Hepatitis B Reactivation after Antiviral Cessation: Implications for PrEP and HIV-HBV coinfection

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Outline

1. Hepatitis B (HBV) and definitions of “cure”
2. Evidence for treatment cessation in HBV
3. Implications for HIV prevention (PrEP)
4. Implications for HIV-HBV coinfection

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Hepatitis B virus (HBV) is a leading cause of death around the world

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- 300 million people with active infection
- 1.5 million new infections each year
- 820,000 deaths each year
- 3- 4 million with HIV-HBV coinfection

Razavi-Shearer D, Lancet Gastroenterol Hepatol 2018

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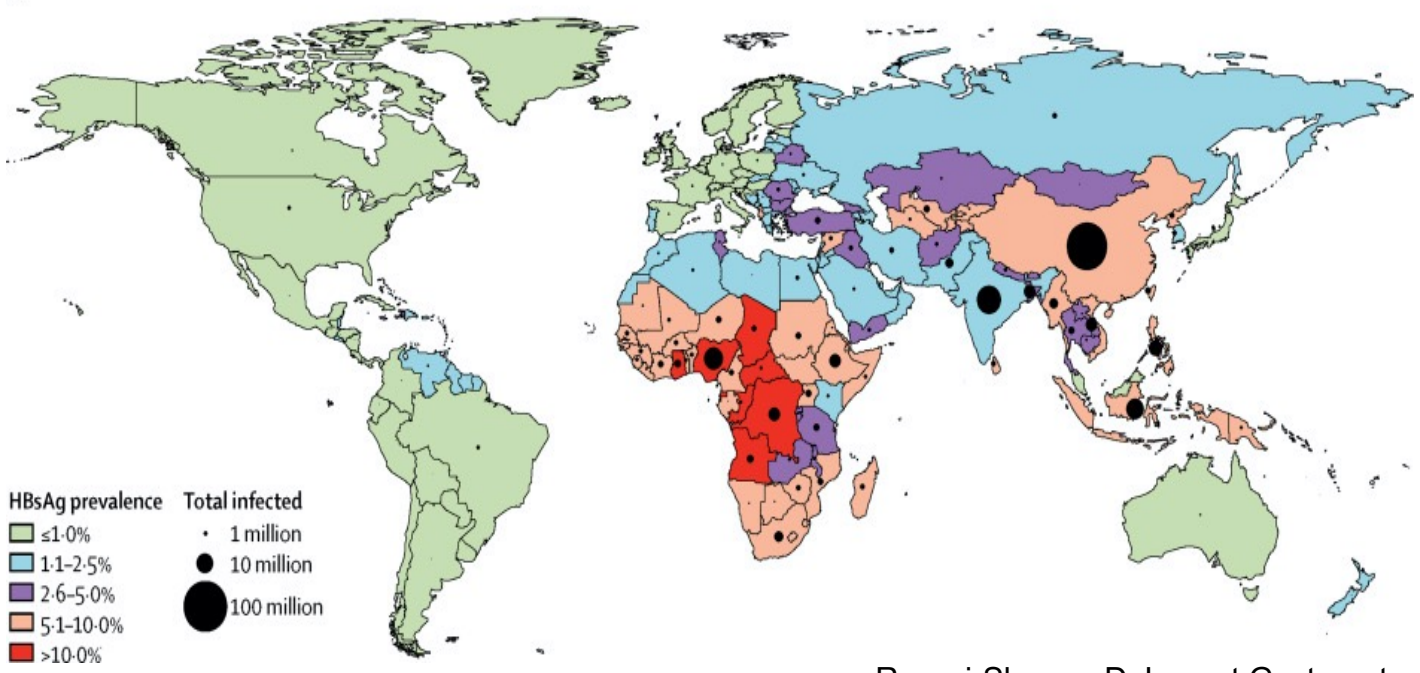
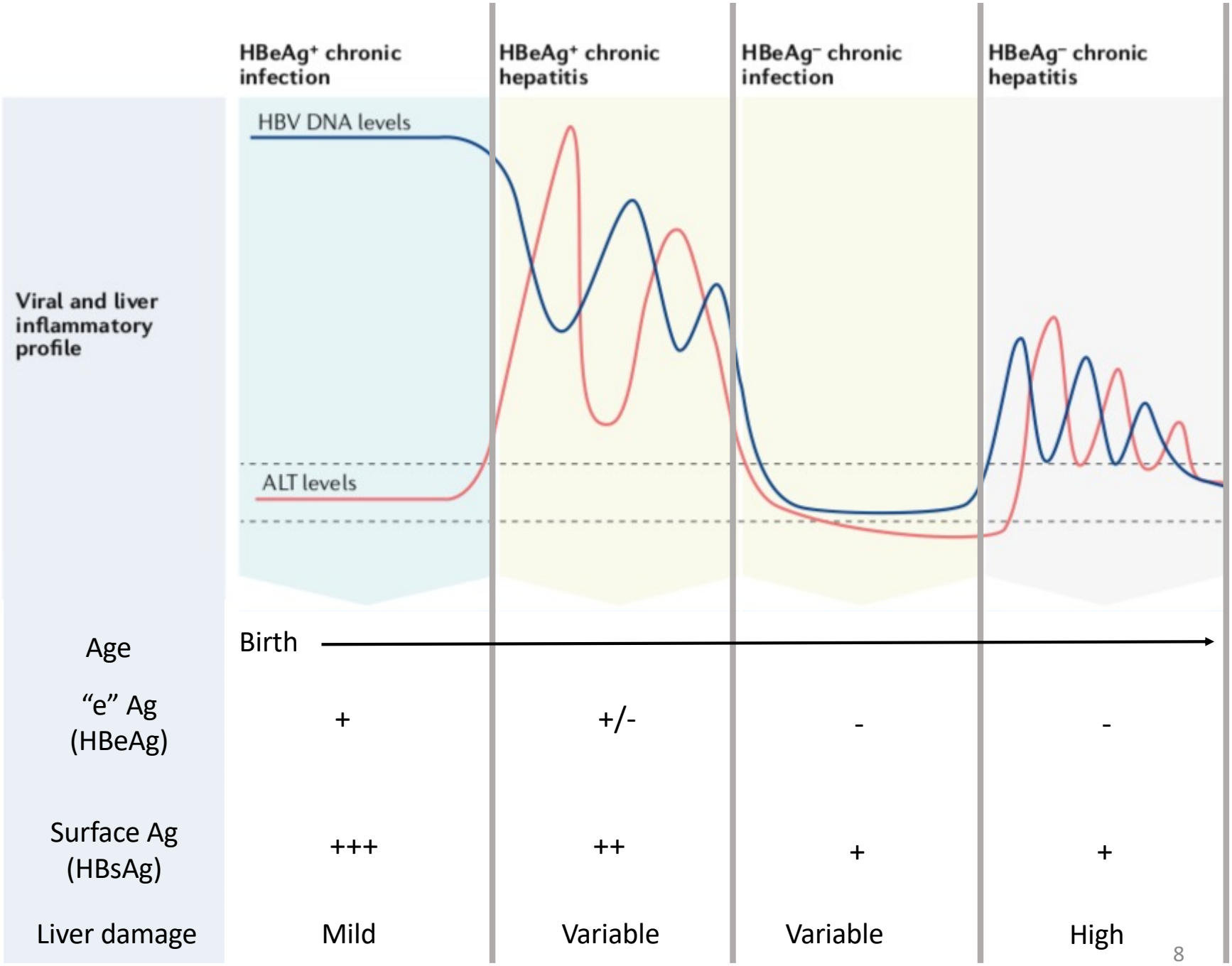


Razavi-Shearer D, Lancet Gastroenterol Hepatol 2018



Adapted from Fanning GC, *Nature Reviews Drug Discovery* 2019

HBV Treatment Goals

Sterilizing Cure

Complete eradication of HBV DNA, including cccDNA

Functional Cure

Sustained loss of HBsAg and serum HBV DNA

Suppression of HBV DNA

Persistence of HBsAg but suppression of HBV DNA

Loss of HBV “e” antigen

Persistence of HBsAg, immunologic control

Limits of Antiviral (NA) Therapy

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Stopping Antiviral Therapy in HBV: Pros and Cons

PRO	CON
• Long-term safety of NA	• Excellent safety profile
• Financial burden of lifelong treatment	• Short-term safety monitoring
• Patient preference	• Fibrosis risk for those who remain HBsAg+
• HBsAg Loss	

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- HBsAg Loss

CON

- Excellent safety profile
- Short-term safety monitoring
- Fibrosis risk for those who remain HBsAg+

Europe (EASL)	North America (AASLD)	Asia-Pacific (APASL)
"May consider" if HBV DNA is undetectable >3 years	"Continue treatment indefinitely unless there is a compelling rationale for discontinuation"	Recommend stopping if HBV DNA is undetectable for >1.5 years following ≥ 2 years of treatment

