Hepatitis B virus persistence

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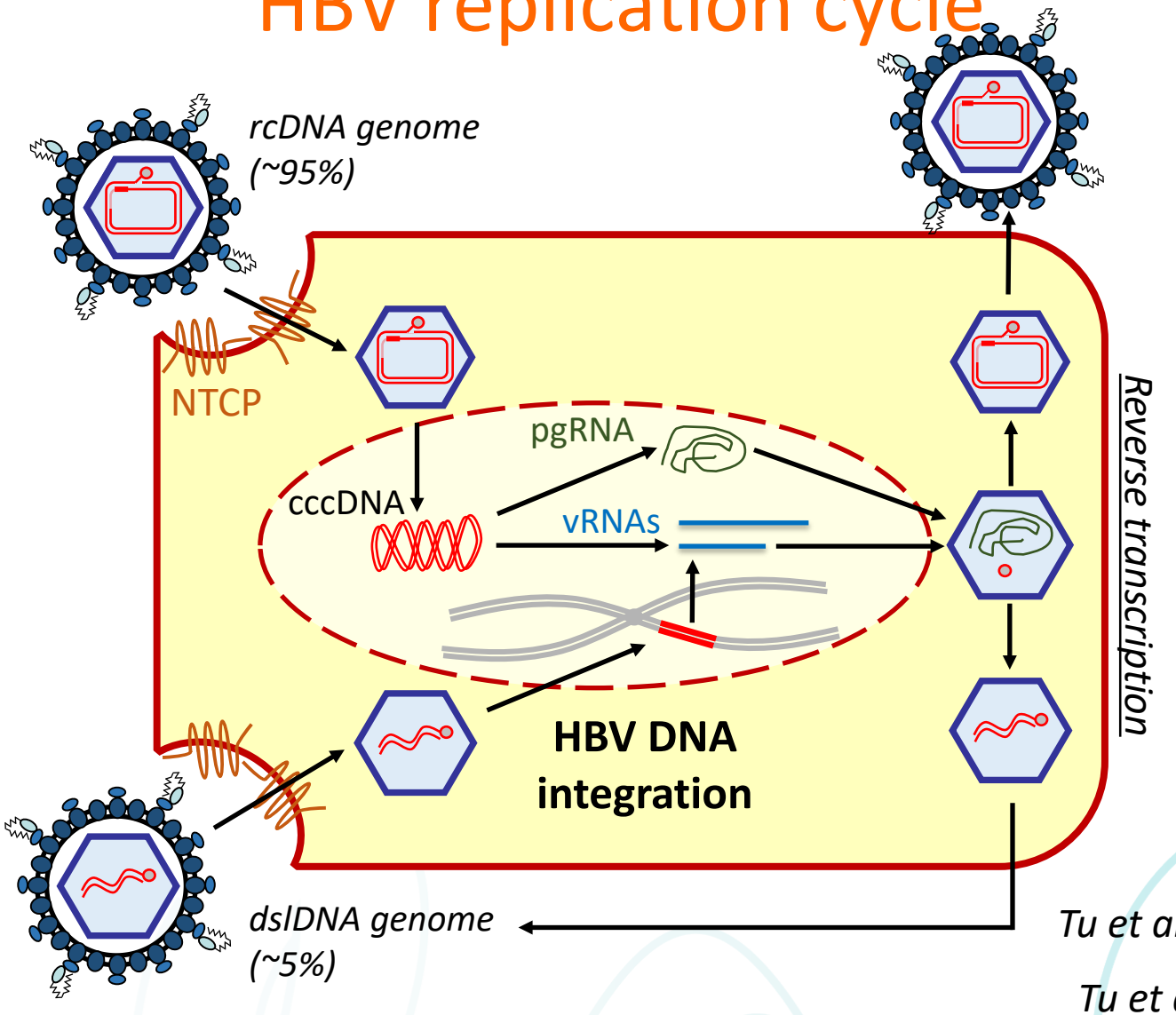
HBV replication cycle



Tu et al. 2018, Viruses

Tu et al. 2018, J Virol

Tu et al. 2021, JHEP Rep

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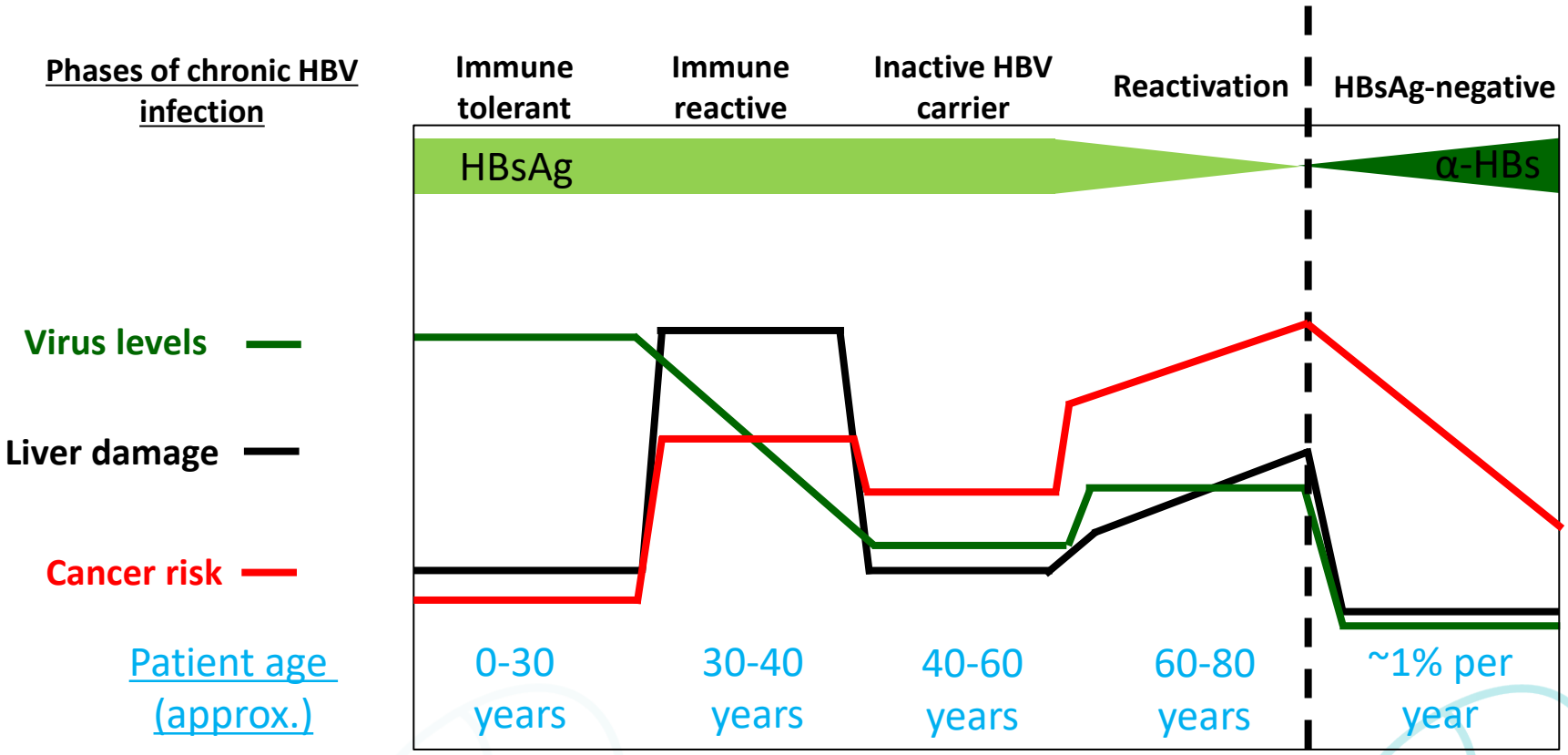
Chronic HBV infection



