# Controversies in HBV
# When to start & when to stop treatment

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# Disclosures

- Research: Abbvie, Enanta, Gilead, Janssen, Wako

- Consulting: Abbvie, Enanta, Gilead, GSK, Roche

# Outline

- **When to start**
  - Current treatment guidelines – EASL, AASLD, CASL
  - Areas of controversy
    - Immunotolerant / HBeAg+ Chronic Infection
    - Milder immune active (EASL vs AASLD)
- **When to stop**
- **What's coming?**

# Outline

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  - Current treatment guidelines – EASL, AASLD, CASL
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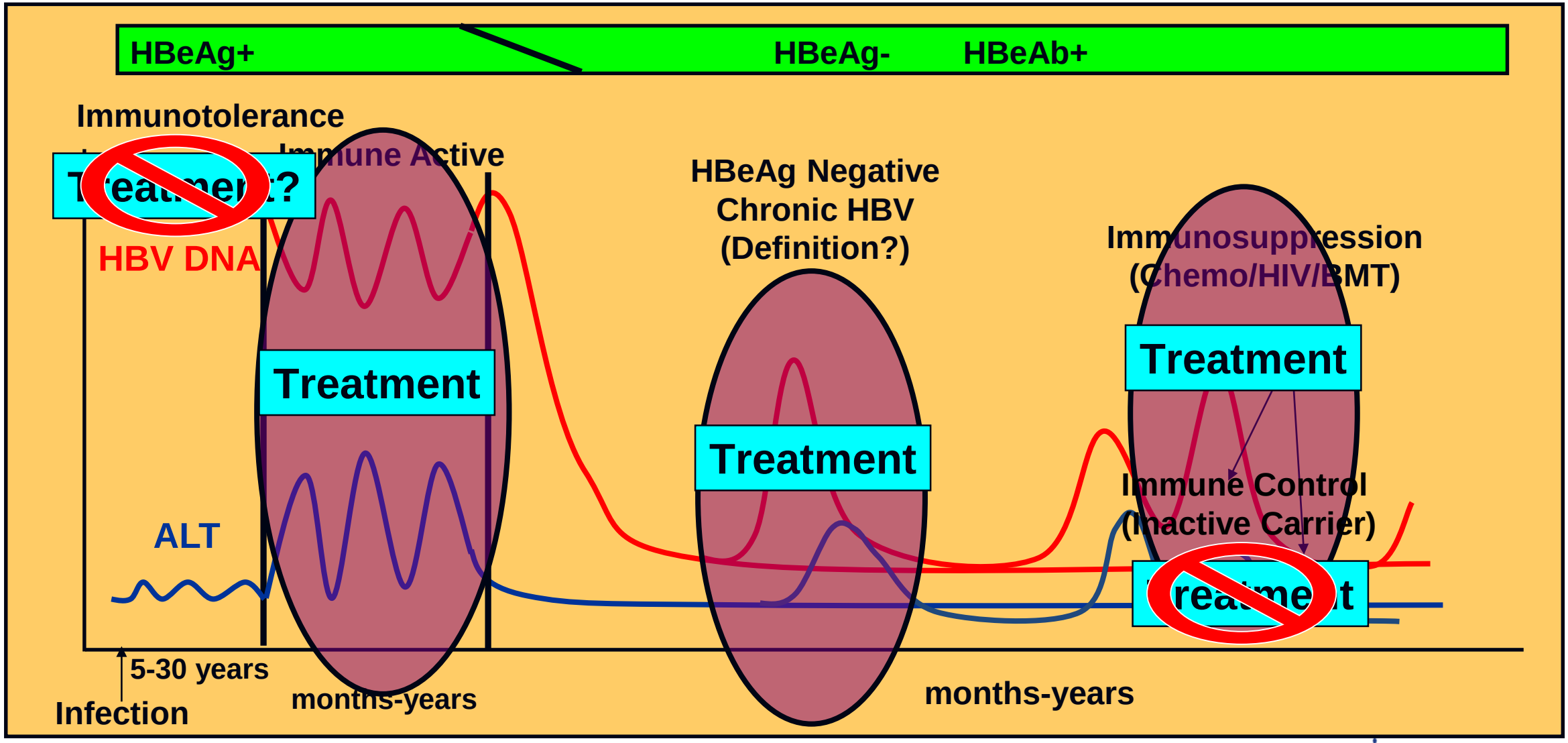
- **When to stop**

- **What's coming?**

# When to treat



# Treatment based on disease phase and risk of progression

| Phase | Immune tolerant | HBeAg-positive CHB | Inactive carrier | HBeAg-negative CHB |
|---|---|---|---|---|
| HBeAg status | Positive | Positive | Negative | Negative |
| HBV DNA | Very high >200,000 IU/mL | >2000 IU/mL | <2000 IU/mL | >2000 IU/mL (fluctuating) |
| ALT | Normal | Elevated | Normal | Elevated (fluctuating) |
| Liver histology | Normal or mild inflammation and limited fibrosis | Inflammation and fibrosis: degree varies | Normal or mild inflammation | Inflammation and fibrosis: degree varies |
| **Disease progression** | Low | **Moderate to high** | No, very low | **Moderate to high** |
| **Treatment** | Not indicated | **Indicated** | Not indicated | **Indicated** |

Adapted Lampertico

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# The guidelines

| | HBeAg + | | HBeAg - | | Cirrhosis | |
|---|---|---|---|---|---|---|
| | **HBV DNA** | **ALT** | **HBV DNA** | **ALT** | **HBV DNA** | **ALT** |
| **AASLD*** | >20,000 IU/mL | ≥2x ULN or significant histologic disease (≥A3 or ≥F2) | >2,000 IU/mL | ≥2x ULN or significant histologic disease (≥A3 or ≥F2) | Detectable | Any |
| **EASL** | >2,000 IU/mL | > ULN and/or significant histological disease | >2,000 IU/mL | > ULN and/or significant histological disease | Detectable | Any |
| **CASL** | >2,000 IU/mL | > ULN or significant histologic disease (≥A3 or ≥F2) | >2,000 IU/mL | >ULN or significant histologic disease (≥A3 or ≥F2) | Detectable | Any |

* ALT ULN of 25 for F and 35 for M

Terrault Hepatology 2018, EASL HBV Guidelines J Hep 2017, Sarin Hepatol Int 2016

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# General agreement

- **Active disease**
  - HBeAg+ or HBeAg-
  - Slight differences in HBV DNA thresholds – rarely relevant
  - Differences in ALT thresholds – more relevant (AASLD: ≥ 2x ULN, EASL: >ULN)
- **Cirrhosis**
  - Any detectable DNA (EASL/AASLDCASL)
  - DNA>2,000 IU/mL or decompensated cirrhosis (APASL)
- **Immunosuppression:**
  - HBsAg-positive +/- HBsAg-/anti-HBc+ (all)
- **Pregnancy:**
  - HBV DNA > 200,000 IU/mL (AASLD, EASL, CASL), HBV DNA 6-7 log IU/mL (APASL)
- **Other scenarios…**
  - **IT/HBeAg+ with chronic infection**: >40 with active biopsy (AASLD), >30 (EASL)
  - **Low level viremia with normal ALT:** without cirrhosis, not recommended
  - **Treat all HBsAg +:** not recommended

# Outline

- Current treatment guidelines – EASL, AASLD, APASL & WHO
- Areas of controversy
  - **Immunotolerant / HBeAg+ Chronic Infection**
    - **Adult**
  - Milder immune active (EASL vs AASLD)
  - Immune control (inactive)

# Treatment during immune tolerant/HBeAg+ with chronic infection phase

**Pros**

- High replication
- High rate of integration
- ?cancer risk
- Transmission risk
- Prevent silent progression

