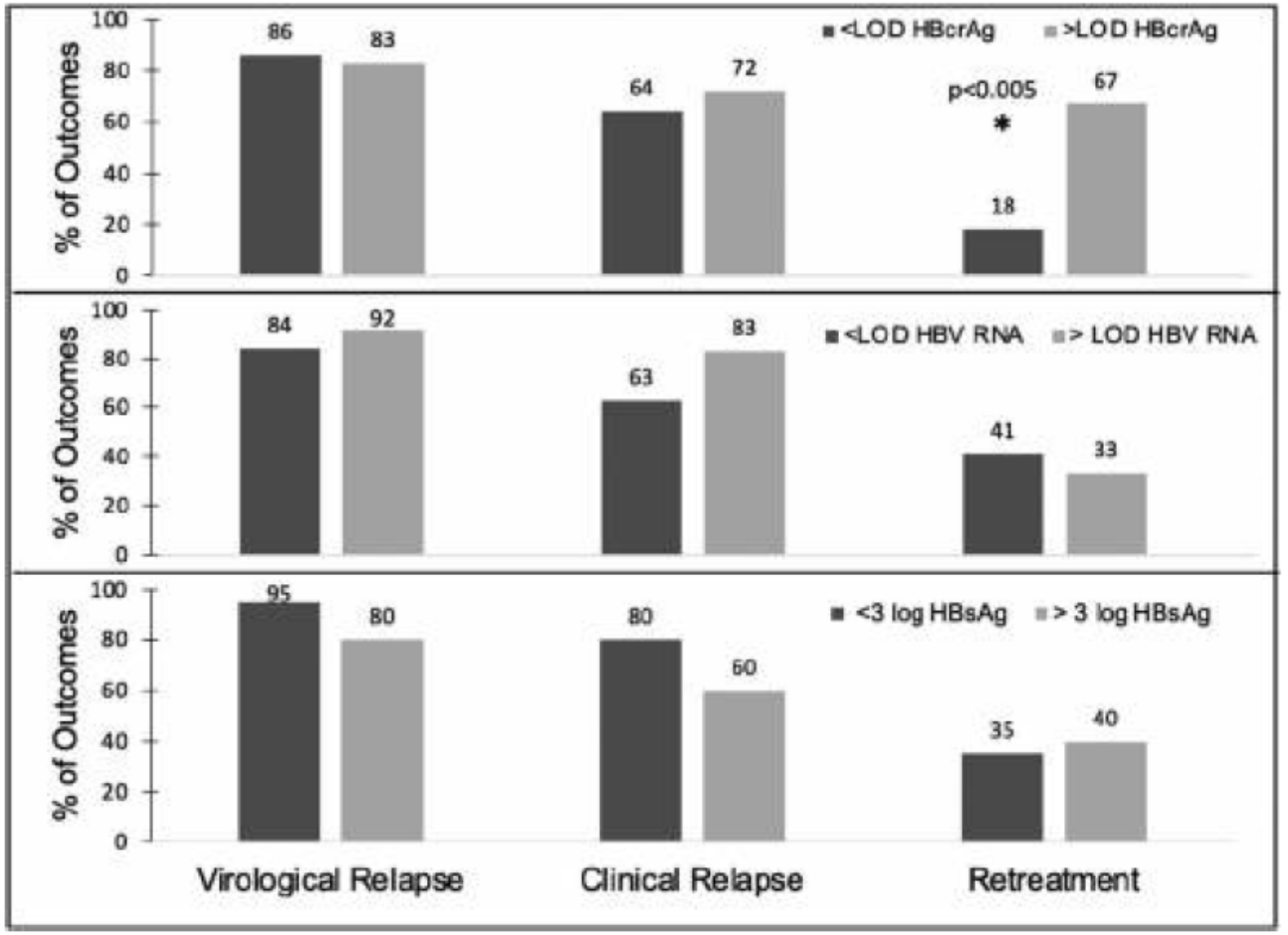


Figure: Relapse and retreatment outcomes for stop patients (n = 45) based on HBcrAg, HBV RNA, and HBsAg levels at end of treatment. Limit of detection (LOD) for HBV RNA and HBcrAg was 160 cp/ml and 3 log U/ml, respectively