Tu, Bühler and Bartenschlager 2017, *Biological Chemistry*
Tu *et al.* 2015, *Liver International*

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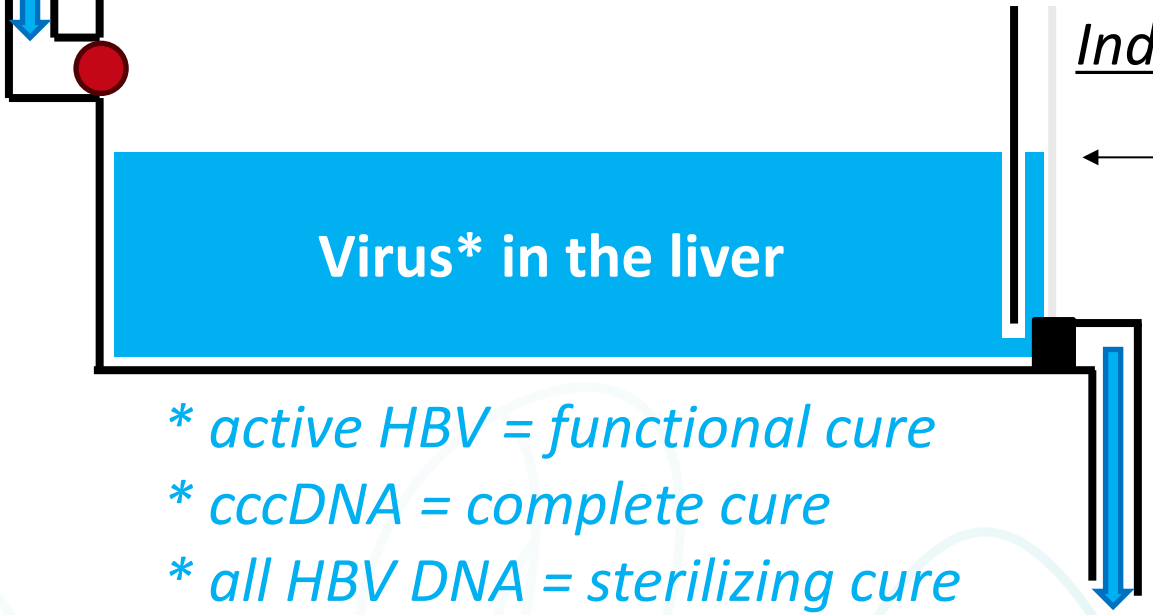
A simplified model of HBV persistence

1) Reduce infection

- Nucs or entry inhibitors to stop new infections
- CAMs to stop new cccDNA
- siRNAs/ASOs to limit virus production



Indicator window (serum)

← **qHBsAg**

HBV RNA?

HBcrAg?