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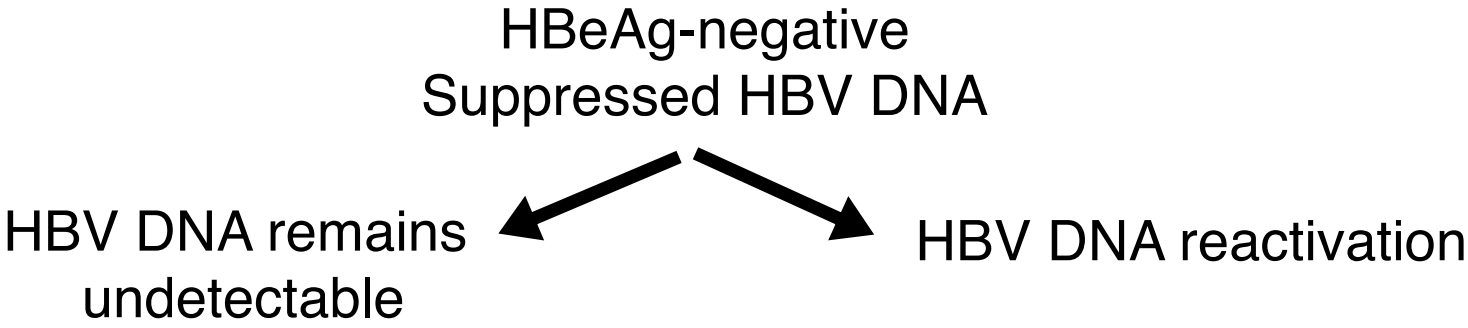
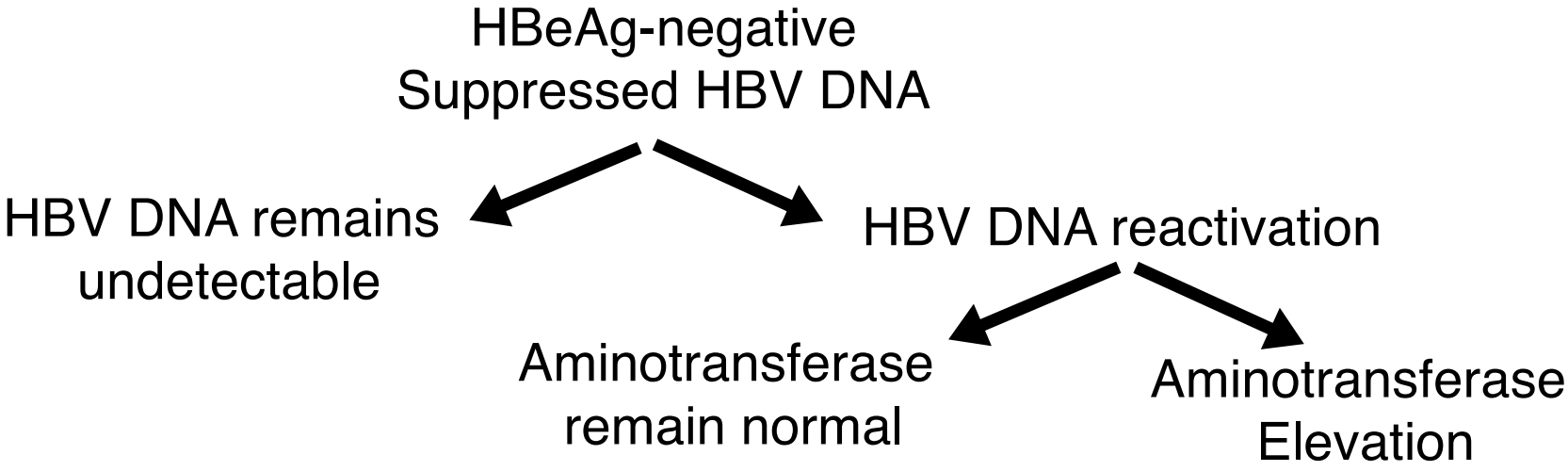
Stopping NA Therapy in Chronic HBV: Possible Outcomes

HBeAg-negative
Suppressed HBV DNA

Stopping NA Therapy in Chronic HBV: Possible Outcomes



Stopping NA Therapy in Chronic HBV: Possible Outcomes



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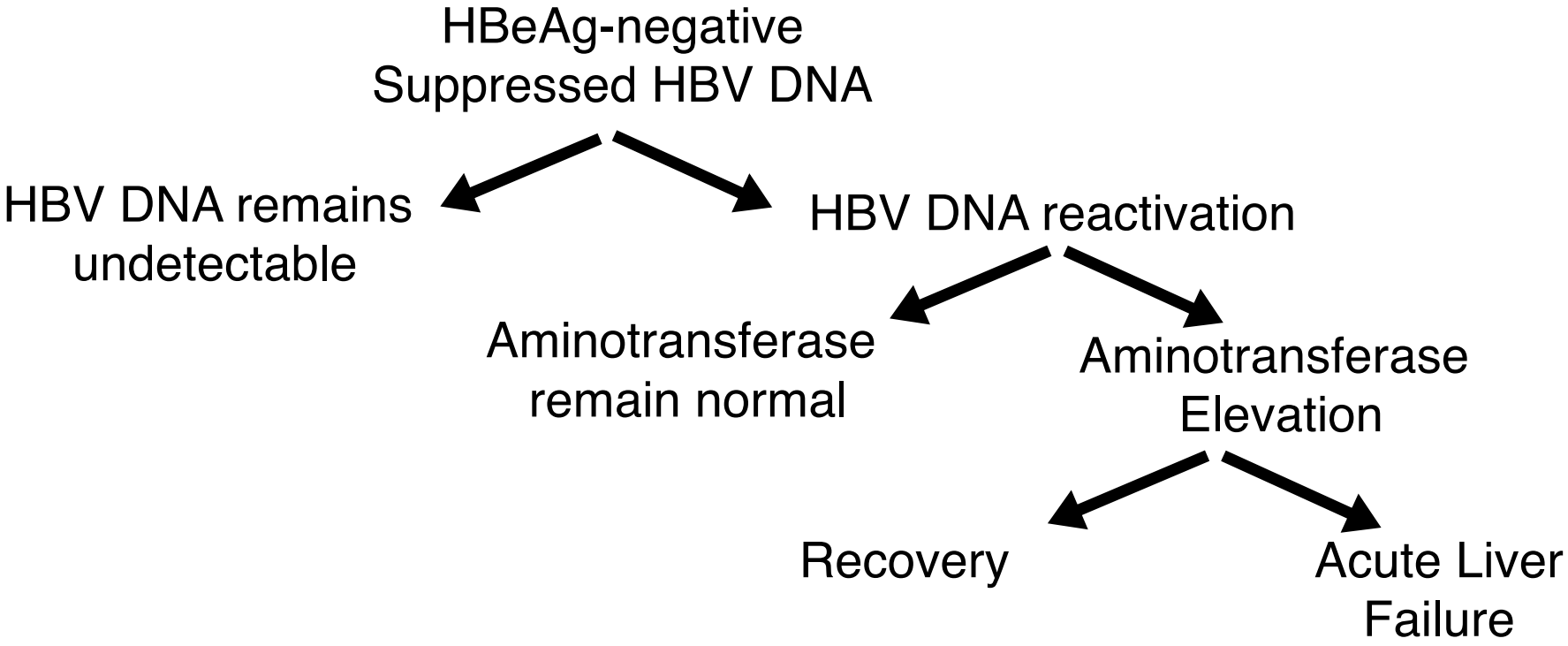