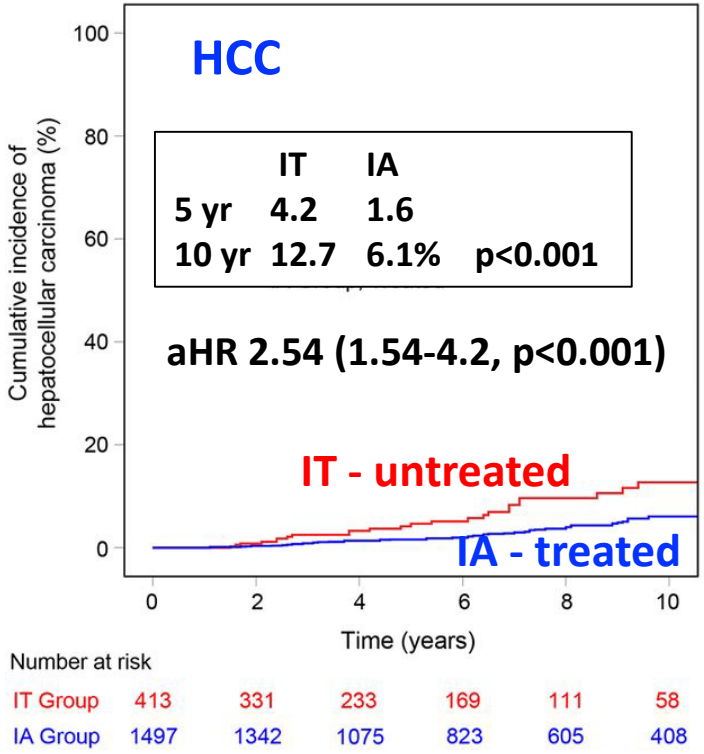
**Cons**

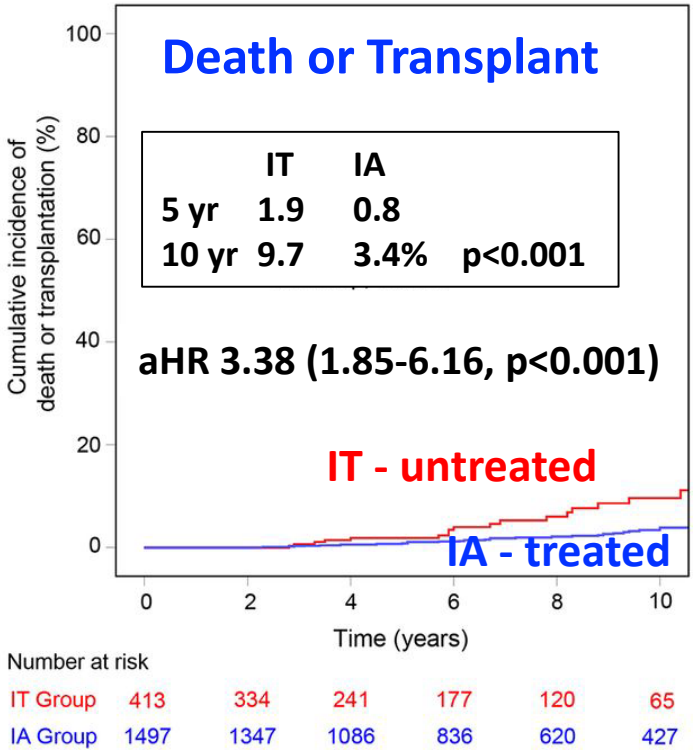
- Ineffective – no HBeAg loss (<5% at 4 yrs), no HBsAg loss
- Integration likely very early – may not be prevented & MOA too late
- No or minimal liver disease, limited progression
- Long-term therapy in young people – adherence, cost, (resistance)

# Is there a risk to leaving IT patients untreated?

Untreated non-cirrhotic HBeAg+ with HBV DNA>20,000 IU/mL
3 groups: **IT (ALT<ULN), IA on treatment (ALT>2xULN), minimally active (ALT 1-2xULN)** followed to death/OLTx

Features
- Stable phase x 1y
- ALT – M 30, F 19
- Median f/u 6.3y
- HR propensity score and IPTW adjusted
- Cirrhosis by US or clinical




*similar w/ propensity score matching

Despite being younger with less fibrosis, IT patients had a higher risk of events than treated IA patients

Kim GA Gut 2018

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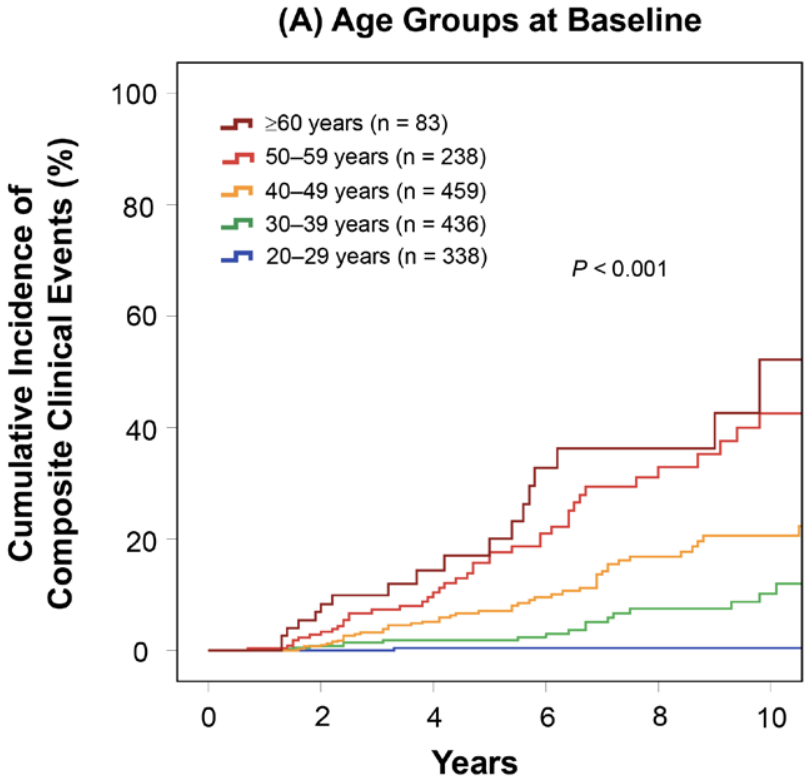
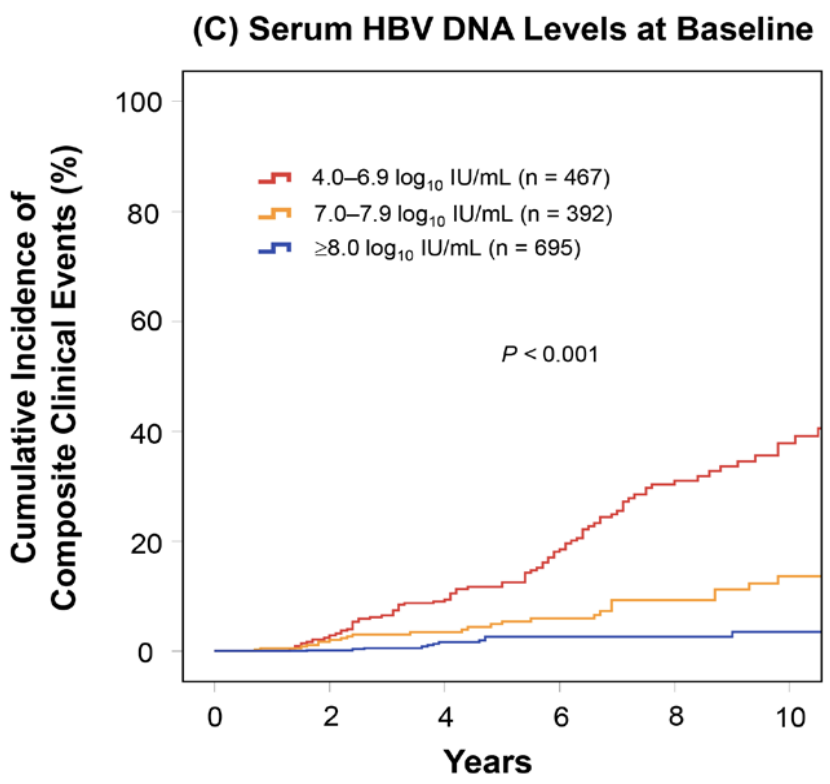
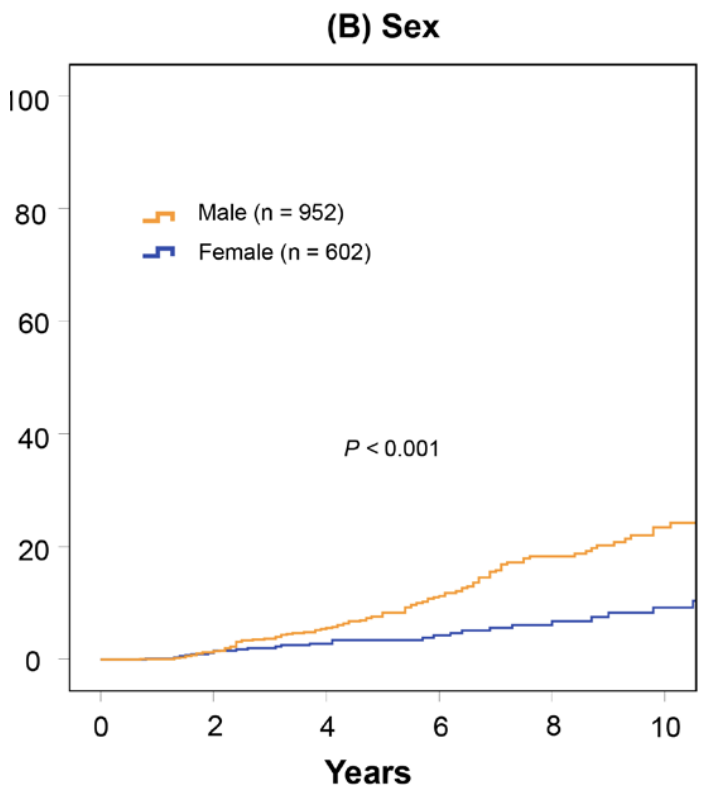
# Risk factors for HCC in IT/MA group




***Biopsy in 45 (resection/OLTx) – 31 (68.9%) – F3/4!***

Increasing age, ***lower*** HBV DNA, male sex & fibrosis associated with risk of HCC