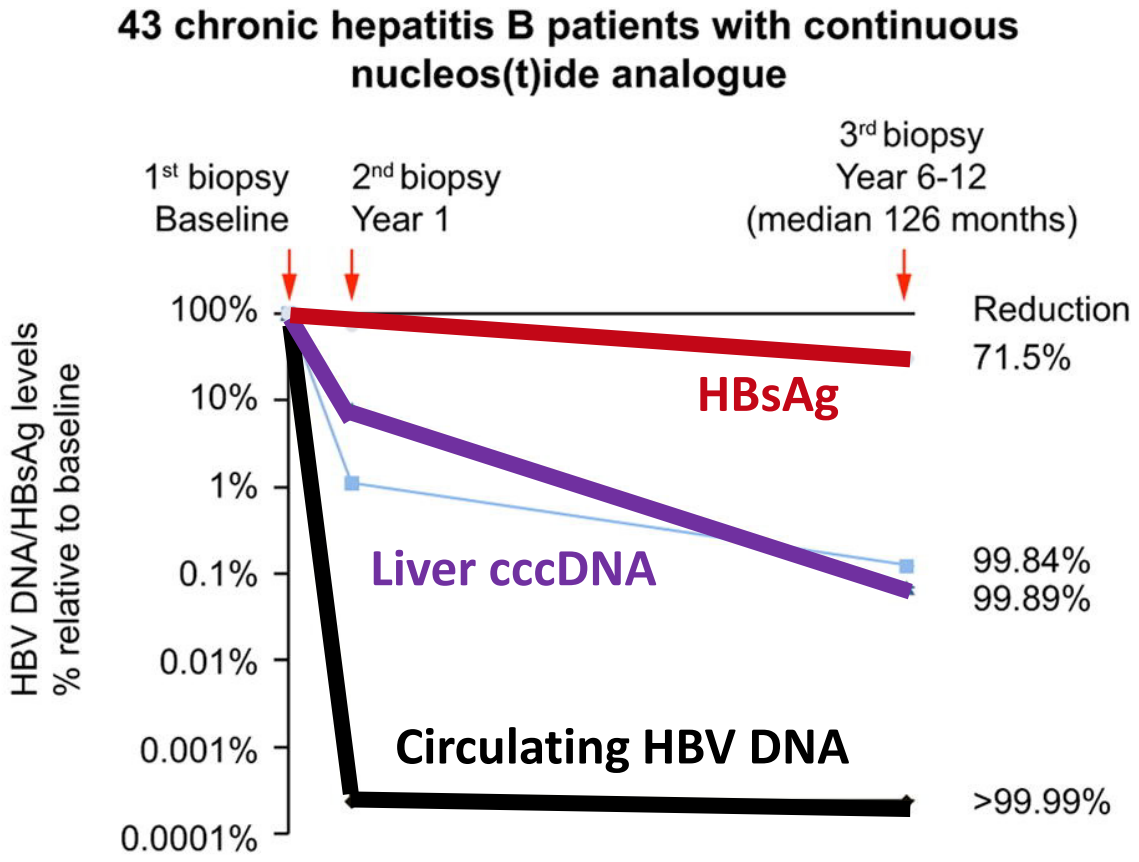
* *active HBV = functional cure*

* *cccDNA = complete cure*

* *all HBV DNA = sterilizing cure*

2) Increase removal rate

Limited HBV reduction with NUCs



NUCs drive very slow cccDNA reduction, but not much HBsAg reduction (integrated)

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Lai et al. 2016 J Hepatol

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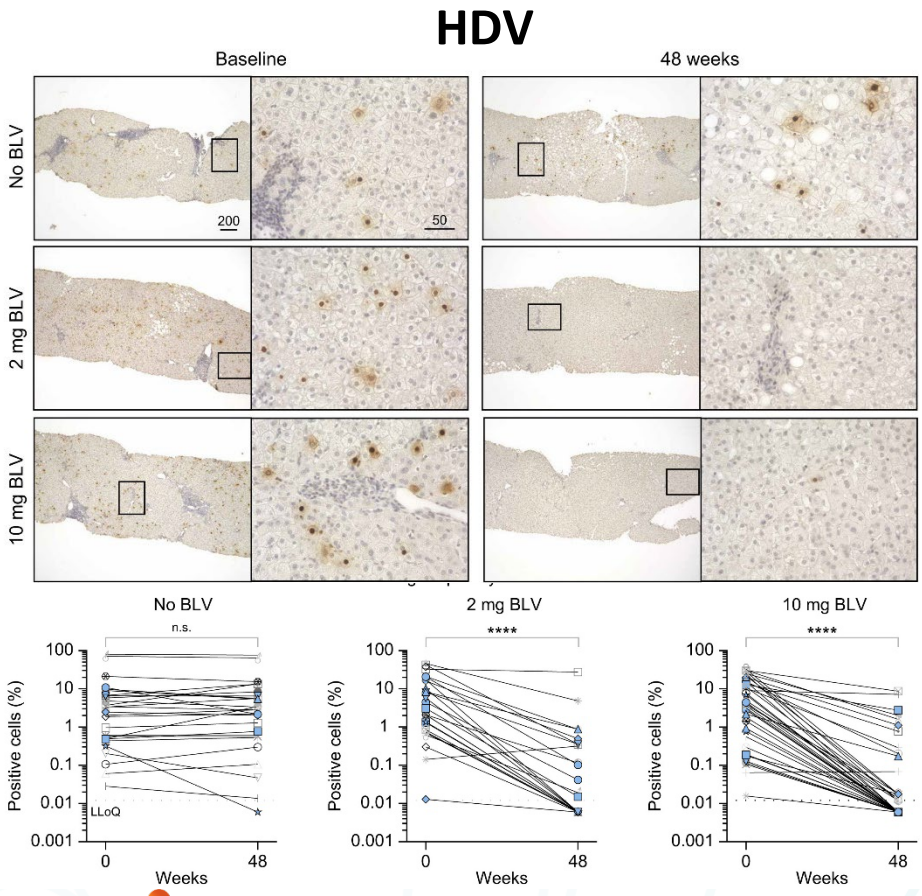
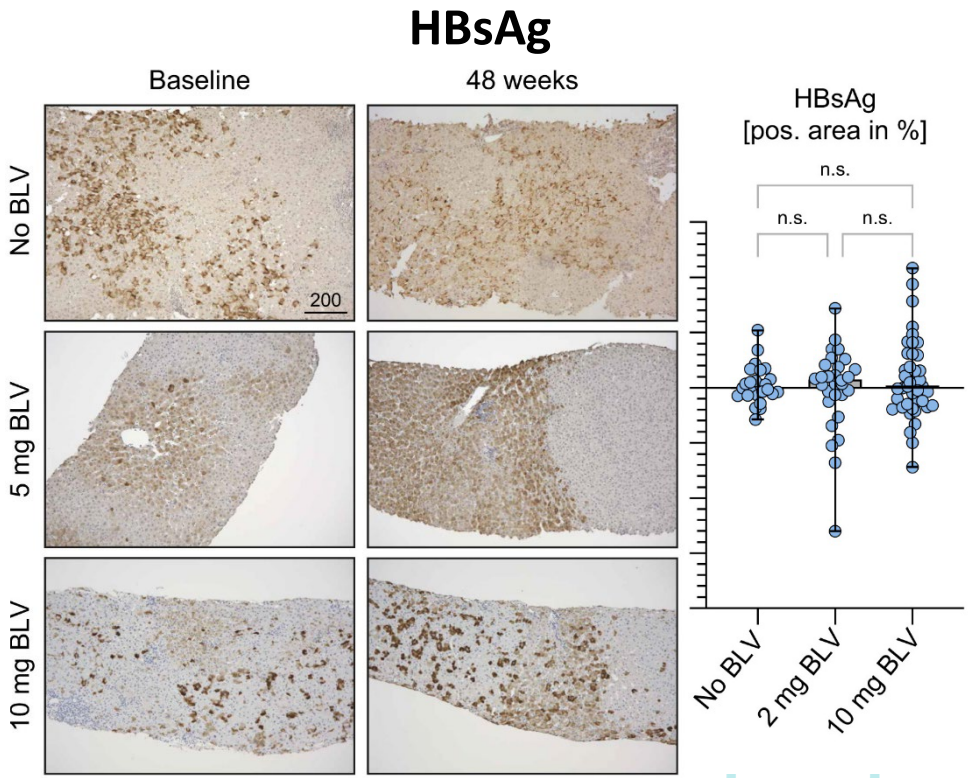
No HBV reduction with entry inhibitors

Limited reduction of HBsAg in majority HBeAg-neg with Bulevertide (HBV/HDV entry inhibitor)





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Combo analysis of 3xMyr trials