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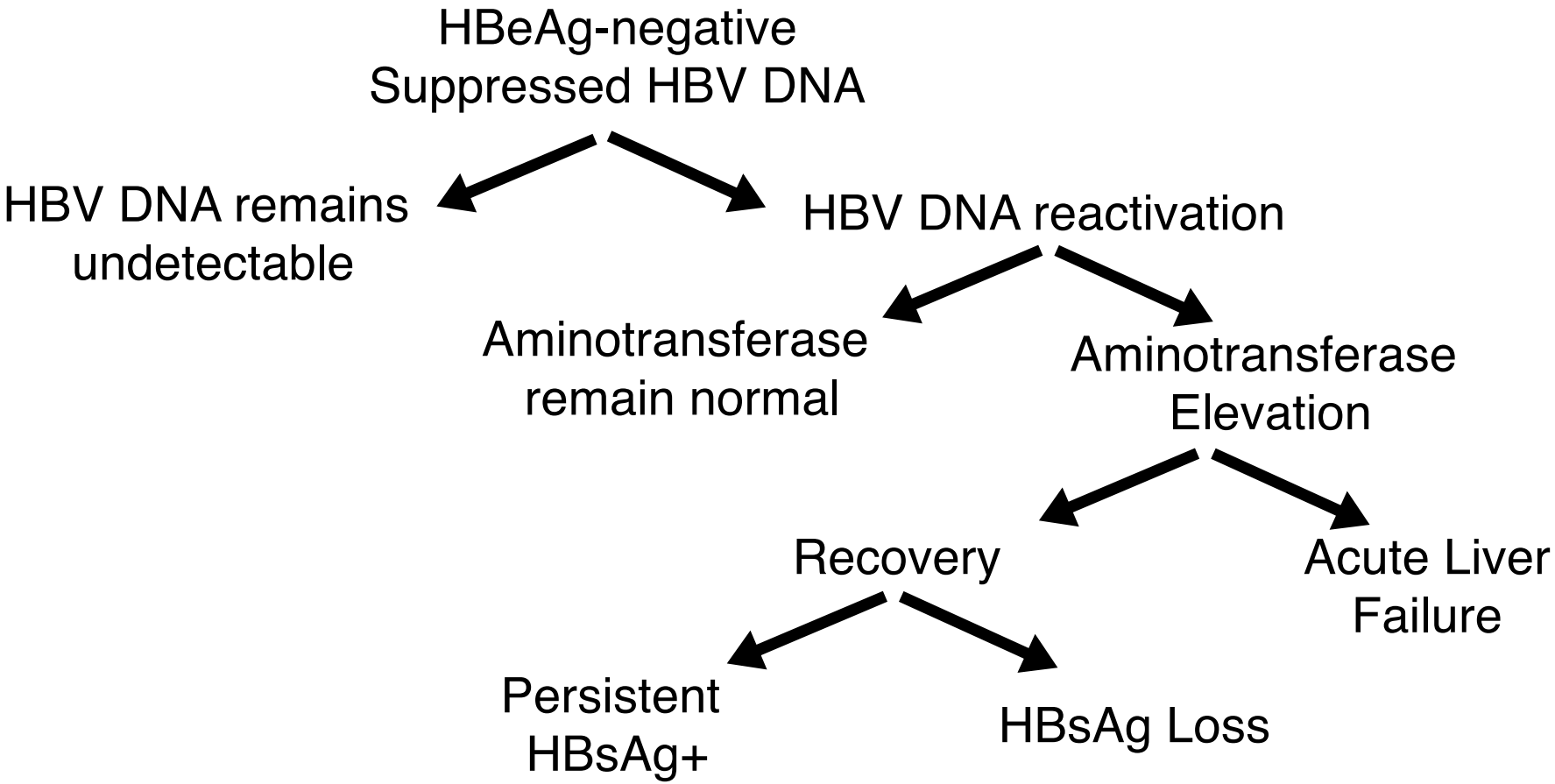

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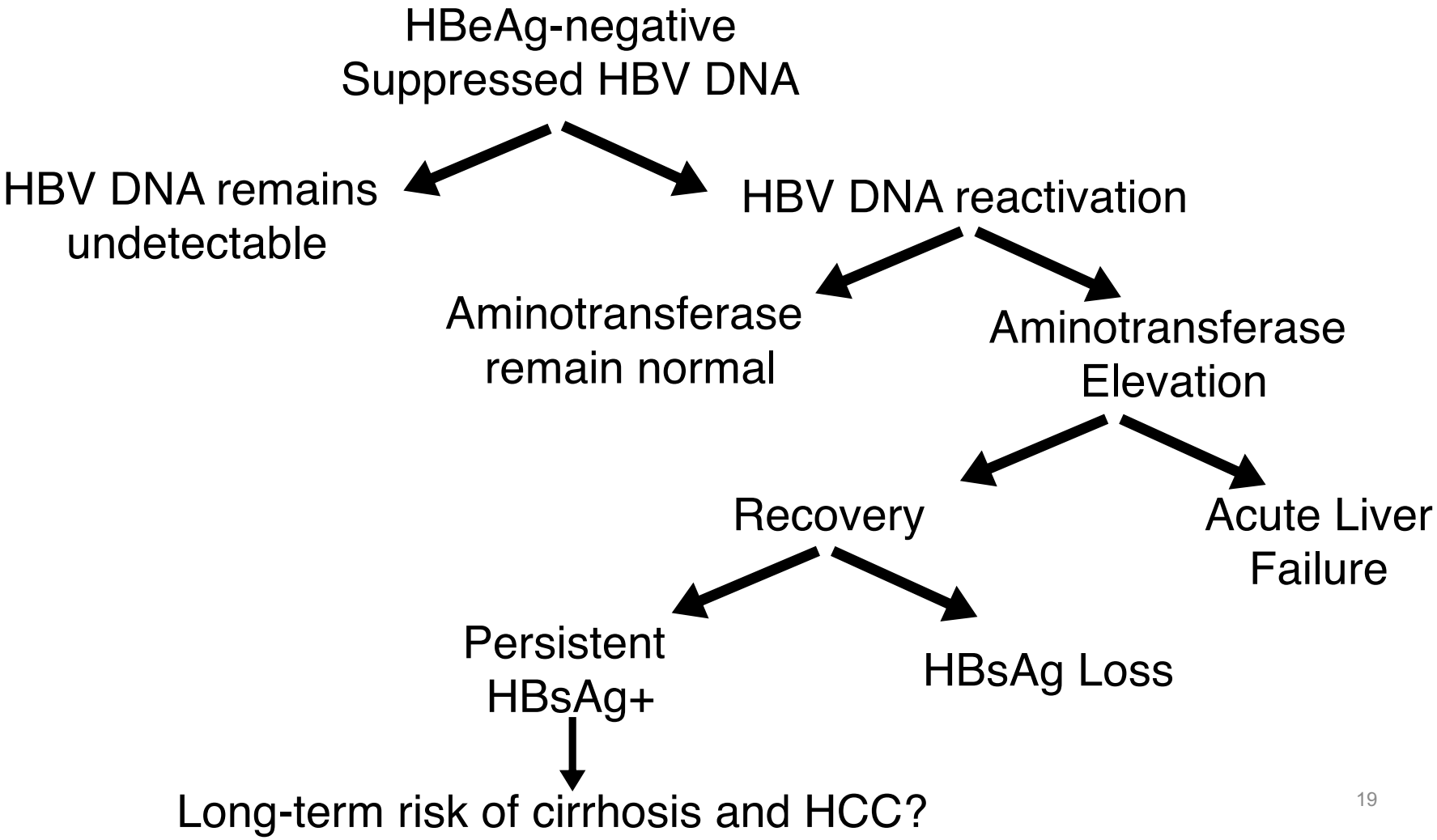
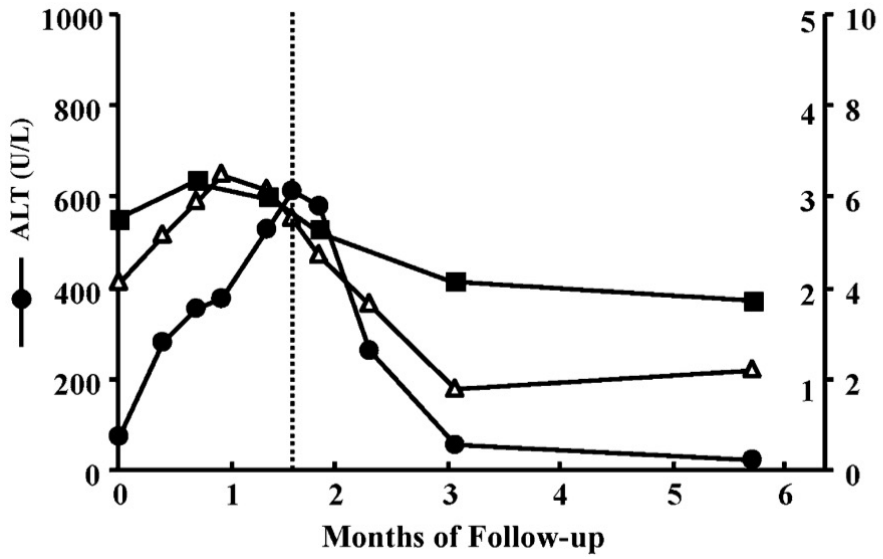
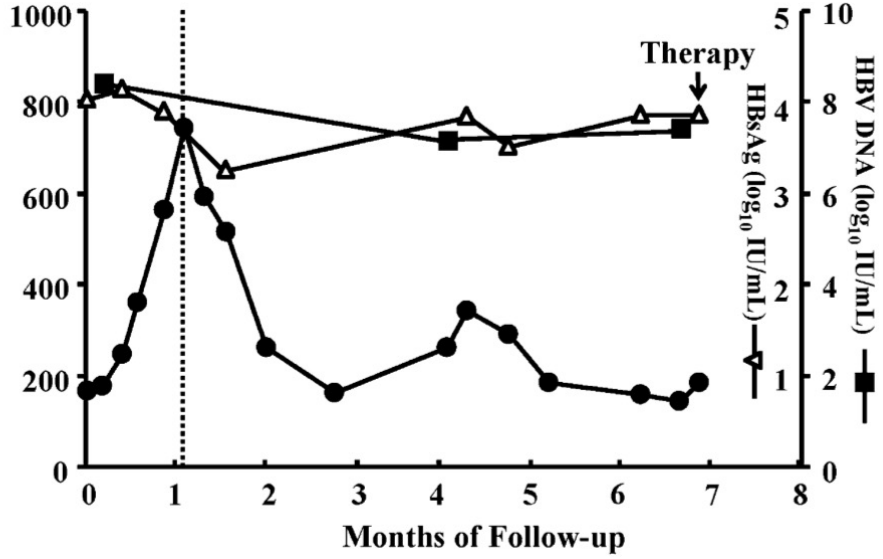


Hepatitis Flares Following Antiviral Cessation: Good or Bad?