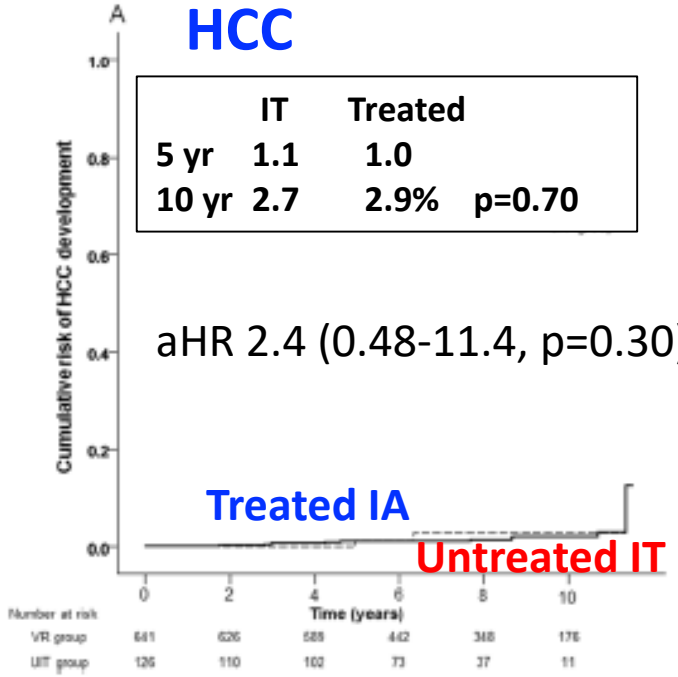
# Not everyone agrees…

Similar design – Korean study of **untreated IT (n=126)** with DNA<20,000 w/ ALT<40 vs vs **treated IA (n=641)** with median 97 m f/u

## HCC

| | IT | Treated | |
|---|---|---|---|
| 5 yr | 1.1 | 1.0 | |
| 10 yr | 2.7 | 2.9% | p=0.70 |

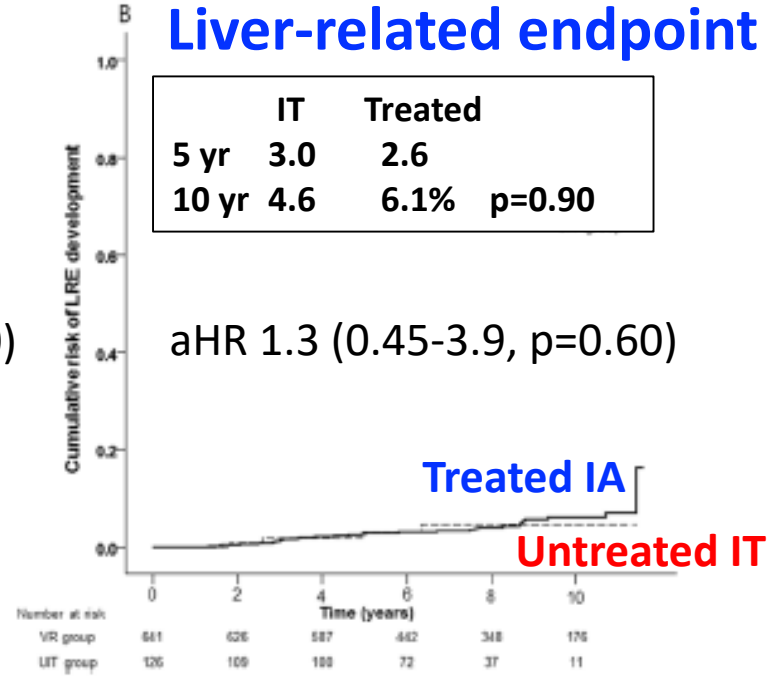
aHR 2.4 (0.48-11.4, p=0.30)




## Liver-related endpoint

| | IT | Treated | |
|---|---|---|---|
| 5 yr | 3.0 | 2.6 | |
| 10 yr | 4.6 | 6.1% | p=0.90 |

aHR 1.3 (0.45-3.9, p=0.60)




- Much lower event rate overall in both groups – unclear why
- **Risk factors for events:** Lower HBV DNA (<10E6) & older age
- **No HCC with HBV DNA>10E6 or with age>40**

Lee Sci Reports Feb 2019

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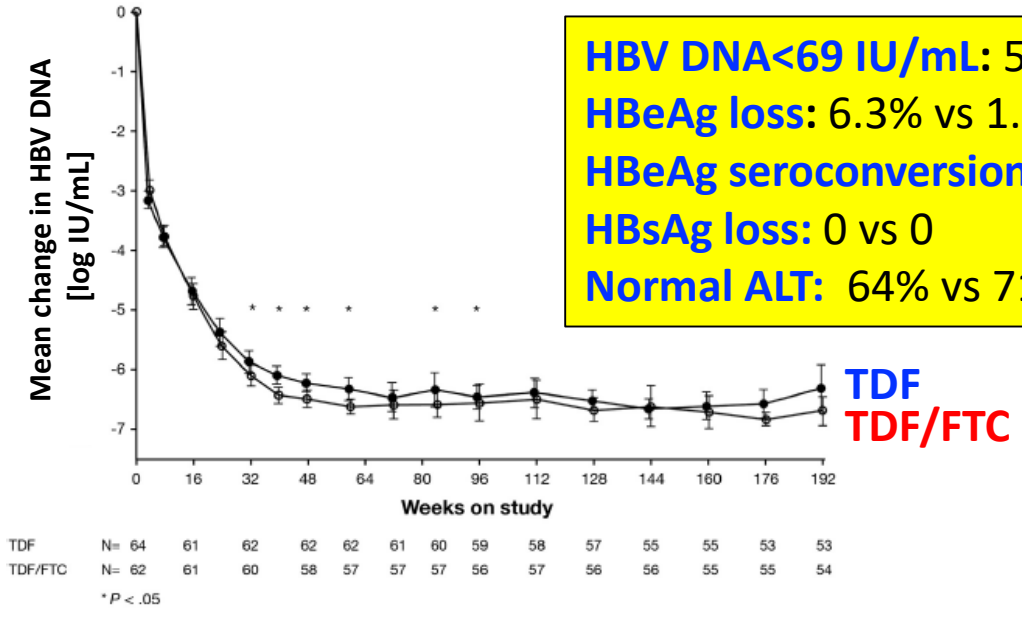
# But would treatment help?

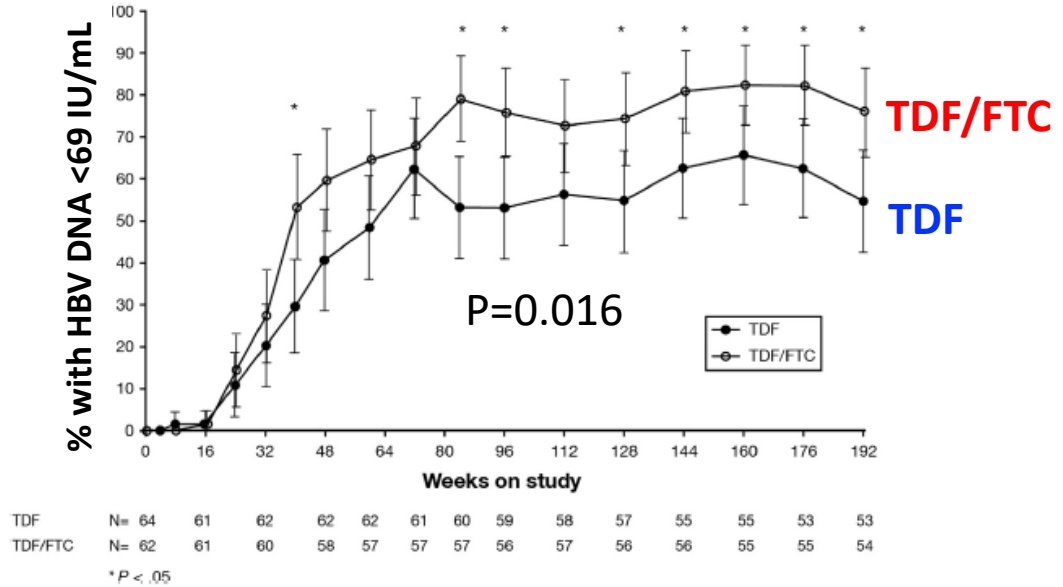
# NA therapy in immunotolerant HBV

Non-cirrhotic HBeAg+ with HBV DNA>1.7E7 log IU/mL, normal ALT (43 M, 34 F)
**TDF vs TDF/FTC x 192 weeks**




**HBV DNA<69 IU/mL:** 55% vs 76%
**HBeAg loss:** 6.3% vs 1.8%
**HBeAg seroconversion:** 4.8% vs 0
**HBsAg loss:** 0 vs 0
**Normal ALT:** 64% vs 71%

**TDF**
**TDF/FTC**




**TDF/FTC**

**TDF**

***Stopping therapy led to prompt rebound in 51 of 52 with 1 ALT flare @ wk 4 but 10 of 20 (50%) by week 15 (peak ALT 1,149 U/L)***

Overall NA therapy ineffective after 4 years – very long-term required…probably not the answer