Allweiss et al. (2024) *J Hep*

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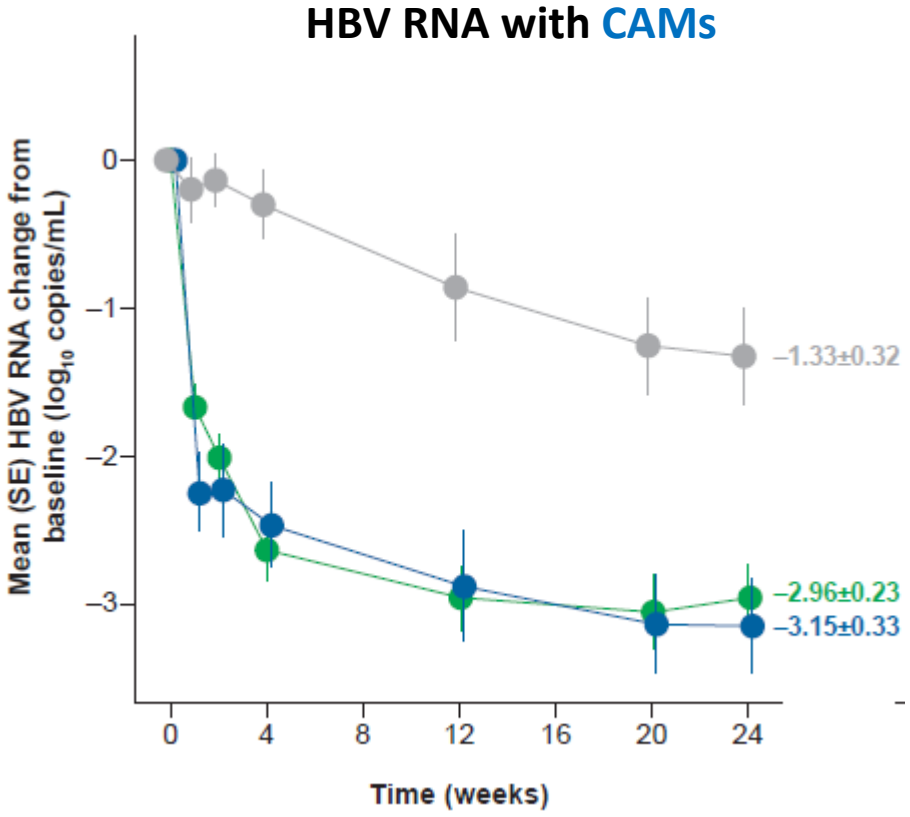
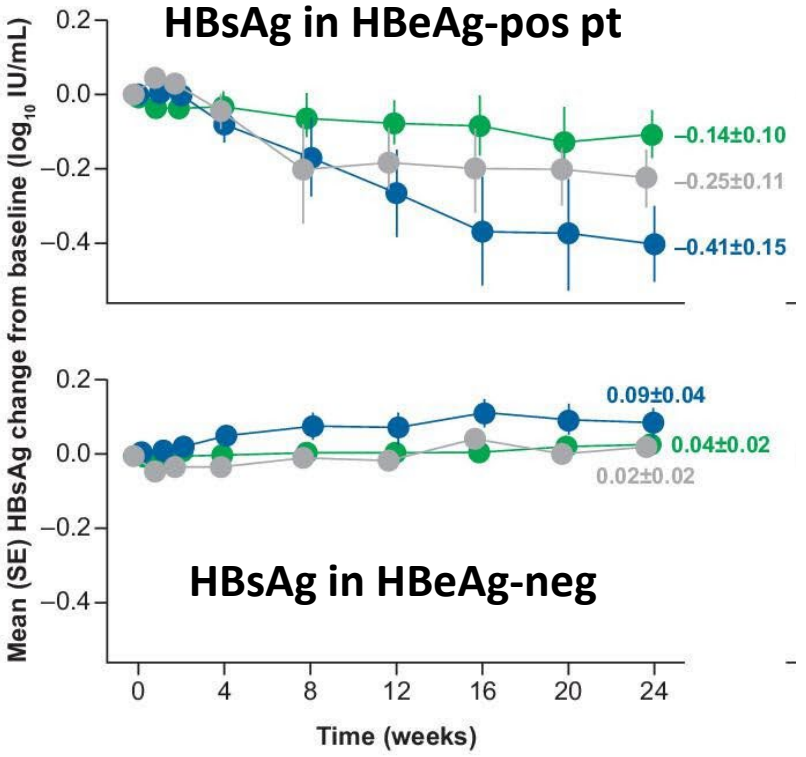
Limited HBV reduction with CAMs





JADE trial of JNJ-56136379

Janssen et al. (2023) *Gut*

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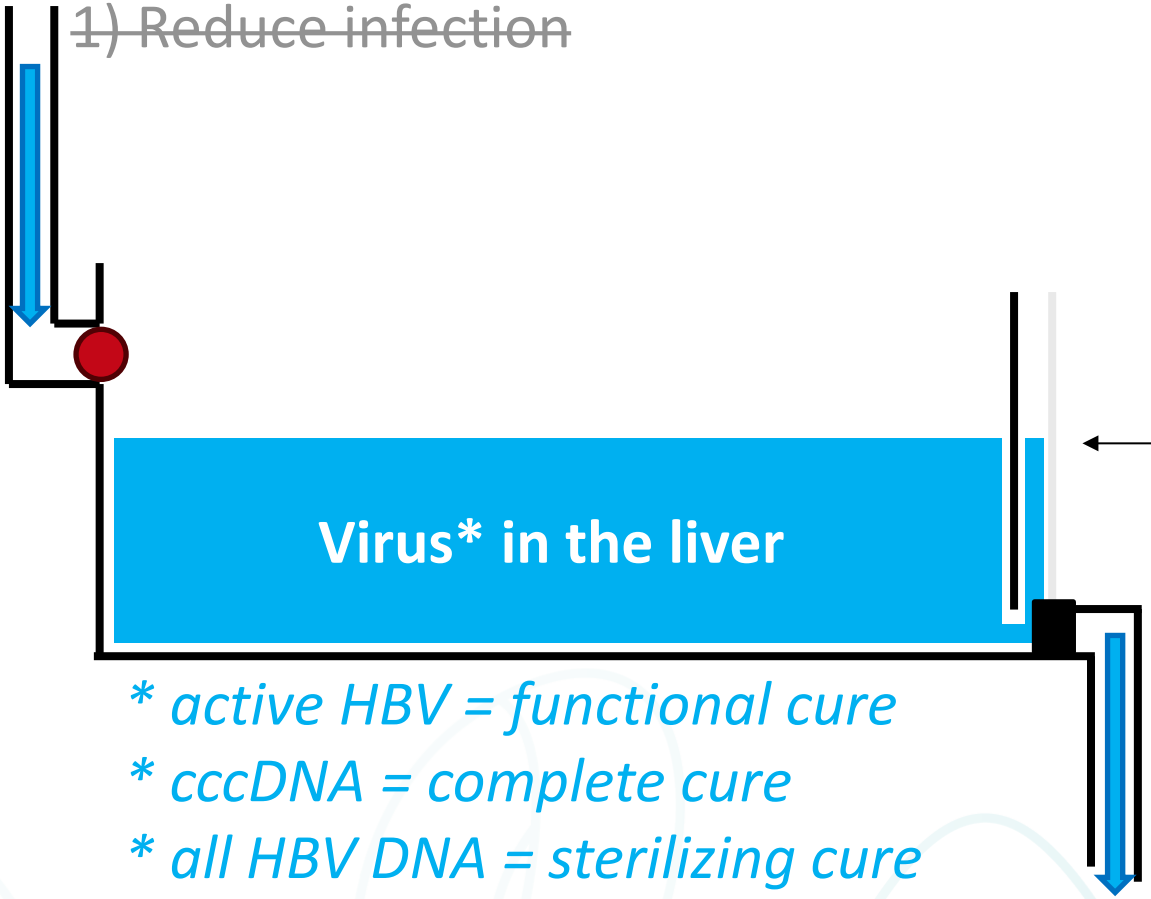
A simplified model of HBV persistence