Retreated
Higher crAg

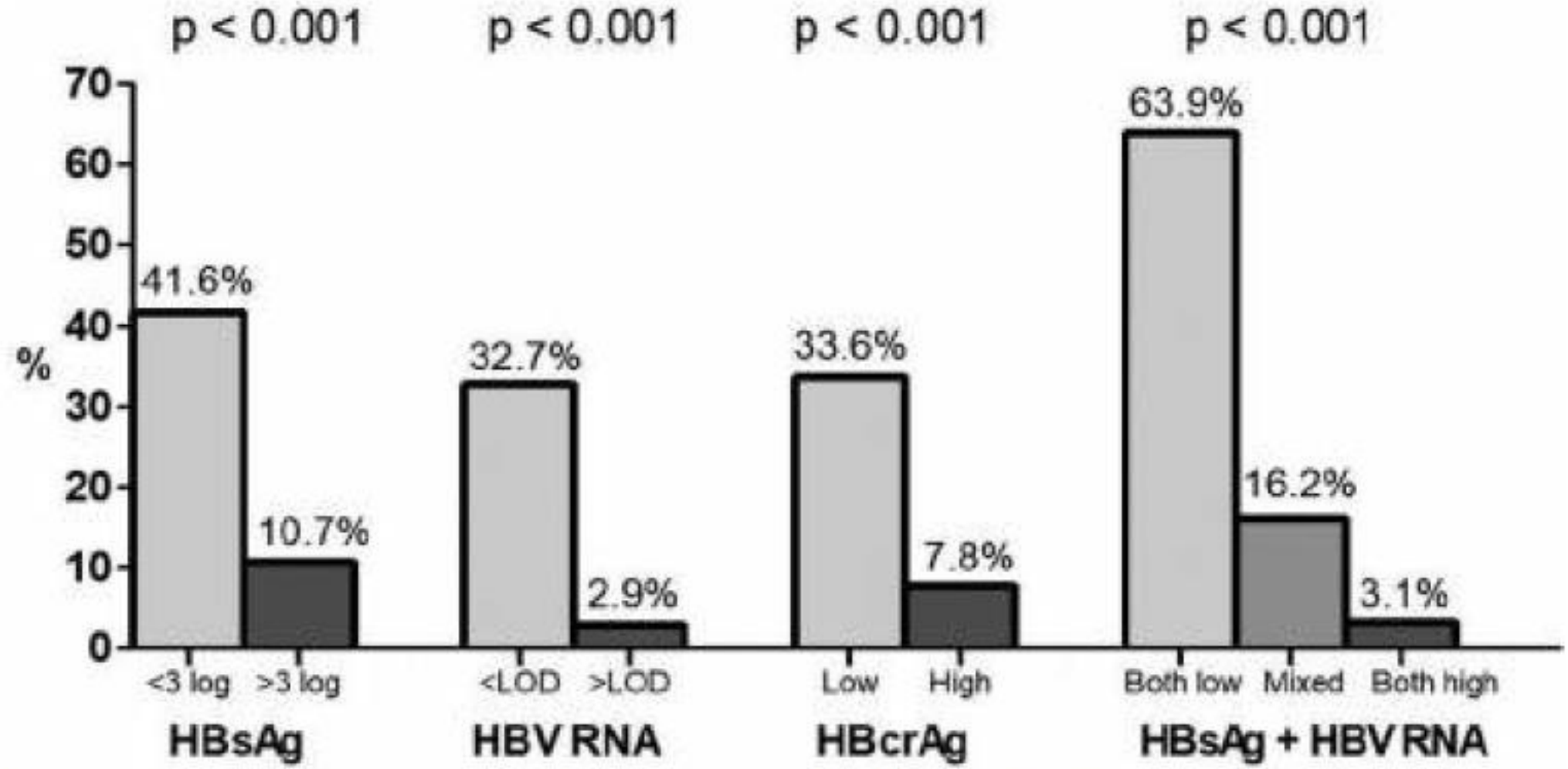


Figure: Rates of sustained response (HBV DNA <2, 000 IU/ml 6 months after treatment withdrawal), according to HBsAg, HBcrAg and HBV RNA levels at end-of-treatment.

Brakenhoff EASL PO-80 3 RTC of Peg IFN d/c n=344

Issues for evaluating when to restart in trials

- Safety first
- **Stringent** Treatment re-initiation criteria for NUC should be predefined in the protocol
  - How to deal with MD/patient preference?
- Monitoring criteria

Issues for evaluating when to restart in trials

Monitoring criteria

- Liver decompensation all agreed to restart
- How frequent to monitor?
- For how long?
- Should criteria differ by type of therapy studied?
  - E.g. siRNA (longer half life) vs CAM vs IM
- Is it possible to standardize monitoring within MOAs?
- Is it possible to standardize monitoring across MOAs?

What to monitor

- ALT, HBV DNA, clinical assessment- sufficient to restart NrtI?
- HBcrAg, HBV RNA, qHBsAg, HBV sp CD8- earlier to predict need to restart?