Chan Gastro 2014, Wong VW J Clin Gastro 2018

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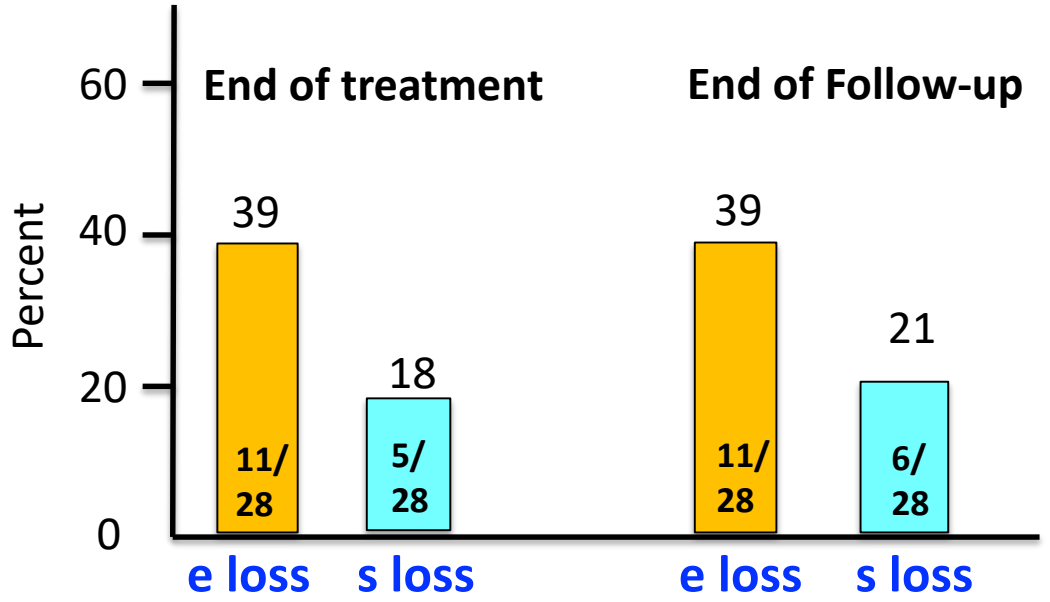
# NA + IFN in Immunotolerant HBV

Children with HBeAg+, HBV DNA>7 log IU/mL and ALT<2xULN with minimal/no activity on bx

**LAM 3 mg/kg/d x 8 weeks and then IFN-alfa 5 MU/m² 3x/week x 44 weeks**




- Promising results – but no predictors of response
- Similar results in prior pediatric trial

Poddar J Vir Hep 2013, D'Antigua J Ped 2006

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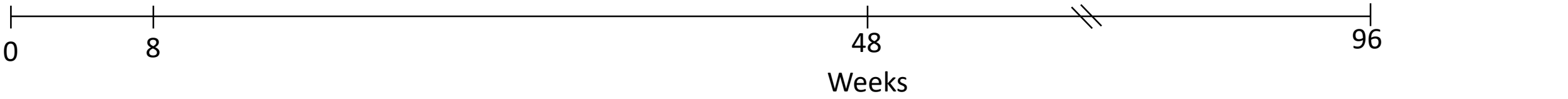
# HBRN IT Study

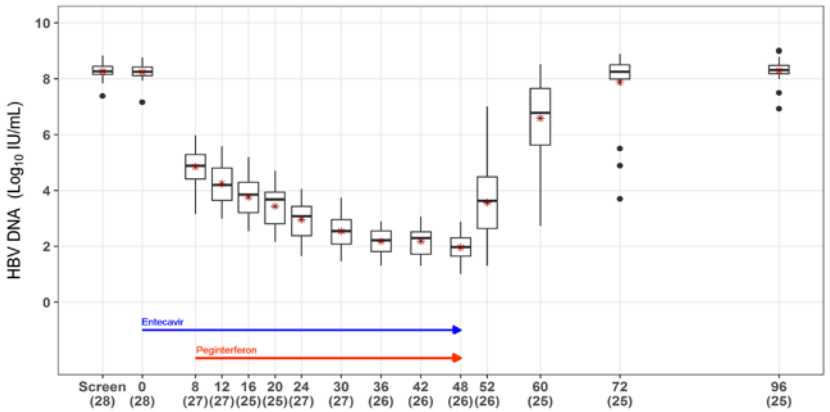
Entecavir 0.5 mg OD

Peginterferon-α 2a 180 µg/week

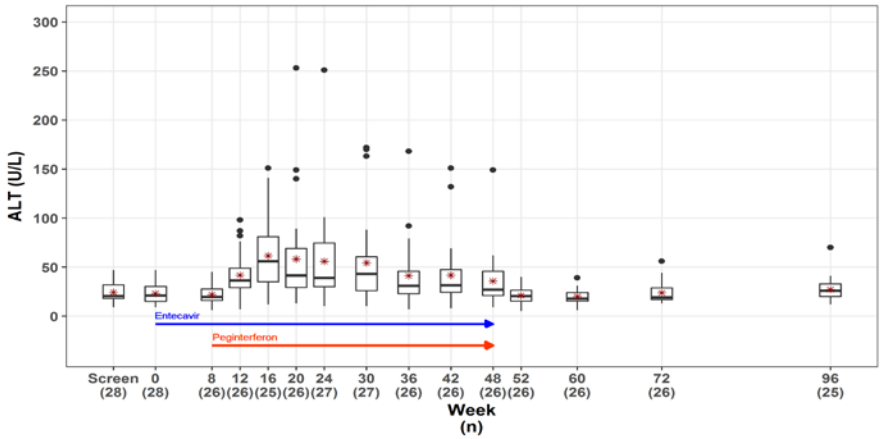
**Primary Endpoint:**
1. HBeAg loss AND
2. HBV DNA ≤ 1,000 IU/mL



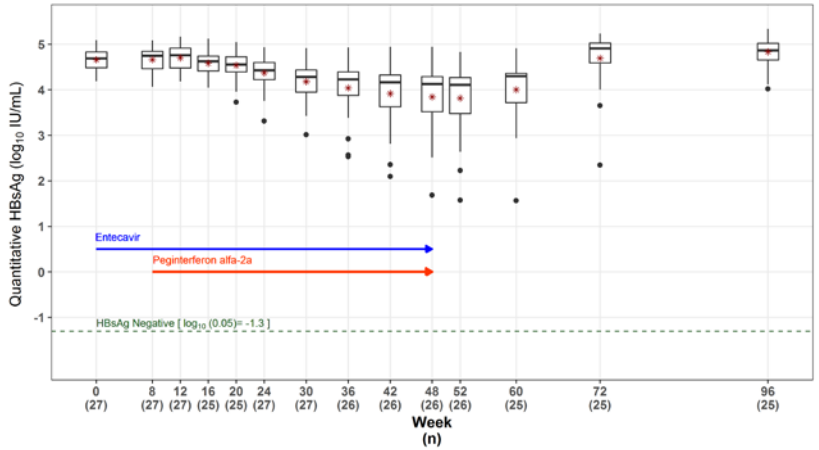

## HBV DNA




## ALT




## HBsAg




- No patients (0 of 28) met primary endpoint (only 1 HBeAg loss but with DNA and ALT increased)
- Some activity with ALT elevations and modest HBsAg decline
- Return to baseline with stopping therapy – back to 'IT'

# So should we treat IT patients?

- Important to carefully define the population
- True ‘IT’ or ‘HBeAg+ Chronic Infection’ → HBV DNA >7 log, ALT truly normal
  - For these patients, appears risk is VERY low – **observation fine**
- As begin transition to IA
  - Decreasing HBV DNA, increasing ALT & increasing age → **risk increases**
  - May consider treatment but with what?
    - For adults – stuck with long-term NA therapy – very imperfect
    - For peds – Dr. Ling will tell you!
    - Hopefully new therapies will be the answer

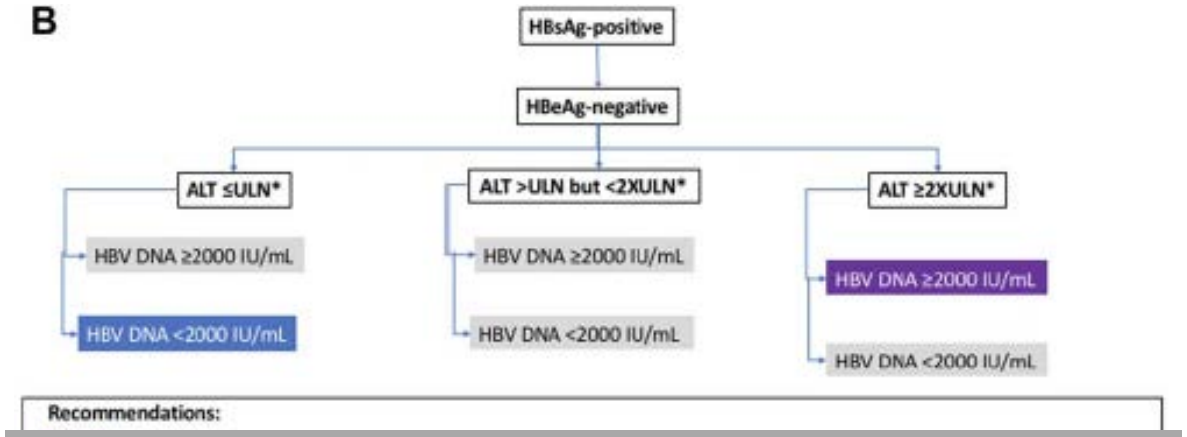
# Outline

- Current treatment guidelines – EASL, AASLD, APASL & WHO
- Areas of controversy
  - Immunotolerant / HBeAg+ Chronic Infection
    - Adult
  - **Milder immune active (EASL vs AASLD)**
  - Immune control (inactive)

# What do we do in the Grey Zone

4 groups:

1. Inactive – ALT<40, HBV DNA<2,000 IU/mL
2. Grey zone 1 – ALT 40-80, HBV DNA<2,000 IU/mL
3. Grey zone 2 – ALT<40, HBV DNA 2,000-20,000 IU/mL
4. Grey zone 3 – ALT 40—80, HBV DNA 2,000-20,000 IU/mL




**IF ALT elevated, exclude other causes & assess disease severity with non-invasive tests +/- liver biopsy. If ≥F2 or ≥A3, treat. If persistent ALT>ULN with HBV DNA>2,000 IU/mL, treat, especially if age>40**

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).