2) Increase removal rate

- Degrade cccDNA directly
- Induce immune response
- Liver turnover => ↓cccDNA

** active HBV = functional cure*

** cccDNA = complete cure*

** all HBV DNA = sterilizing cure*

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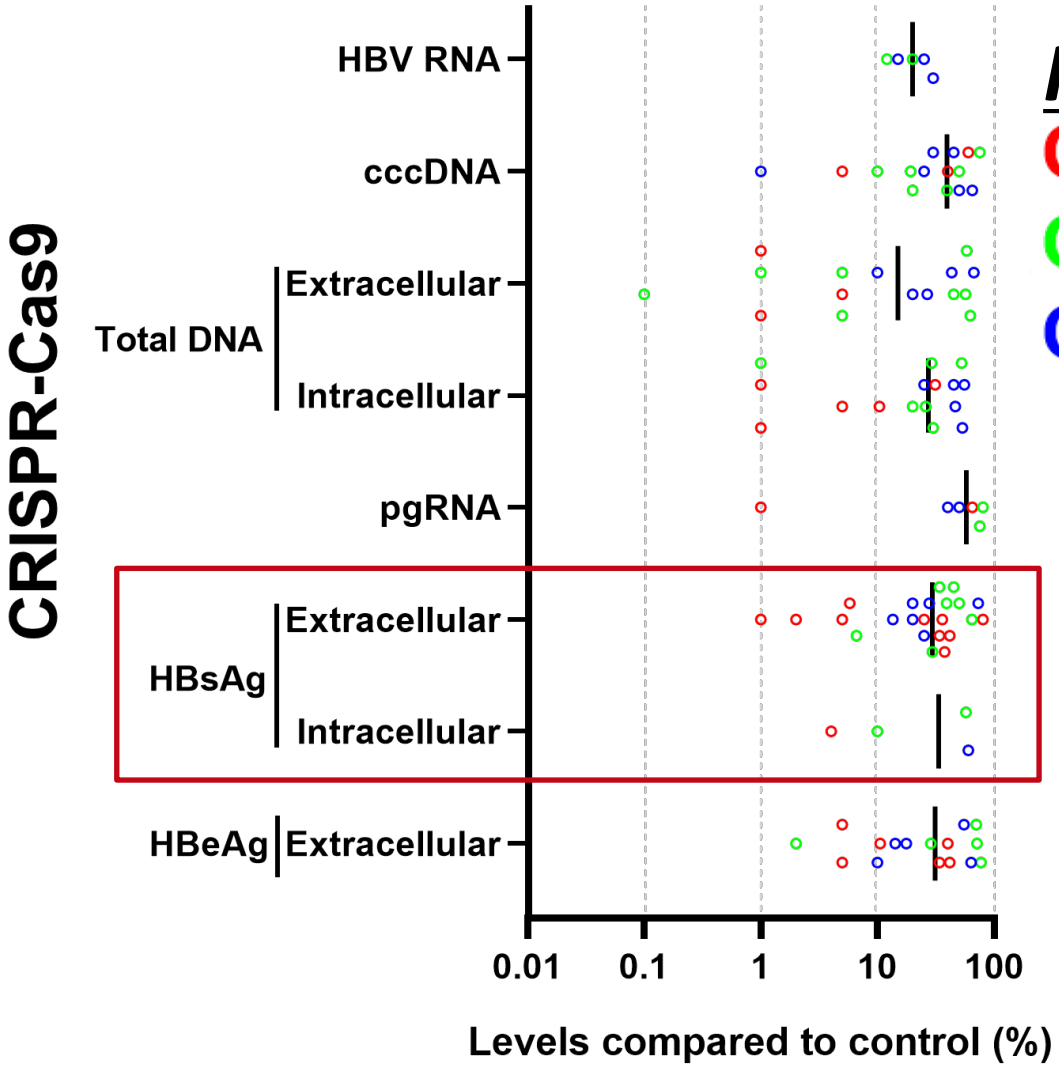
Removing virus-infected cells

- Direct targeting of HBV DNA (CRISPR, TALENS, ZFN, base editors, etc)
- Nuc stop
- Immunomodulators to induce killing of infected cells (IFN, TLR agonists, IAP inhibitors, etc.)