HOST-DOMINATING FLARE



VIRUS-DOMINATING FLARE

Liaw, Hepatology Intl 2019

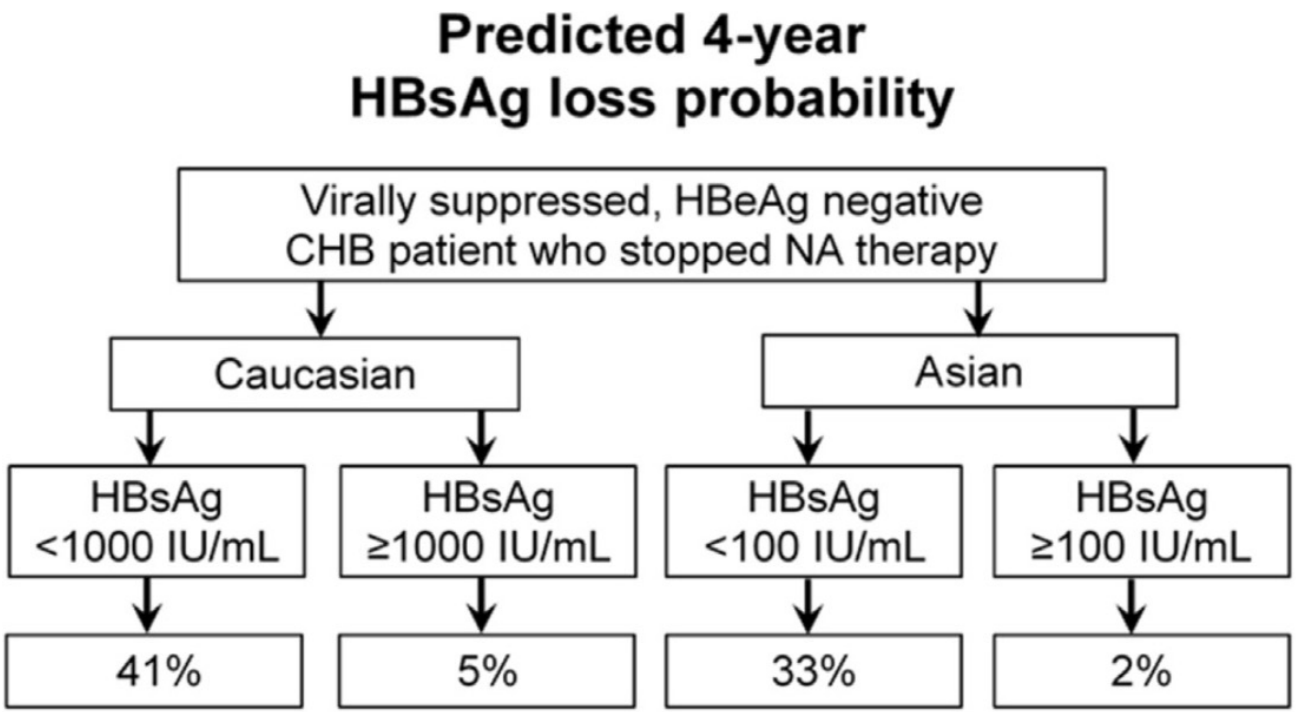
Events following antiviral cessation in chronic HBV mono-infection

Event	Estimated frequency (12 months post-withdrawal)
HBV DNA reactivation ("Virological Relapse")	65- 80%
Hepatitis flares ("Clinical Relapse")	35%
HBeAg reversion	9%
Acute liver failure ("Fulminant Hepatitis")	<1%*
HBsAg loss ("Functional Cure")	2 - 4%
Long-term risk of cirrhosis and hepatocellular carcinoma	???

* Subject to reporting bias and differing definitions

HBsAg loss following antiviral cessation in chronic HBV

RETRACT-B Study: 1552 people from 13 centres in North America and Europe who stopped NA therapy, followed for 48 months



Hirode, Gastroenterology 2022

Would you stop antiviral therapy in someone with HBeAg-negative infection?

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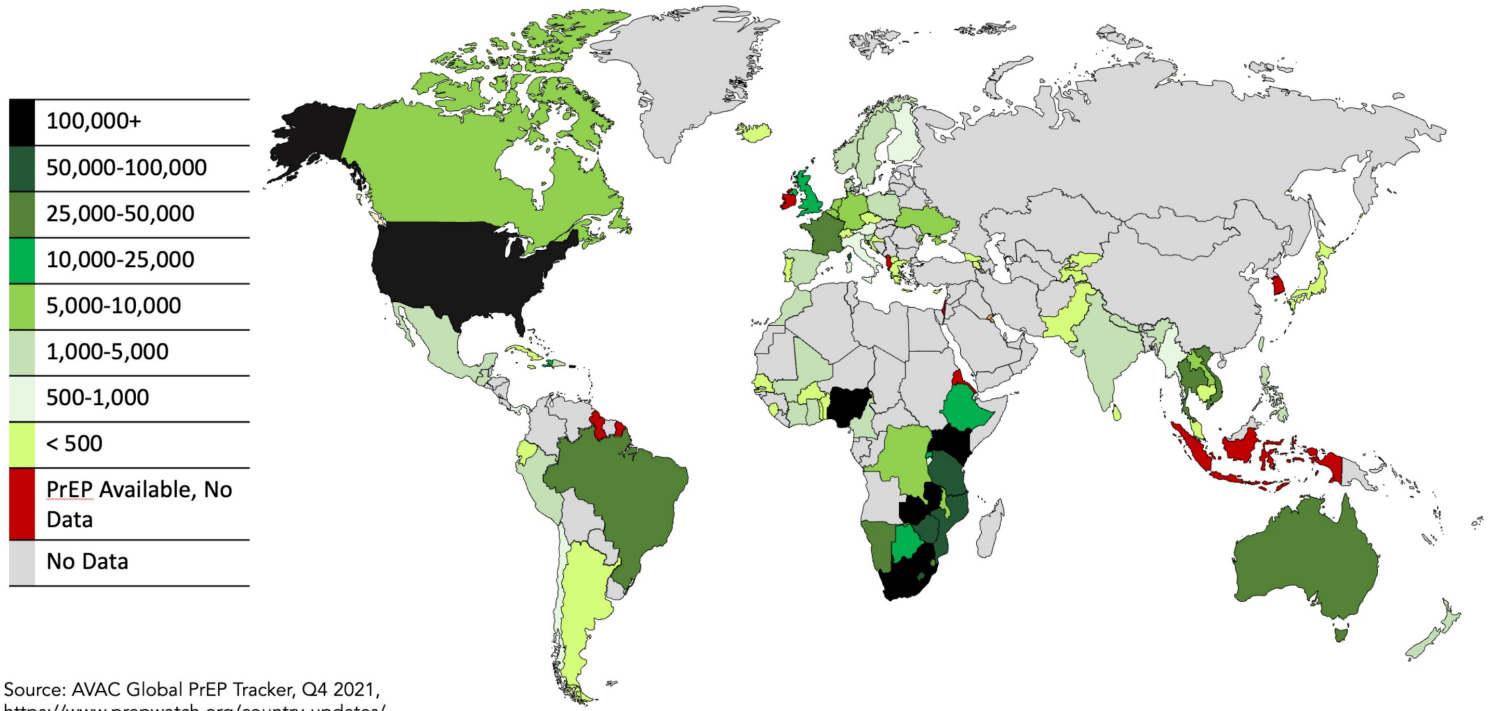
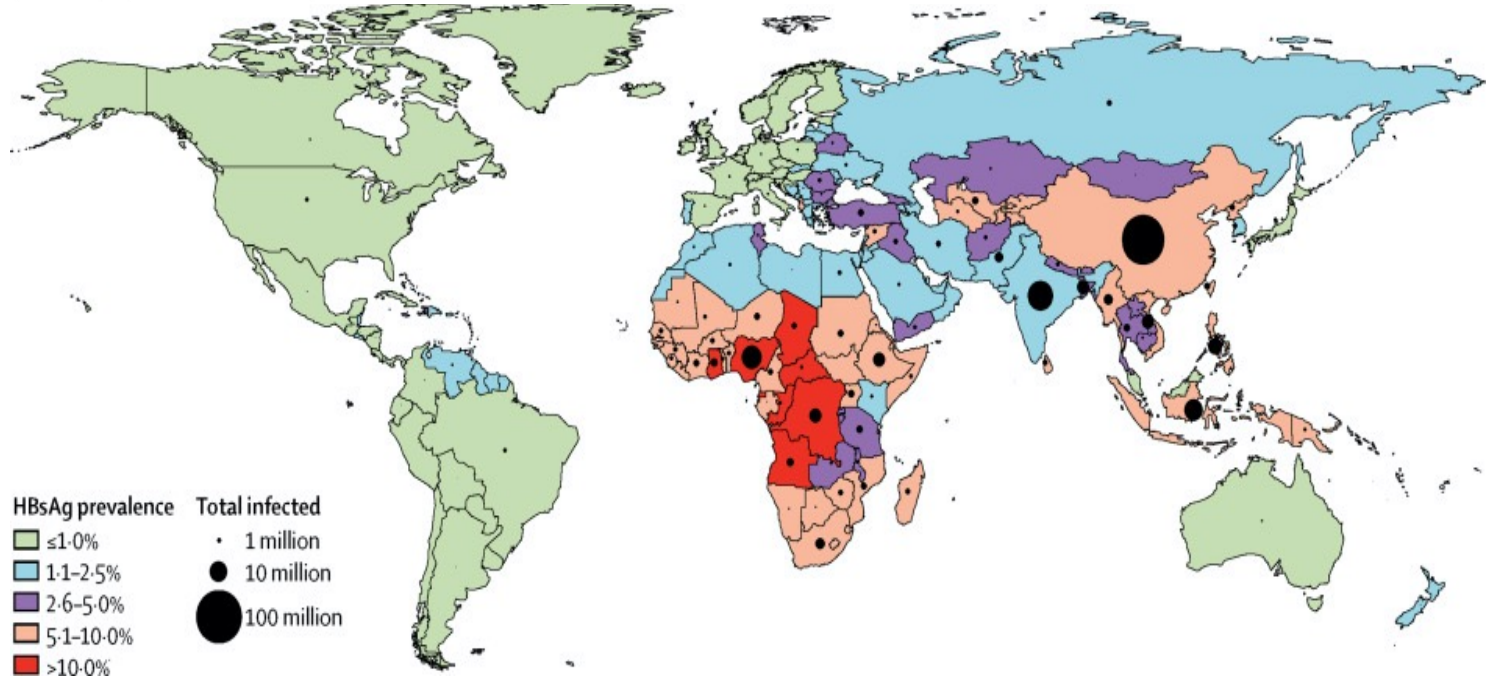
Using PrEP to prevent HIV infection in people with chronic HBV