# CASL/EASL vs AASLD

**Eligible HBeAg-negative non-cirrhotic CHB (n=2,322)**
**ALT ULN = 19 F and 30 M**

**Pre-active phase (n = 1370)**
HBV DNA ≥ 2000 IU/mL
and ALT < 2 × ULN

**HBeAg (-) hepatitis (n = 952)**
HBV DNA ≥ 2000 IU/mL
and ALT ≥ 2 × ULN

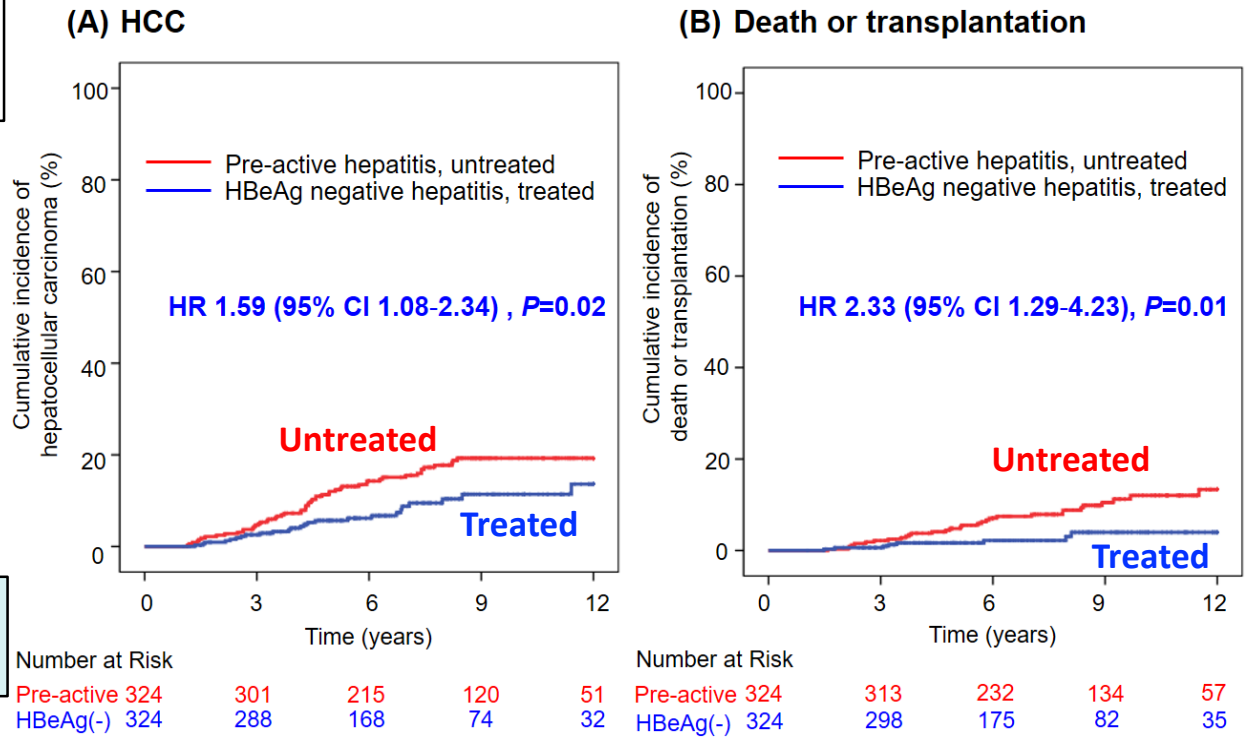
Exclusions (n=158)
Transition to HBeAg-negative hepatitis within 6 months

Exclusions (n=427)
Refused or did not receive antiviral treatment

**Pre-active hepatitis, untreated (n=1,212)**

**HBeAg (-) hepatitis, treated (n=525)**

**Cumulative Incidence of HCC and Death/Transplantation in Matched cohorts (13,164 PY, median 4.7 yr F/U)**




Elevated HBV DNA with minimal ALT elevation associated with worse outcomes…***should AASLD lower the threshold for treatment?***

Choi et al. AASLD 2018, Abstract 2146

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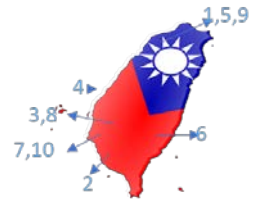
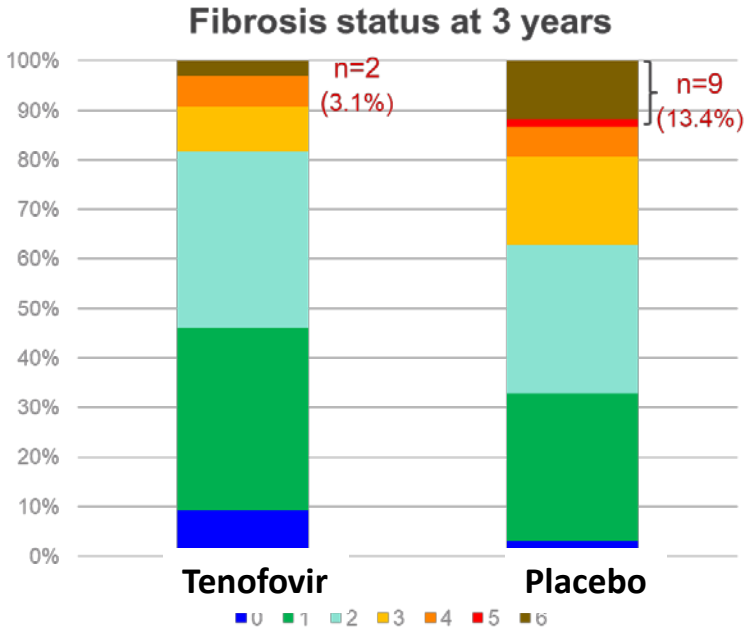
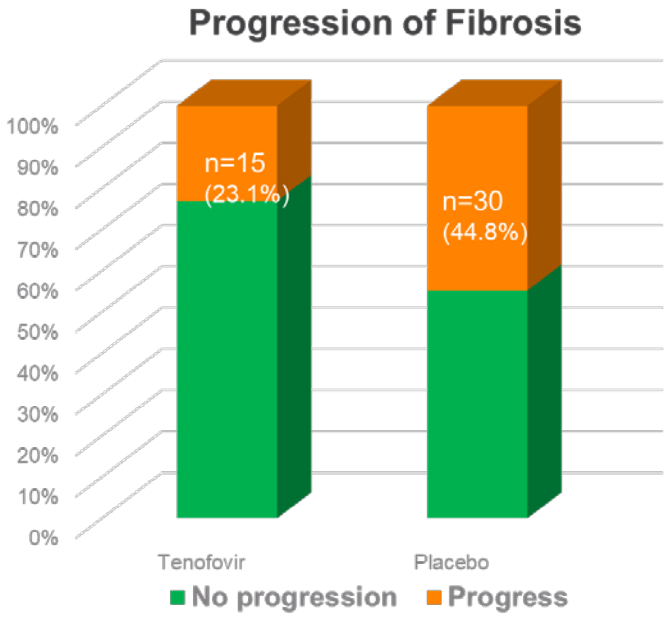
# RCT of TDF for minimal ALT elevation




Double blind RCT of CHB with **HBV DNA>2,000 IU/mL and ALT 40-80** (1-2x ULN) with paired liver bx @ 0 & 3 y




For cirrhosis (Ishak 5 or 6), RR: 0.23 (95% CI, 0.06~0.88; *P*=0.05)




For any increase in Ishak fibrosis; RR: 0.52 (95% CI, 0.31~0.85; *P*=0.01)

**Findings**

- TDF treatment associated with:
  - Less fibrosis progression (RR 0.52
  - Less development of cirrhosis (RR 0.23)
  - Reduced inflammatory score, ALT and HBV DNA

**Caveats**

- More advanced fibrosis (Ishak 3/4) in placebo arm 27% vs 12%
- Entecavir used for 'flares' (ALT>2xULN)…10 placebo patients

Intriguing…need a closer look but may support use of NA therapy with ALT<2x ULN

Hsu YC et al., AASLD 2018, Abstract 0264

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# Bottom line on minimal ALT elevation

- Current AASLD guidelines are probably reasonable
  - Lots of caveats to low level ALT elevation
    - Biopsy showing activity or fibrosis
    - If persistent ALT>ULN, especially if over age 40
    - APASL - family history of cirrhosis/HCC
- Unlikely to have ‘strong evidence’ to guide this – low absolute risk so need huge trials and/or long f/u
- But leave some ambiguity
  - Poor adherence with doing ‘recommended biopsies’
- May be simpler to extend to any ALT elevation with HBV DNA>2,000…
  - ie like CASL/EASL