Cutting HBV with genetic "scissors"

Effect size reported by 36 HBV CRIPSR studies



In vitro HBV models

O - Transfection

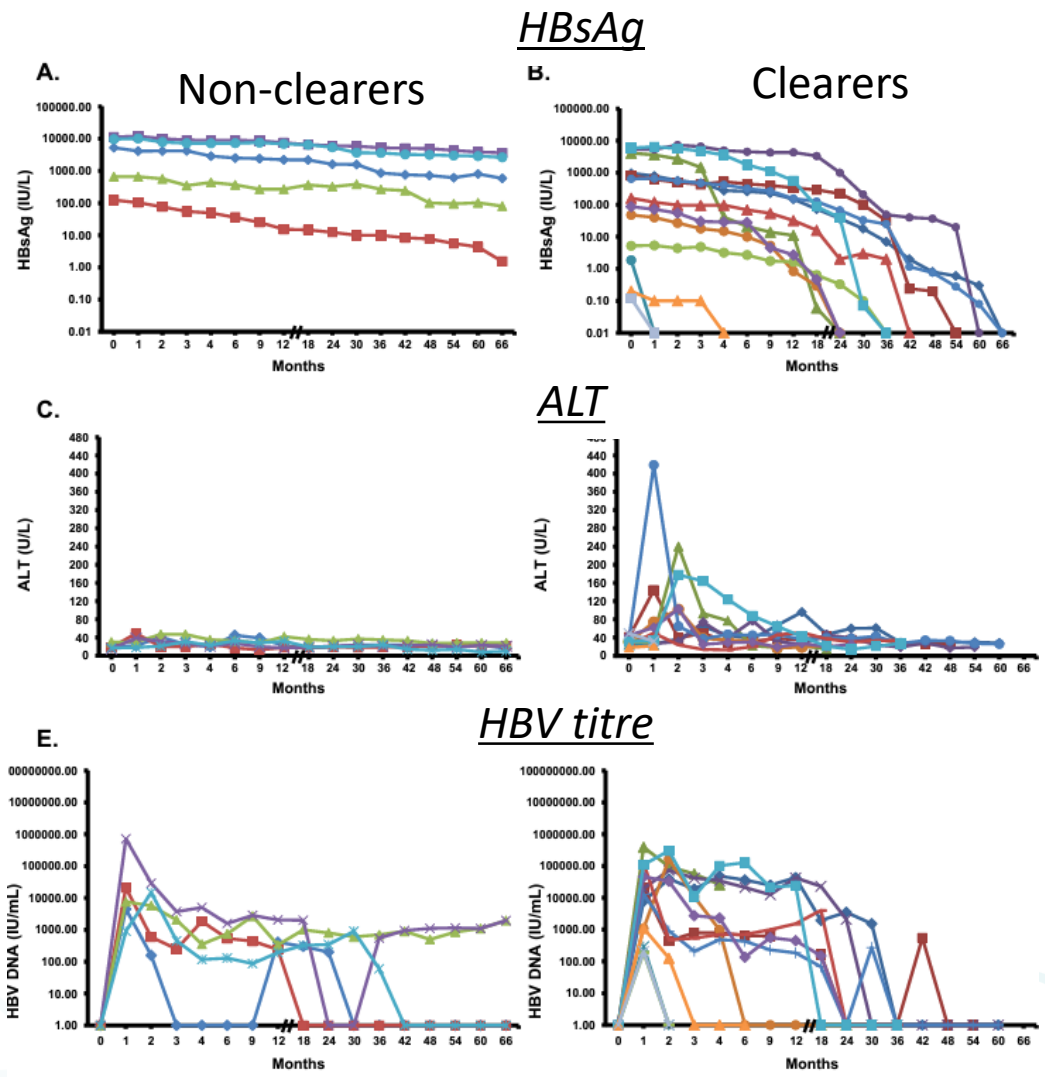
O - Integration

O - Infection (*in vitro*)

Effect size is relatively low in all models

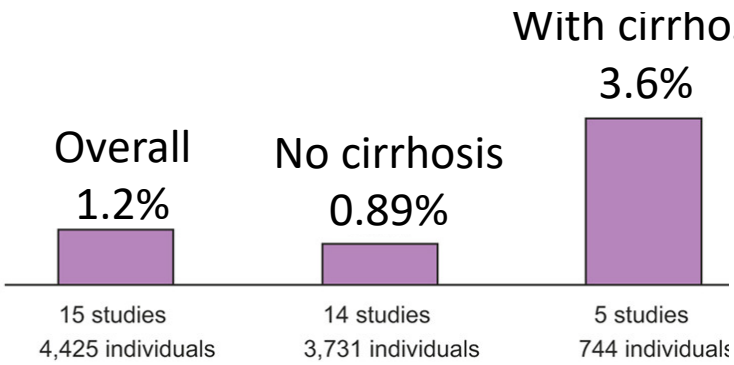
Zhang and Tu (2023)
Clinics in liver disease