- HIV-HBV coinfection results in accelerated liver damage, high mortality
- Shared routes of transmission, shared risk factors
- In HBV-endemic countries, most people with chronic HBV acquire infection at birth or early childhood
- PrEP is being scaled up in HBV-endemic countries



Source: AVAC Global PrEP Tracker, Q4 2021, https://www.prepwatch.org/country-updates/



PrEP is an opportunity to expand HBV screening and treatment

Countries with any PrEP program in yellow

Tenofovir-based PrEP

Potent inhibitor of HIV and HBV

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PrEP Scale-up in sub-Saharan Africa

>25 countries with a PrEP program

1.2 million PrEP initiations

Were DK, Lancet HIV 2021

Mohareb AM, *Under Review*

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Ethical and Safety Concerns

Access to antiviral therapy (TDF) for PrEP and not HBV treatment

Antiviral cessation in chronic HBV

Were DK, Lancet HIV 2021
Mohareb AM, *Under Review*

Most PrEP trials excluded people with HBV…except iPrEx

iPrEx randomized 2499 people to TDF/FTC v placebo

6 participants in the TDF/FTC arm had HBsAg+ (< 0.5%)

Solomon, JAIDS 2016

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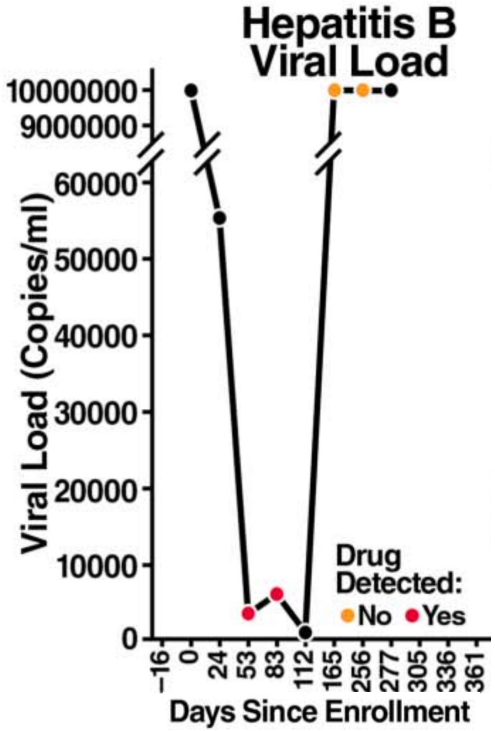

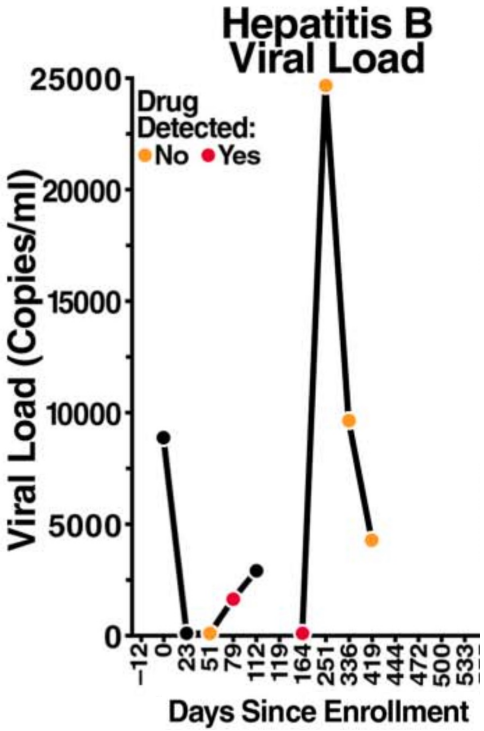

Solomon, JAIDS 2016

What is your approach to initiating PrEP in people with chronic HBV?

Chronic Hepatitis B Infection Among Preexposure Prophylaxis Users Enrolled in a Population-Based Program in British Columbia, Canada

Open Forum Infectious Diseases

BRIEF REPORT

Kyle A. Thompson,[1] Gabriel Blank,[2] Junine Toy,[1] David M. Moore,[1,2] Nathan Lachowsky,[3] Nicanor Bacani,[1] Wendy Zhang,[1] Paul Sereda,[1] Viviane D. Lima,[1,2] Rolando Barrios,[1] Julio S. G. Montaner,[2] and Mark W. Hull[1,2]