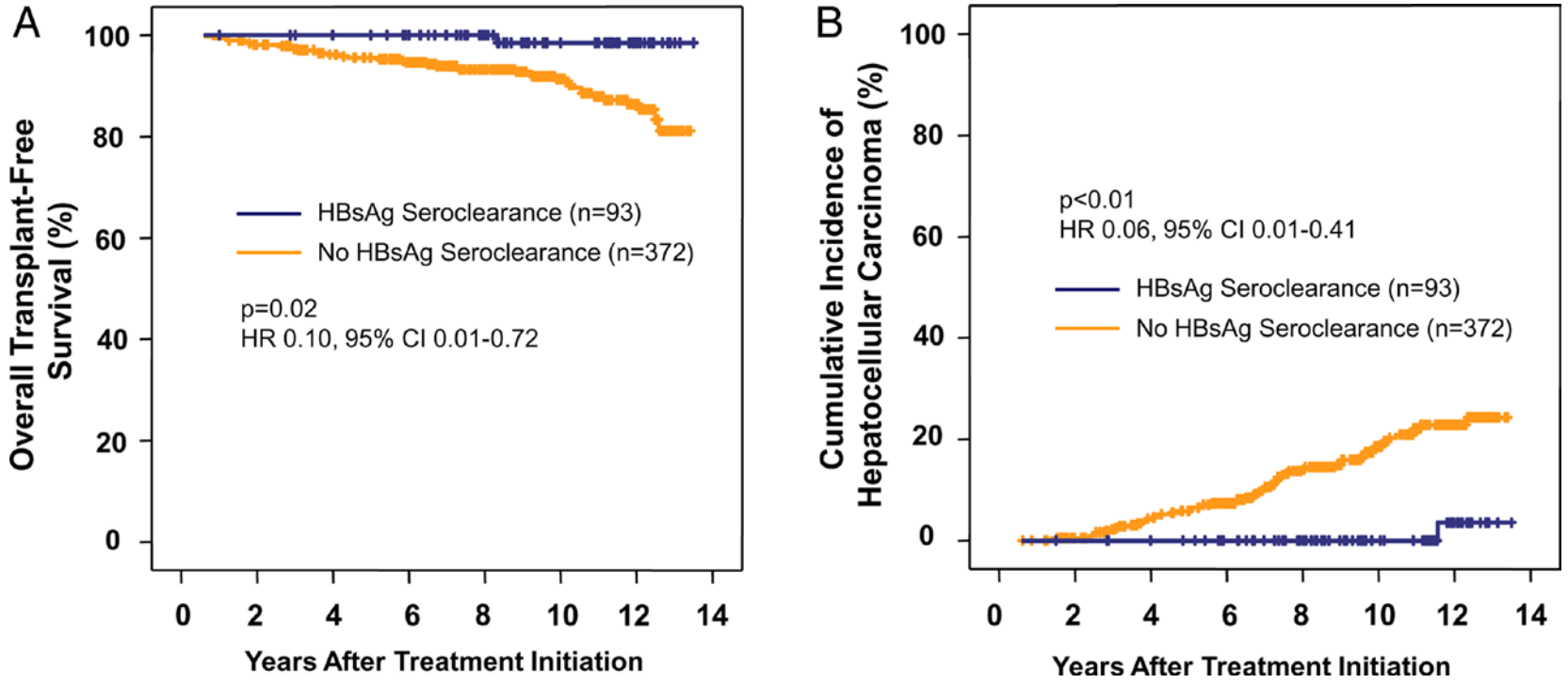
# Summary ‘When to Start’

- **Immune active**
  - HBeAg +/- with HBV DNA>2,000 IU/mL and elevated ALT
- **Immune tolerant**
  - Consider in older patients (>40), if fibrosis on fibroscan or ?FHx HCC
- **Starting immunosuppressive therapy – almost anything**
  - If HBsAg +ve → treat
  - If anti-HBc +ve – more selective, only potent immunosuppression (ritux/BMT)

# When can we stop?

# HBsAg loss is a good thing

- **110/5409 patients had NA-induced HBsAg loss (0.33 annual clearance rate) and discontinued NA (LAM,ETV)**
- **Of these 110 patients, 1 developed HCC and 1 died**




Kim et al, Gut 2013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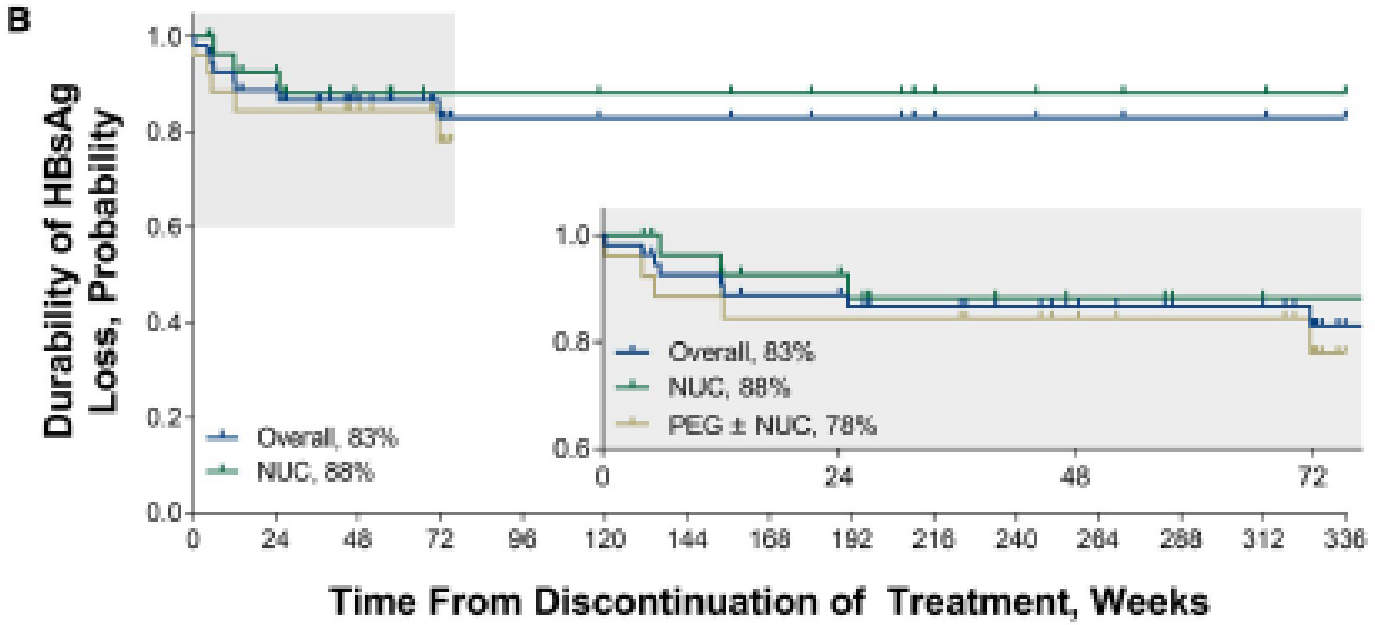
# HBsAg loss is durable

1,381 patients NA or IFN → 55 with confirmed sAg loss




NA 88%
Overall 83%
IFN 78%

| n at Risk (Events) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | 55 (0) | 44 (6) | 31 (7) | 22 (8) | 11 (8) | 10 (8) | 10 (8) | 9 (8) | 8 (8) | 6 (8) | 5 (8) | 4 (8) | 3 (8) | 3 (8) | 0 (8) |
| NUC | 29 (0) | 23 (2) | 14 (3) | 11 (3) | 11 (3) | 10 (3) | 10 (3) | 9 (3) | 8 (3) | 6 (3) | 5 (3) | 4 (3) | 3 (3) | 3 (3) | 0 (3) |
| PEG ± NUC | 26 (0) | 21 (4) | 17 (4) | 11 (5) | 0 (5) | | | | | | | | | | |

No clear predictors of durability – anti-HBs common but not important



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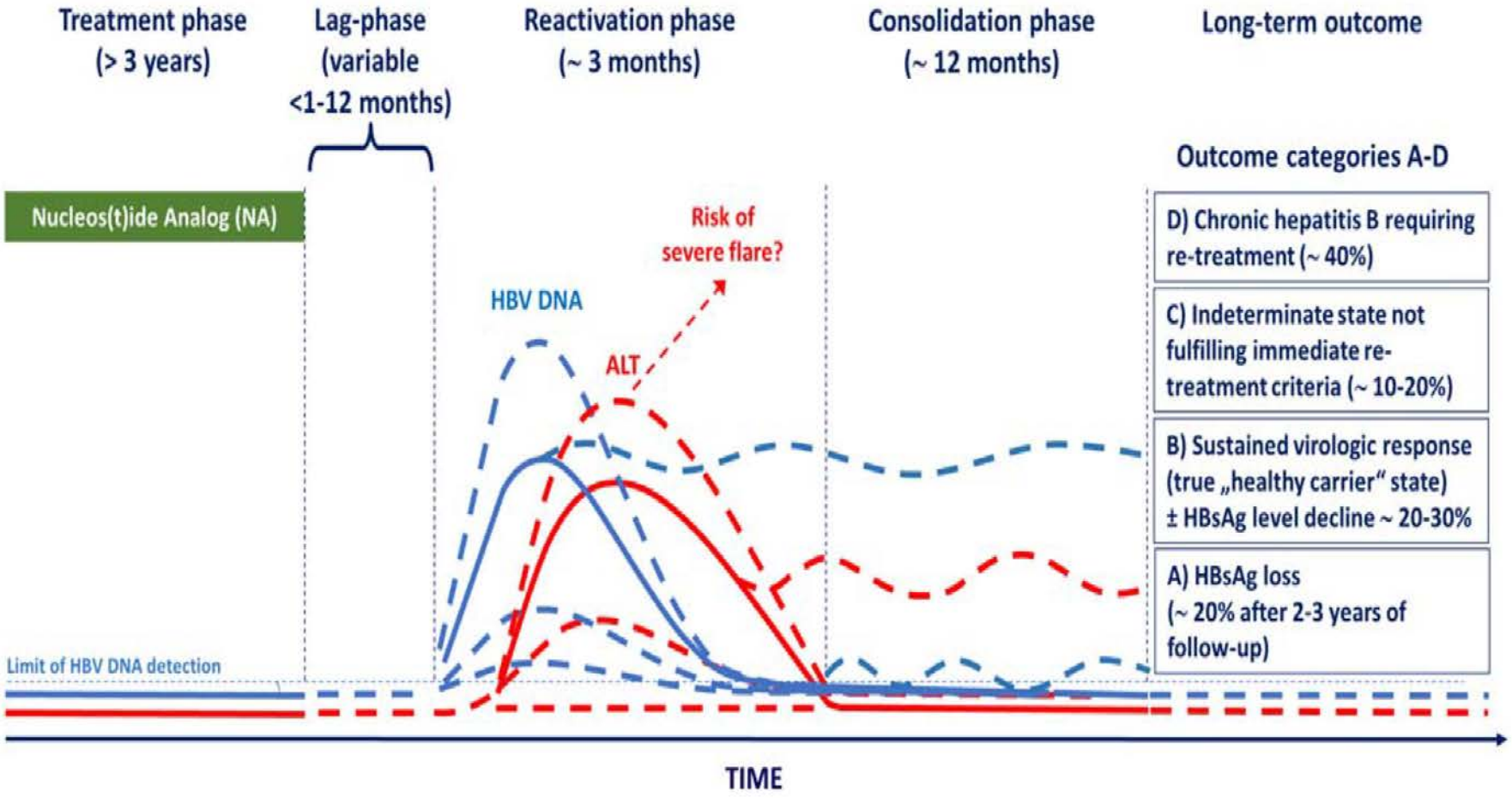
# What about before HBsAg loss?