Clearing HBV by stopping NUCs

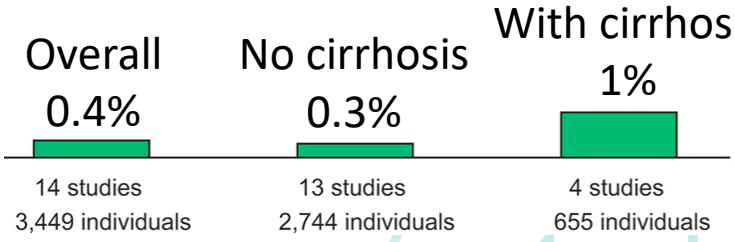


Hadziyannis *et al*. (2012), *Gastroenterology*

Severe flares and decompensation

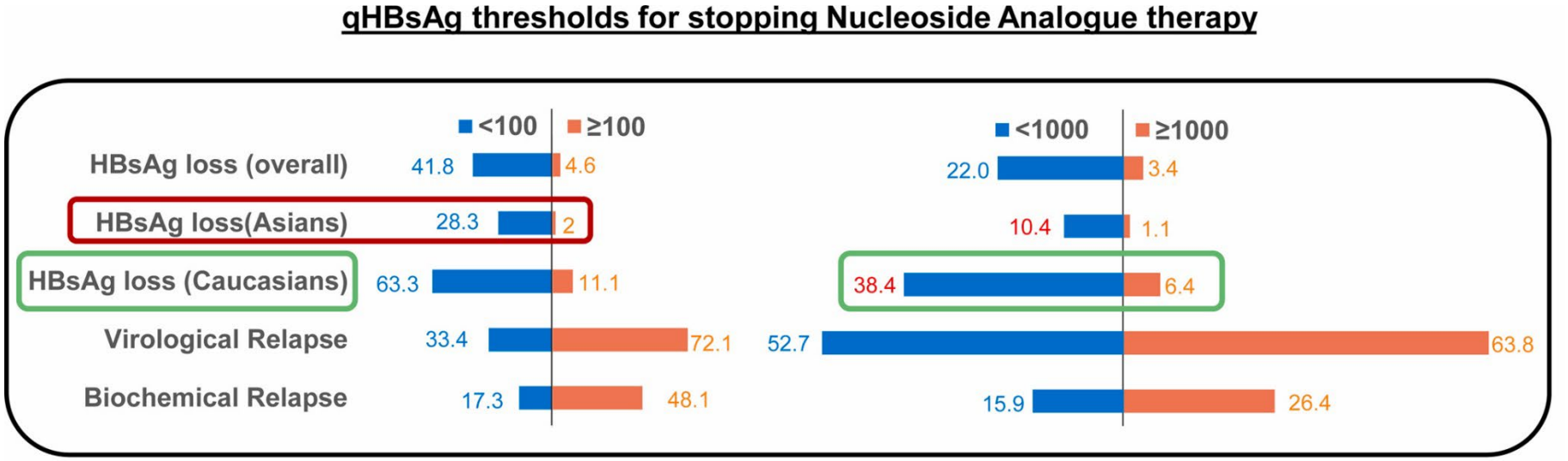


Death or liver transplant



Tseng *et al*. (2022), *JHEP Reports*

Clearing HBV by stopping NUCs



Lim *et al*. (2024), Clin Gastro Hep

Clinical Gastroenterology and Hepatology

Does HBsAg itself induce persistence?

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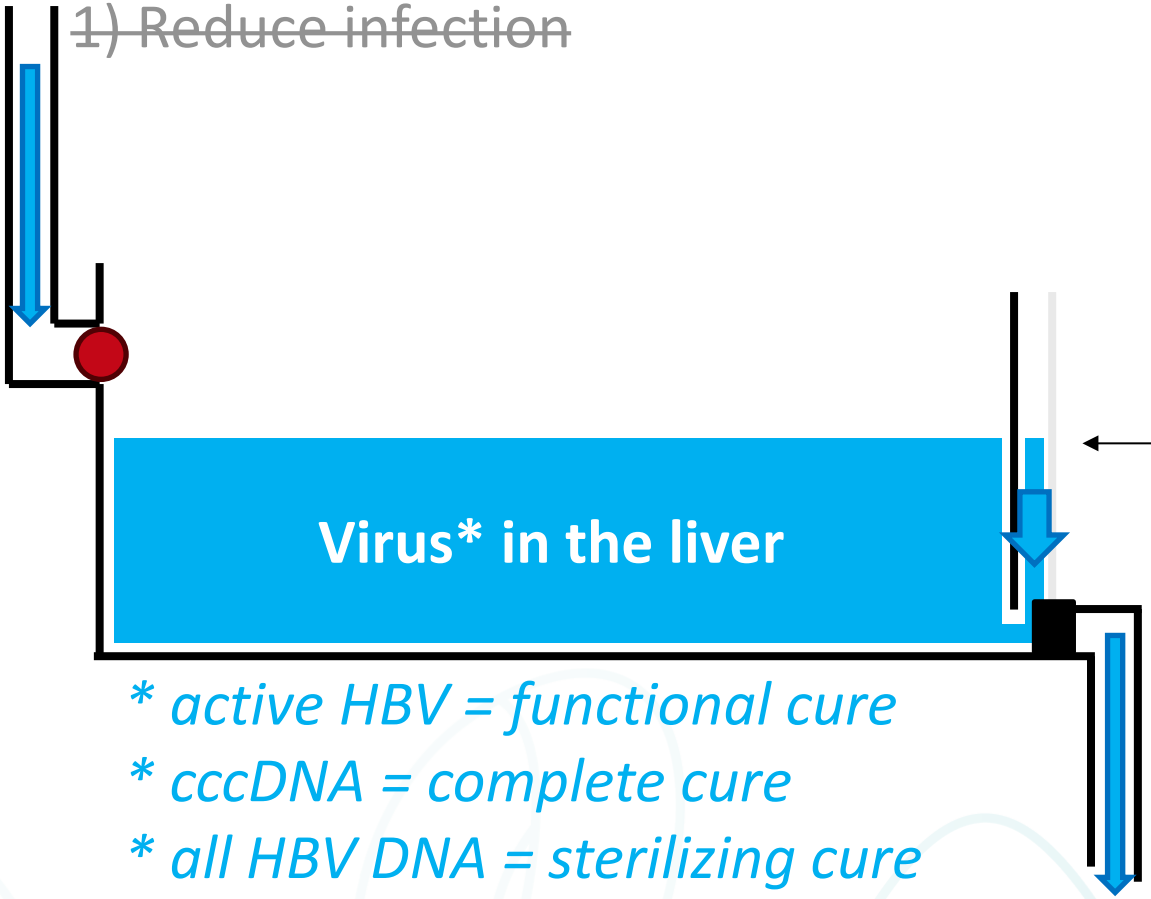
A simplified model of HBV persistence



- Sponging up anti-HBs
- Immune modulation?