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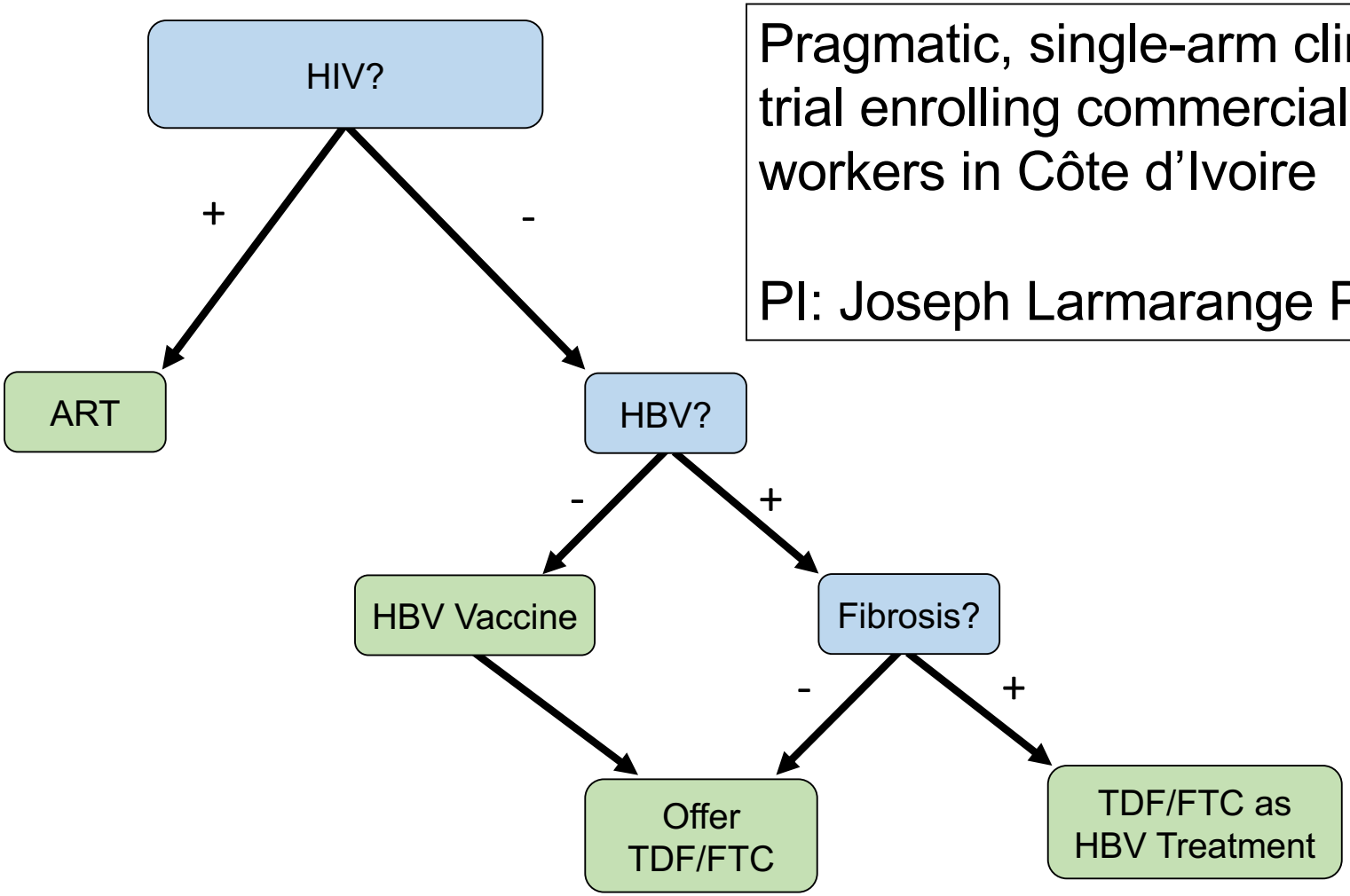
Among 4760 PrEP users:

- 1845 had laboratory results available to review
- 41 with HBV = 19 laboratory-confirmed + 22 recorded history
  - 29 (71%) had any HBV DNA measurement
  - 22 (54%) had repeat HBV DNA measurements
  - 21/22 (95%) achieved undetectable HBV DNA

ANRS 12381 PRINCESSE Trial (Côte d'Ivoire)



Pragmatic, single-arm clinical trial enrolling commercial sex workers in Côte d'Ivoire

PI: Joseph Larmarange PhD

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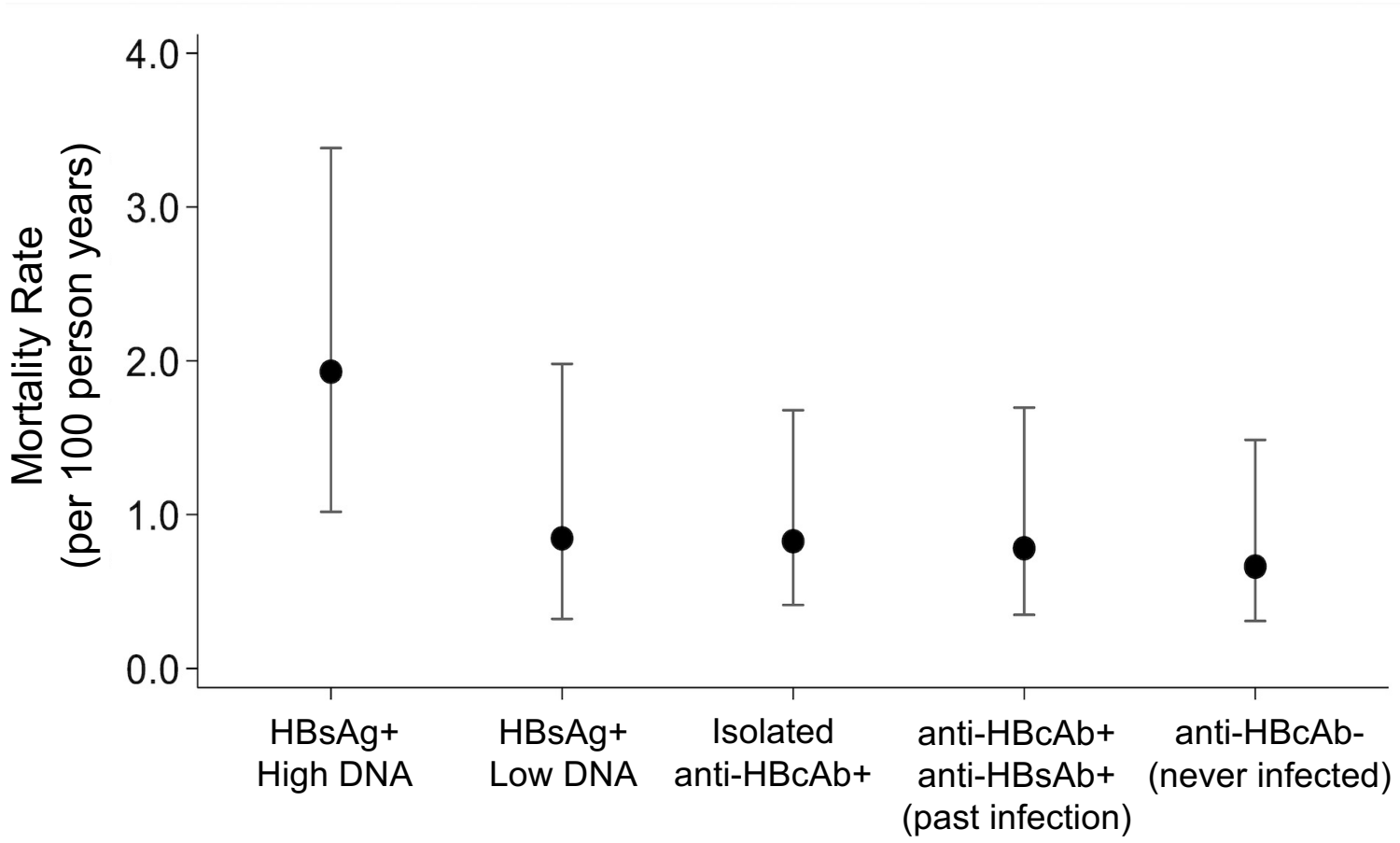
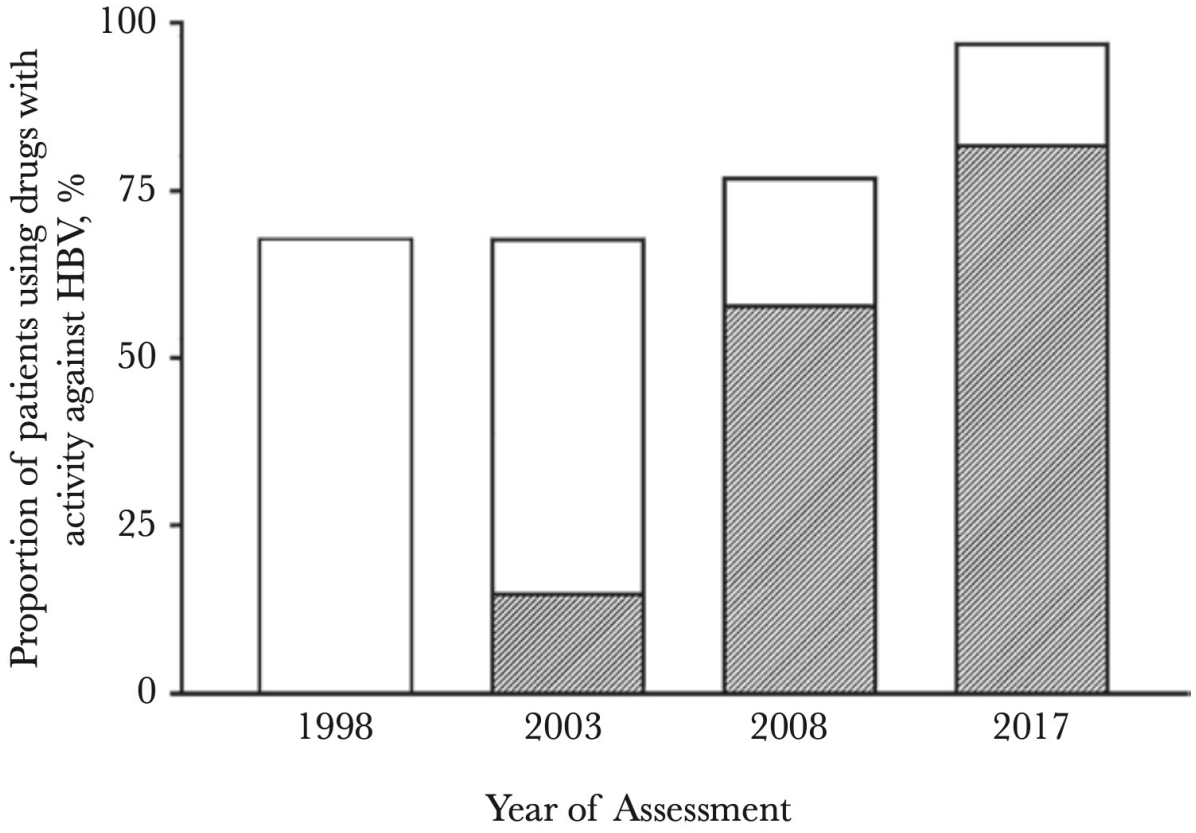
High mortality associated with HIV-HBV coinfection despite immediate ART