- HBsAg loss is rare on therapy (~1%/year)
- Perhaps stopping leads to flare and immune control…
- Perhaps stopping leads to flare and bad outcome…

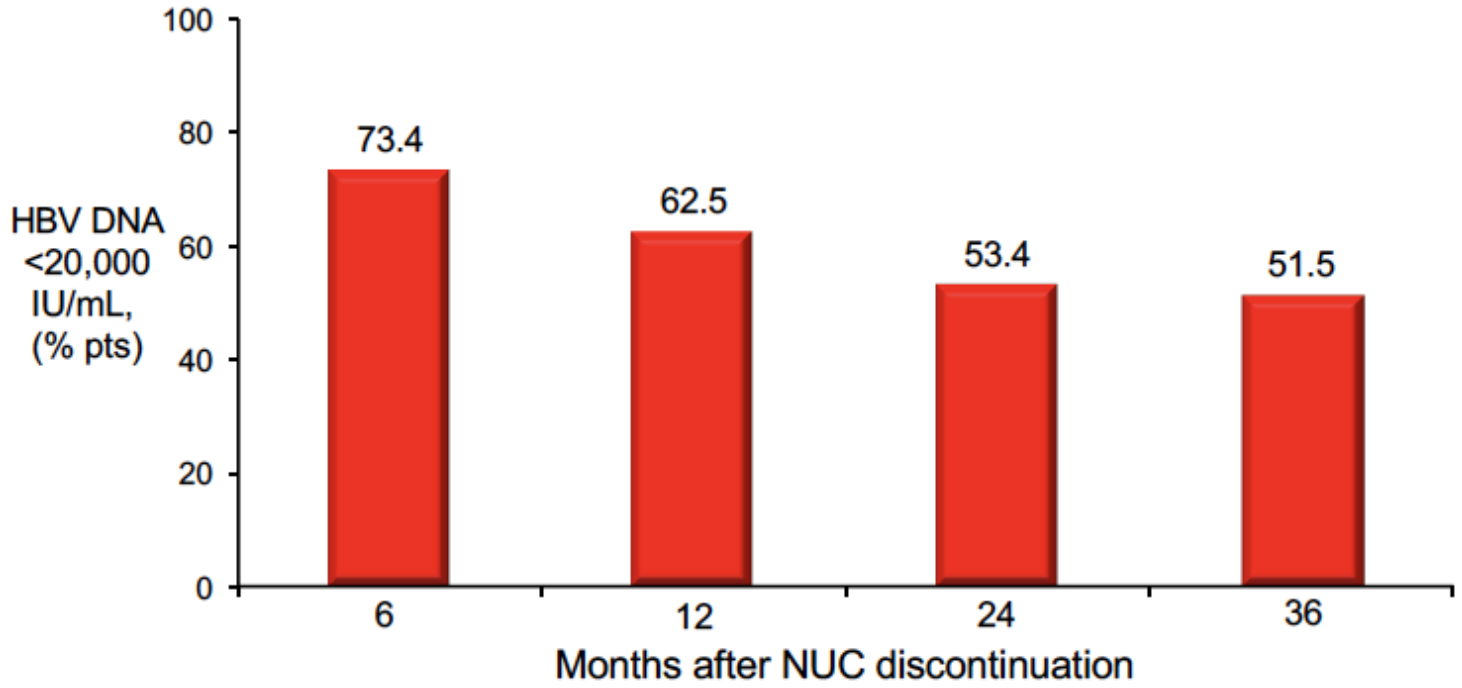
# What about stopping NA Therapy in eAg-negative CHB before sAg loss? The good, the bad and the indeterminate outcome




Lampertico & Berg Hepatology 2018, Berg T et al. J Hep 2017, Liem S et al. AASLD 2018