← **HBsAg**

2) Increase removal rate

** active HBV = functional cure*

** cccDNA = complete cure*

** all HBV DNA = sterilizing cure*

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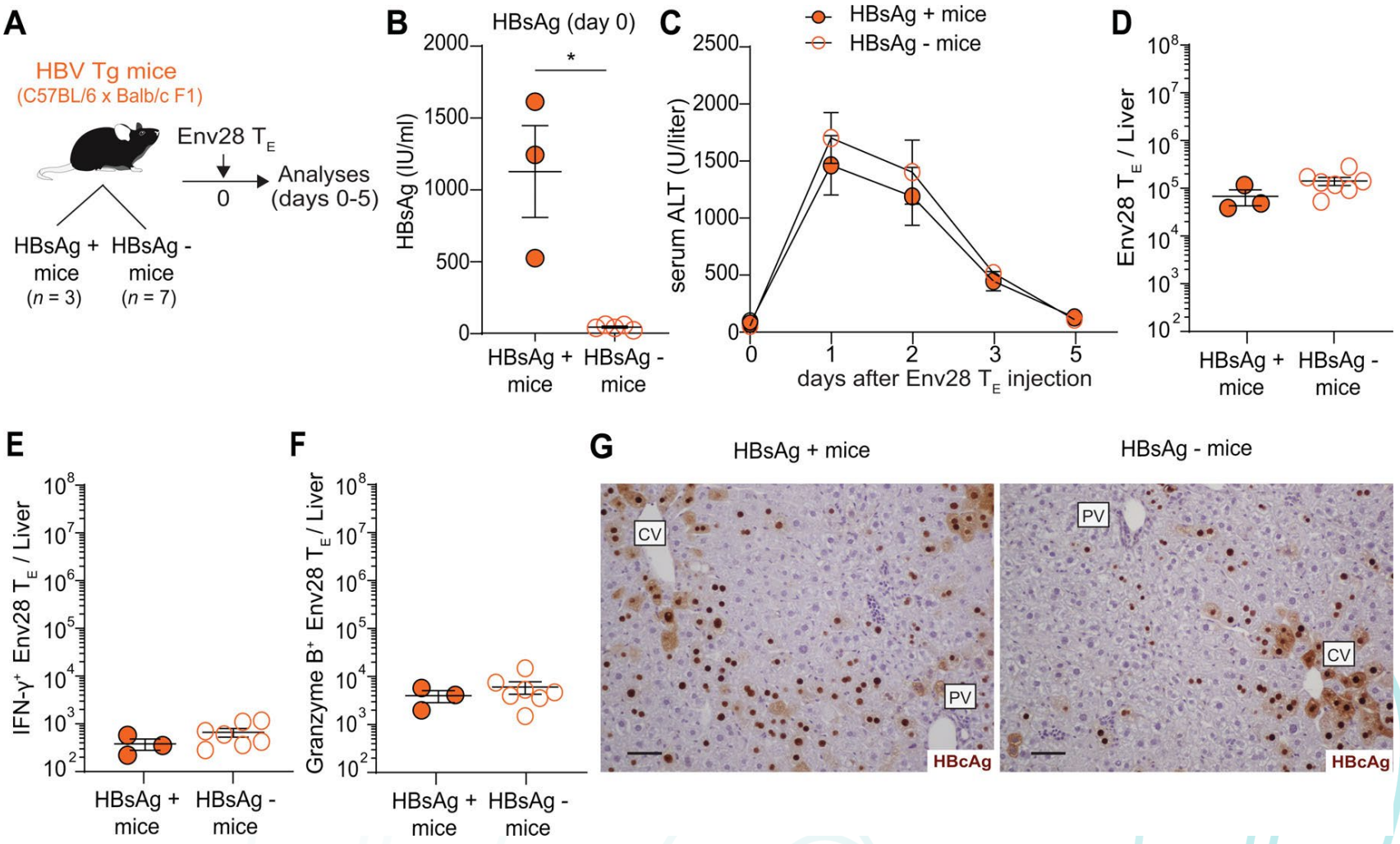
Clearing HBs alters immune cells minimally



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Fumagalli et al (2020), *J Exp Med*

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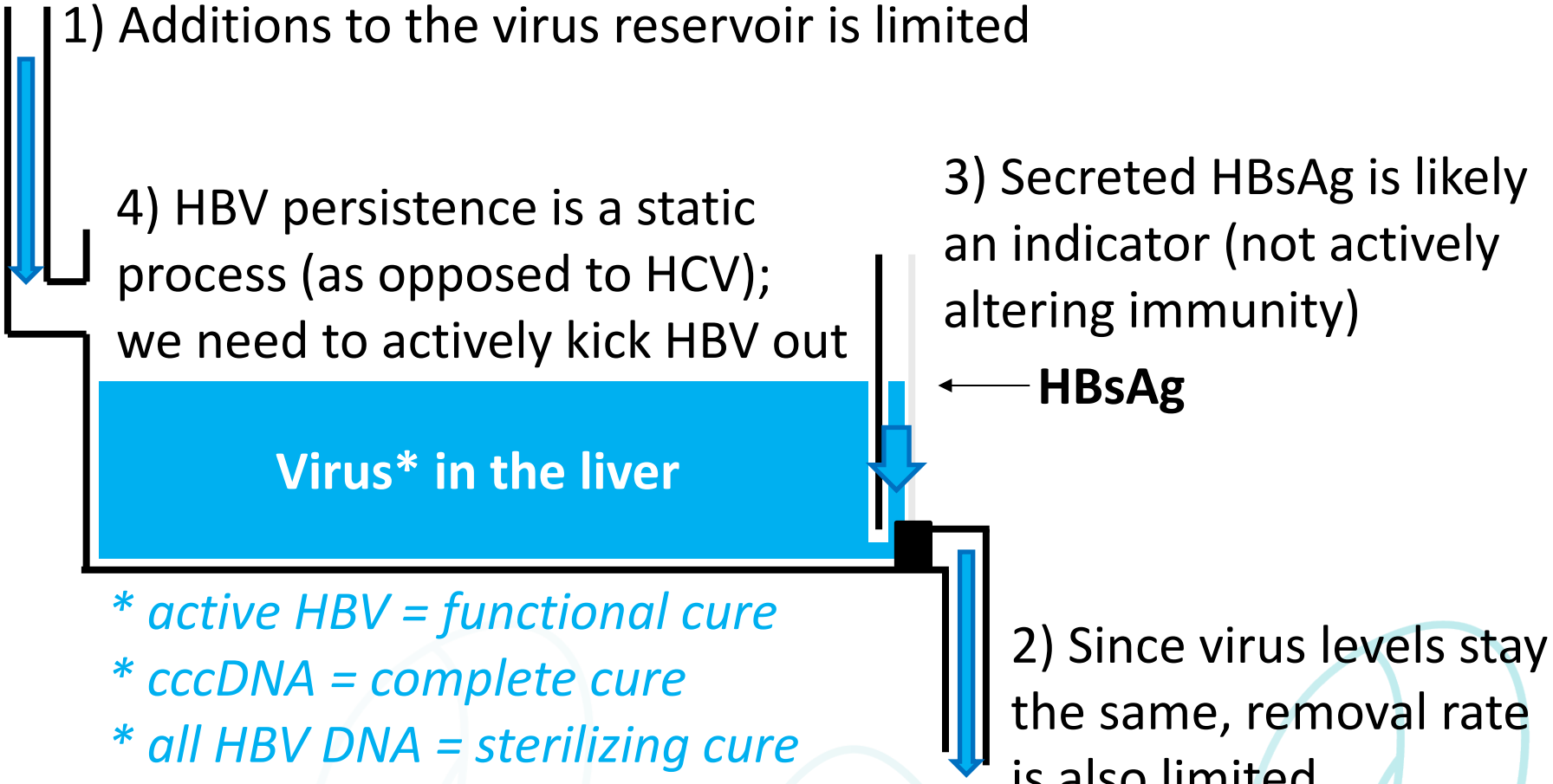
Summary


1) Additions to the virus reservoir is limited
4) HBV persistence is a static process (as opposed to HCV); we need to actively kick HBV out
3) Secreted HBsAg is likely an indicator (not actively altering immunity)
HBsAg
Virus* in the liver
* active HBV = functional cure
* cccDNA = complete cure
* all HBV DNA = sterilizing cure
2) Since virus levels stay the same, removal rate is also limited

Questions?