Mohareb AM, et al. J Viral Hepatitis 2021

Tenofovir-based ART may not always be used in HIV-HBV coinfection



ATHENA Cohort

>1300 people with HIV-HBV

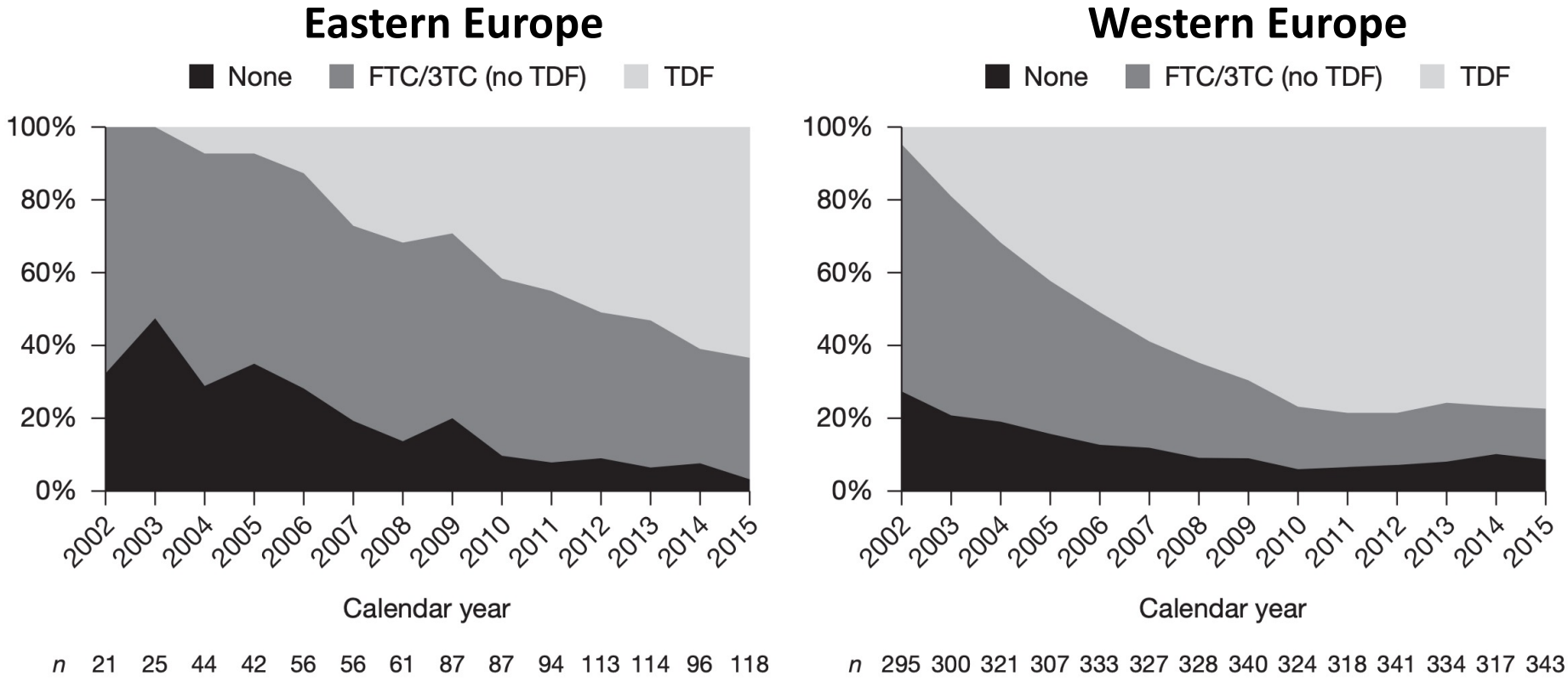
Shaded area (80%) on TDF or TAF

White area (15%) on 3TC or entecavir

<5% no HBV-active ART

van Welzen, OFID 2020

HBV-active ART used in people with HIV-HBV coinfection in EuroSIDA Cohort



Peters, Antiviral Therapy 2018

Transitioning off tenofovir-based ART in people with HIV-HBV coinfection

- ART Simplification: non-inferiority of 2-drug (3TC/DTG) ART versus 3-drug (TDF/FTC/DTG) ART

- Long-acting, tenofovir-free ART regimens

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How would you counsel someone with HIV-HBV coinfection who preferred to switch of tenofovir-based ART?

Summary

1. Antiviral therapy suppresses HBV DNA but results in a low rate of HBsAg loss (“cure”).

2. Most people with chronic HBV who stop antiviral therapy have HBV DNA reactivation, and some achieve HBsAg loss.

3. All people who stop antiviral therapy should be monitored for hepatitis flares, particularly in the first 1- 2 years.

4. Emerging data about HBV treatment cessation may help inform PrEP safety in people with HBV and management of HIV-HBV coinfection.

Thank you –
Mentors and Collaborators

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Arthur Kim

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Evaluation Center

Côte d'Ivoire

Menan Gérard Kouamé

Patrick Coffie

Serge Paul Eholié

Everyone at PAC-CI

Europe

Anders Boyd

Xavier Anglaret

Joseph Larmarange

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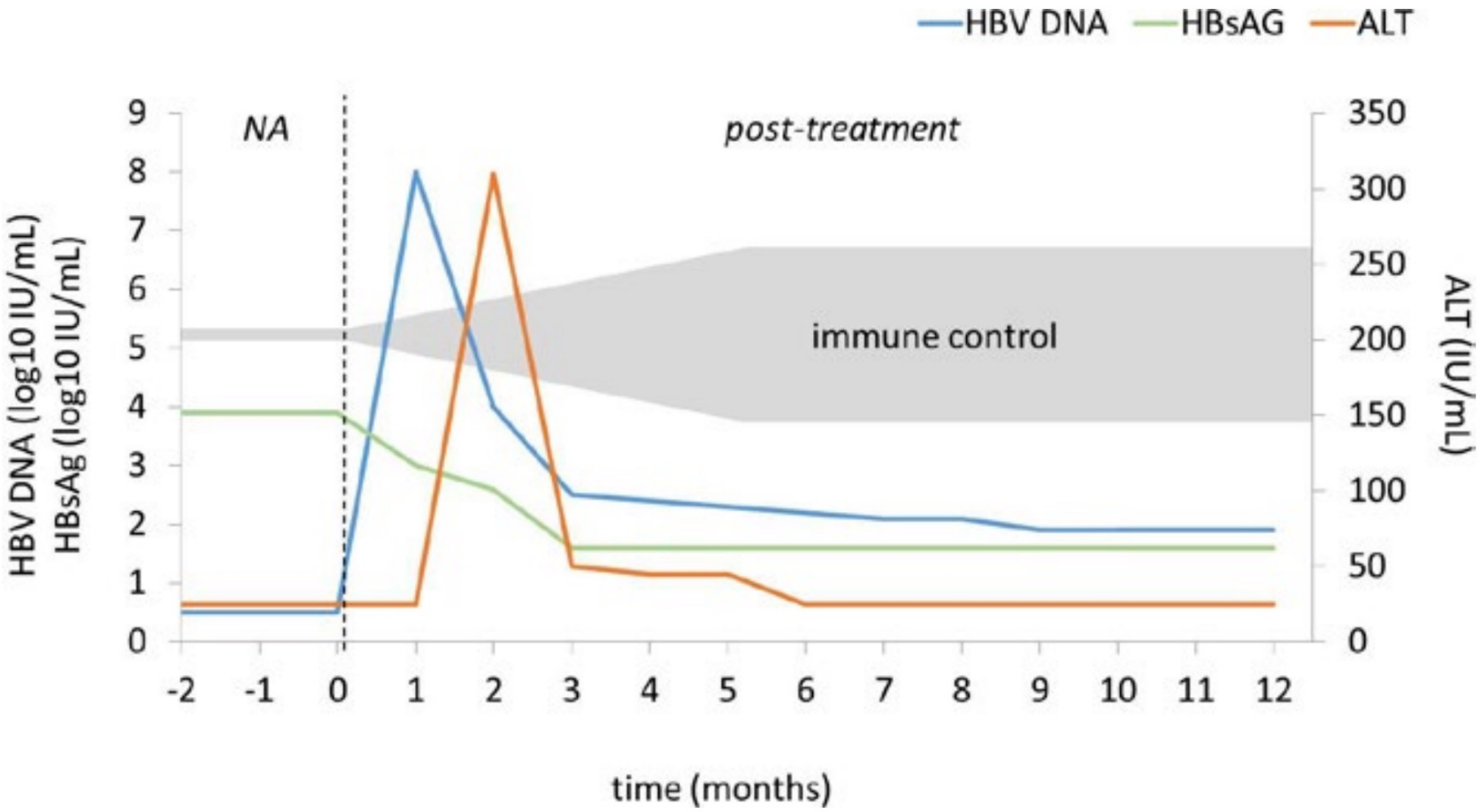
Harvard University Center for AIDS Research