# Virological remission after NA cessation

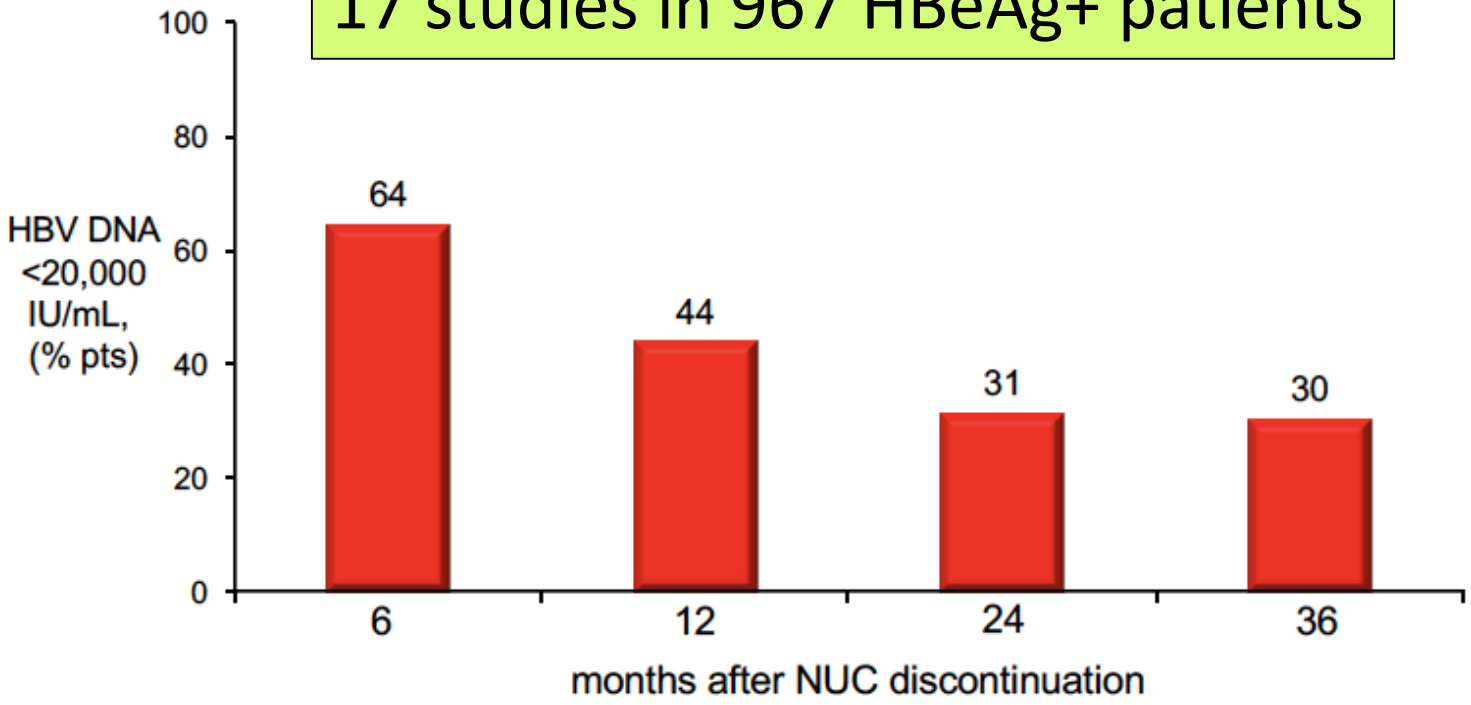
14 studies in 733 HBeAg+ patients




Pooled HBsAg loss ~1%, Durable biochemical remission ~76%

# And in HBeAg-negatives?

17 studies in 967 HBeAg+ patients




Pooled HBsAg loss ~1.7%, Durable biochemical remission ~57%

# Can we predict who will do well?

25 studies with 1716 patients were included

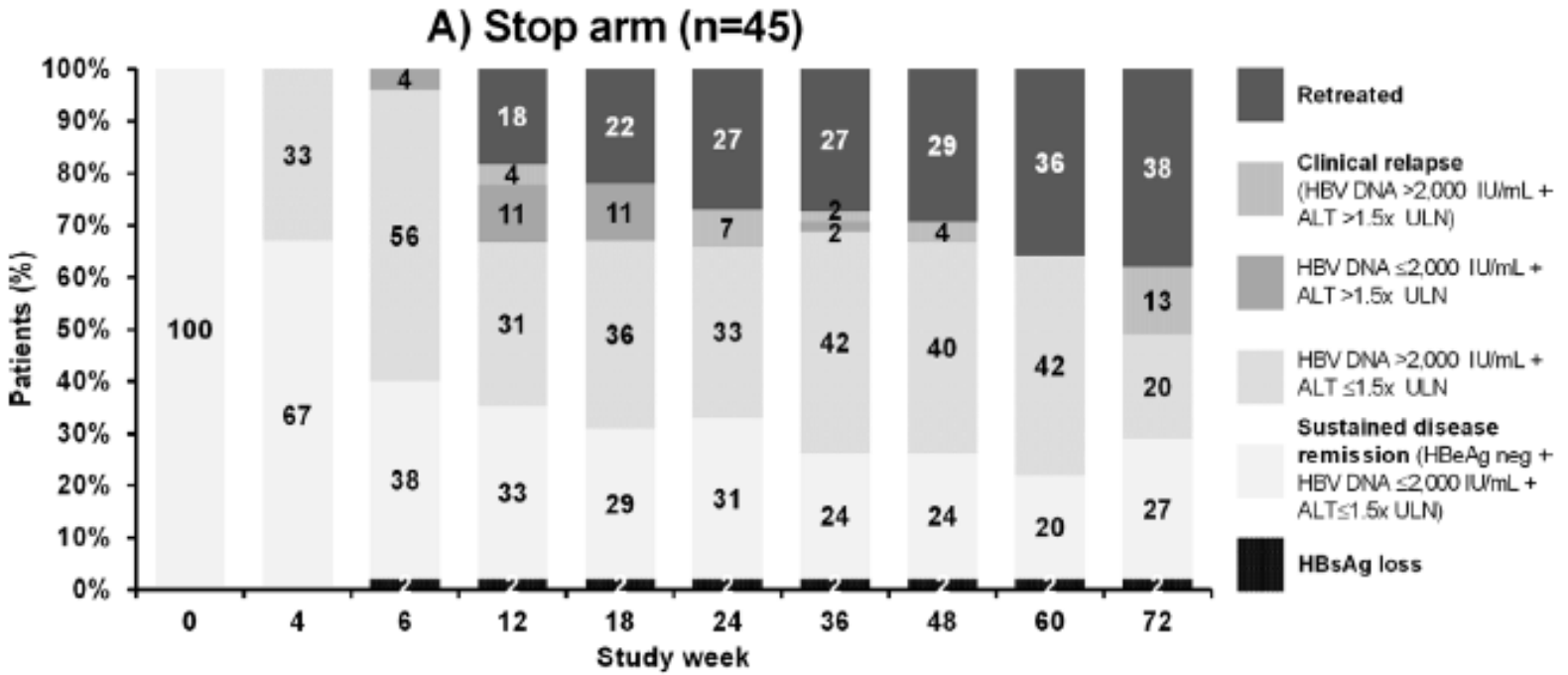
| Variables | HBeAg pos | HBeAg neg |
|---|---|---|
| Age | not consistent data | |
| Viral genotype (B/C) | not consistent data | |
| ETV/TDF vs LAM | not consistent data | |
| Lower qHBsAg at EOT | not consistent data | |
| Timing of HBeAg seroconversion | not consistent data | - |
| Duration of consolidation therapy | not consistent data | - |
| Duration of VR on therapy | no | **yes*** |

*VR rates at 12 months after NA discontinuation were **36%** in studies with duration of on-therapy VR ≤24 months and **75%** in studies with duration of on-therapy VR>24 months (**OR: 5.45, 95% CI 1.68-17.70; P=0.005**).

# Prospective stop study

67 non-cirrhotic HBeAg-ve patients with DNA suppressed >3 yrs randomized (2:1) to stop or continue

Retreatment criteria
- HBeAg +
- DNA>2000 + ALT>600 x 1
- DNA>2000 + ALT>200 x 2
- DNA>20,000 x 2




- Relatively high rate of retreatment or clinical relapse – only 27% sustained off-trt response
- Retreatment more common if started HBeAg +ve before NA therapy
- No HBsAg loss, no significant decline in quant HBsAg

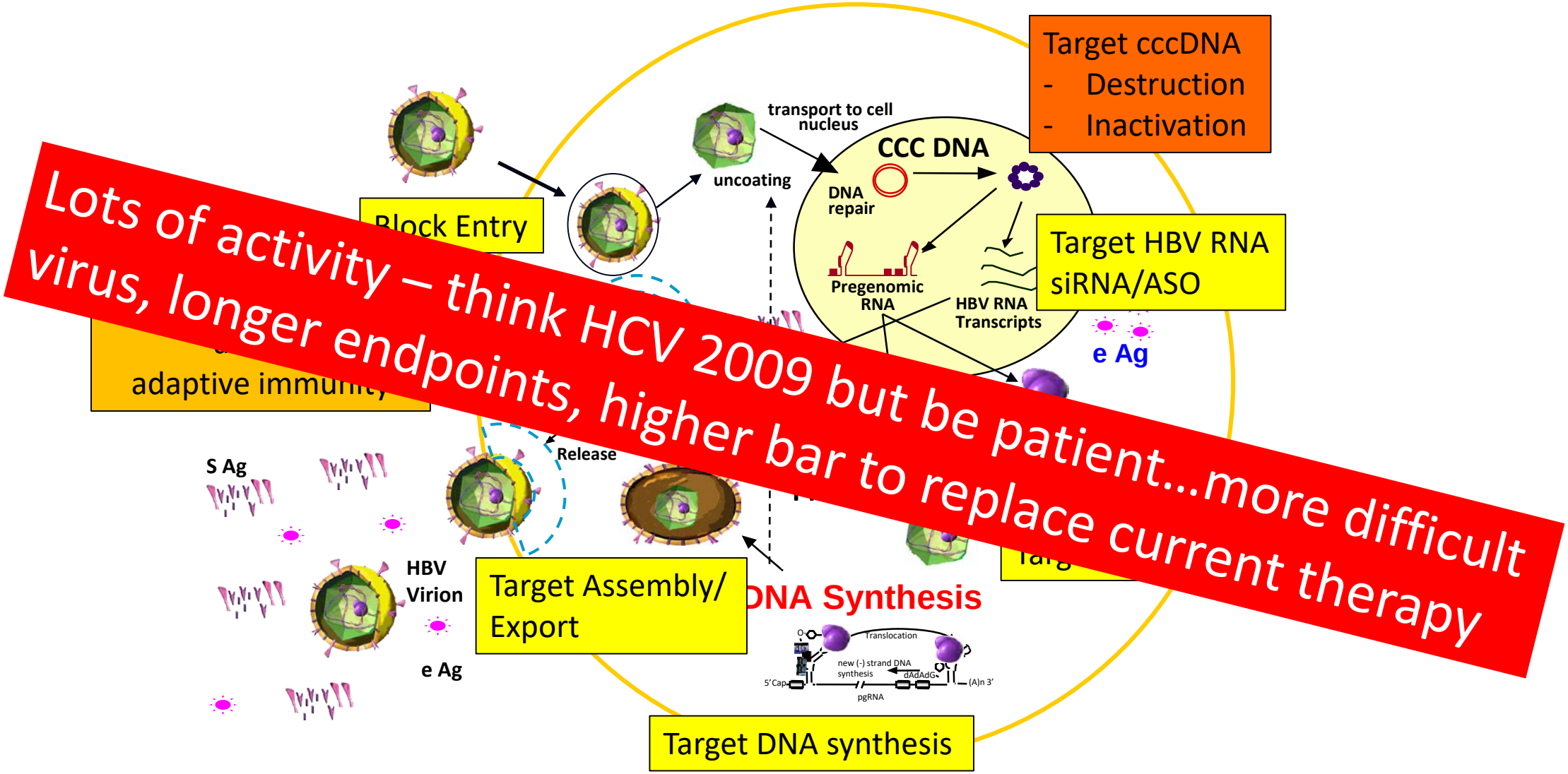
# Bottom line on stopping

- Be Careful!!
- **Do not stop if:**
  - Cirrhotic
  - Ever cirrhotic (can be deceiving after long-term NA)
  - Still HBeAg-positive (should be negative at least 1 and probably > 3 yr)
  - Any concerns about follow-up – monthly!

- **May consider:**
  - Minimal fibrosis
  - Adherent with follow-up
  - If you stop → monthly ALT and HBV DNA → **DNA will rise, do not retreat unless there is an ALT flare** – exact threshold unclear…but probably be conservative

# So if NA is not the cure…what's coming?

# Potential targets in the lifecycle




Lots of activity – think HCV 2009 but be patient…more difficult virus, longer endpoints, higher bar to replace current therapy

# Summary

- **When to start**
  - No big changes here – IA patients (elevated DNA and ALT)
  - Consider in immune tolerant patients only if older or fibrotic (or FHx)

- **When to stop**
  - Be careful
  - With prolonged HBeAg loss and DNA suppression, reasonable if minimal fibrosis and adherent with follow-up

- **Lots on the horizon** – hopefully something new in 3-5 years