MGH ECOR Fund for Medical Discovery

Charles A. King Trust Fellowship

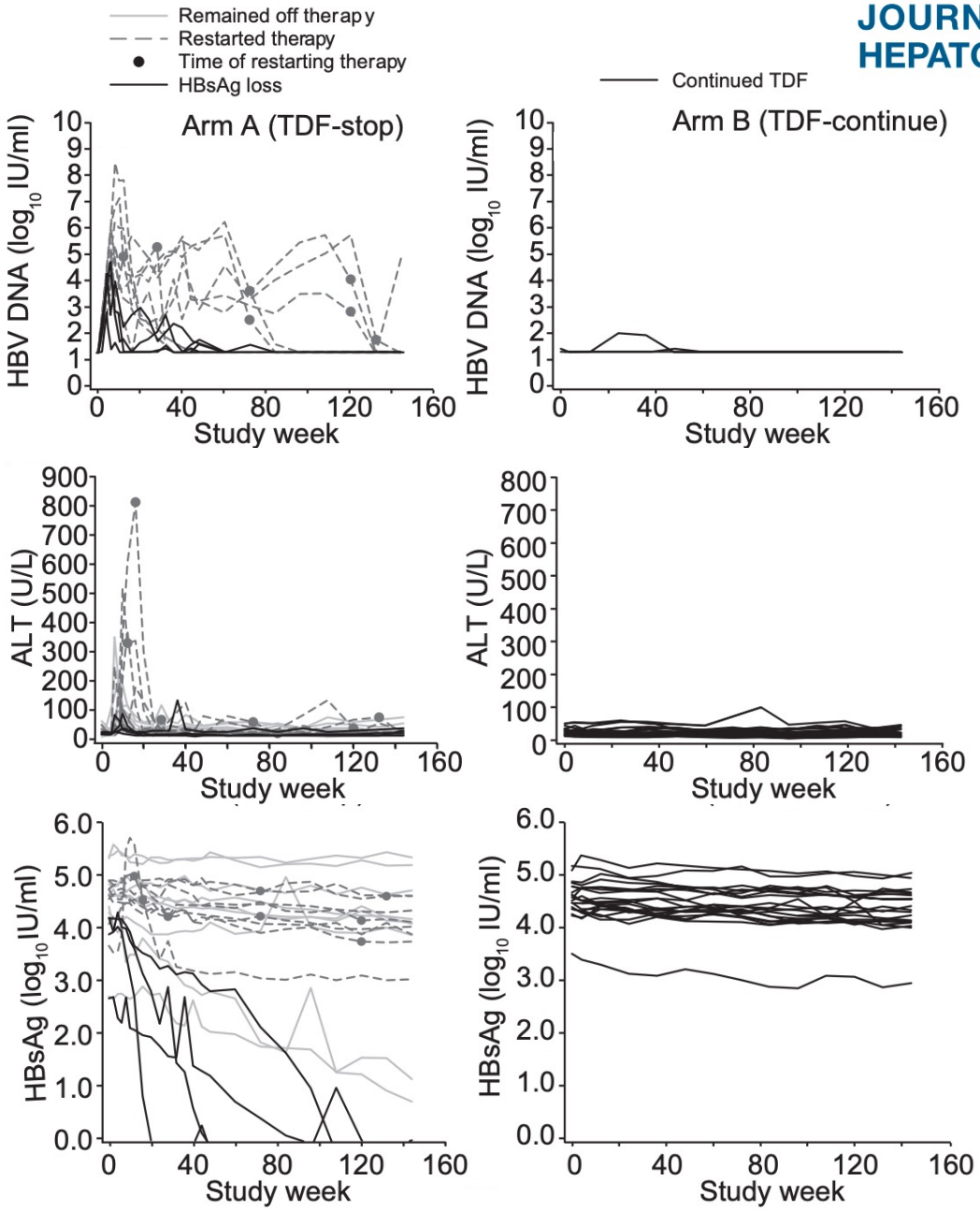
Appendix

Stopping NA Therapy in Chronic HBV: Possible Outcomes



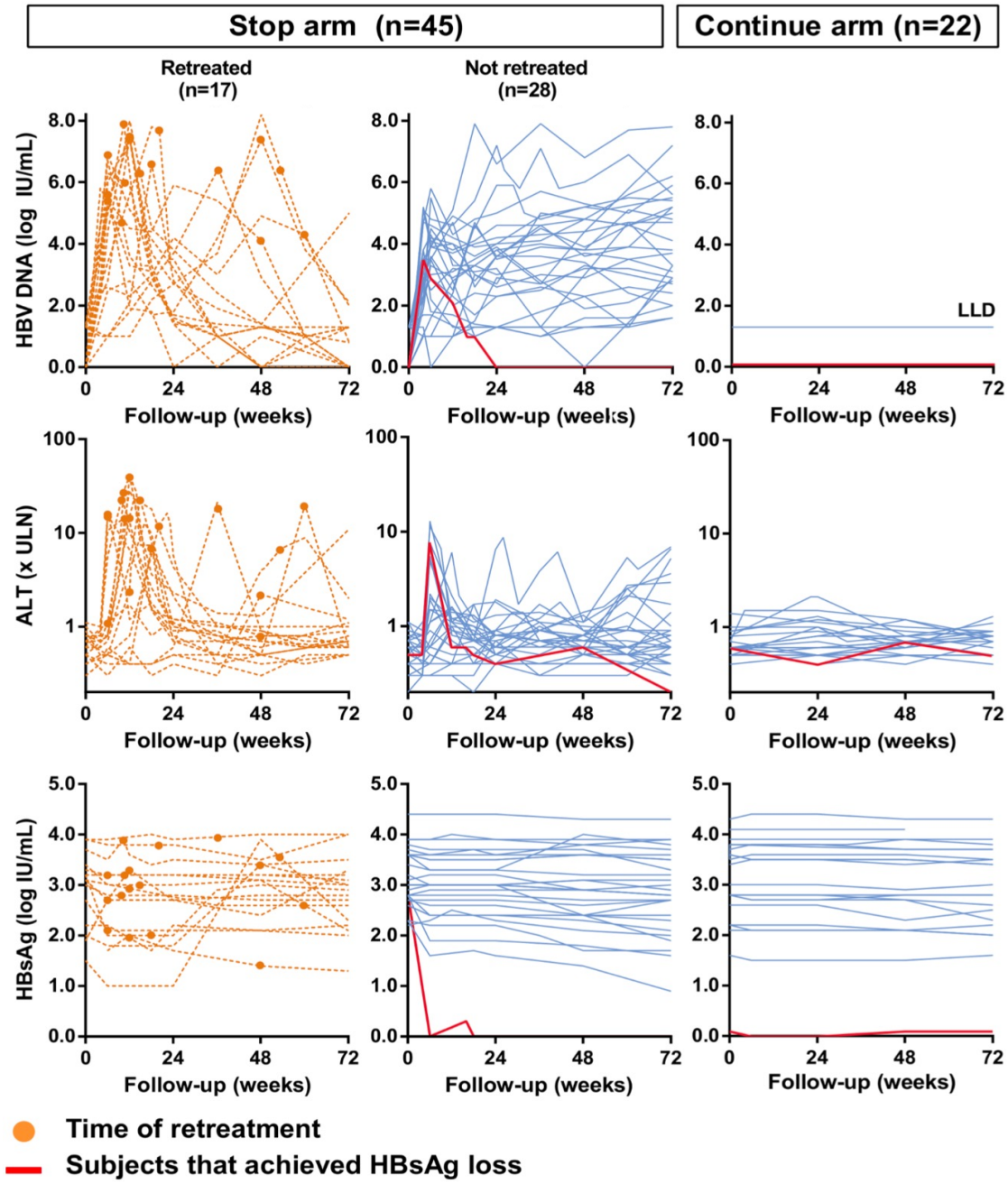
Van Bömmel, Liver International 2018

Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients – FINITE study☆



JOURNAL OF HEPATOLOGY

Berg, J Hepatology 2017



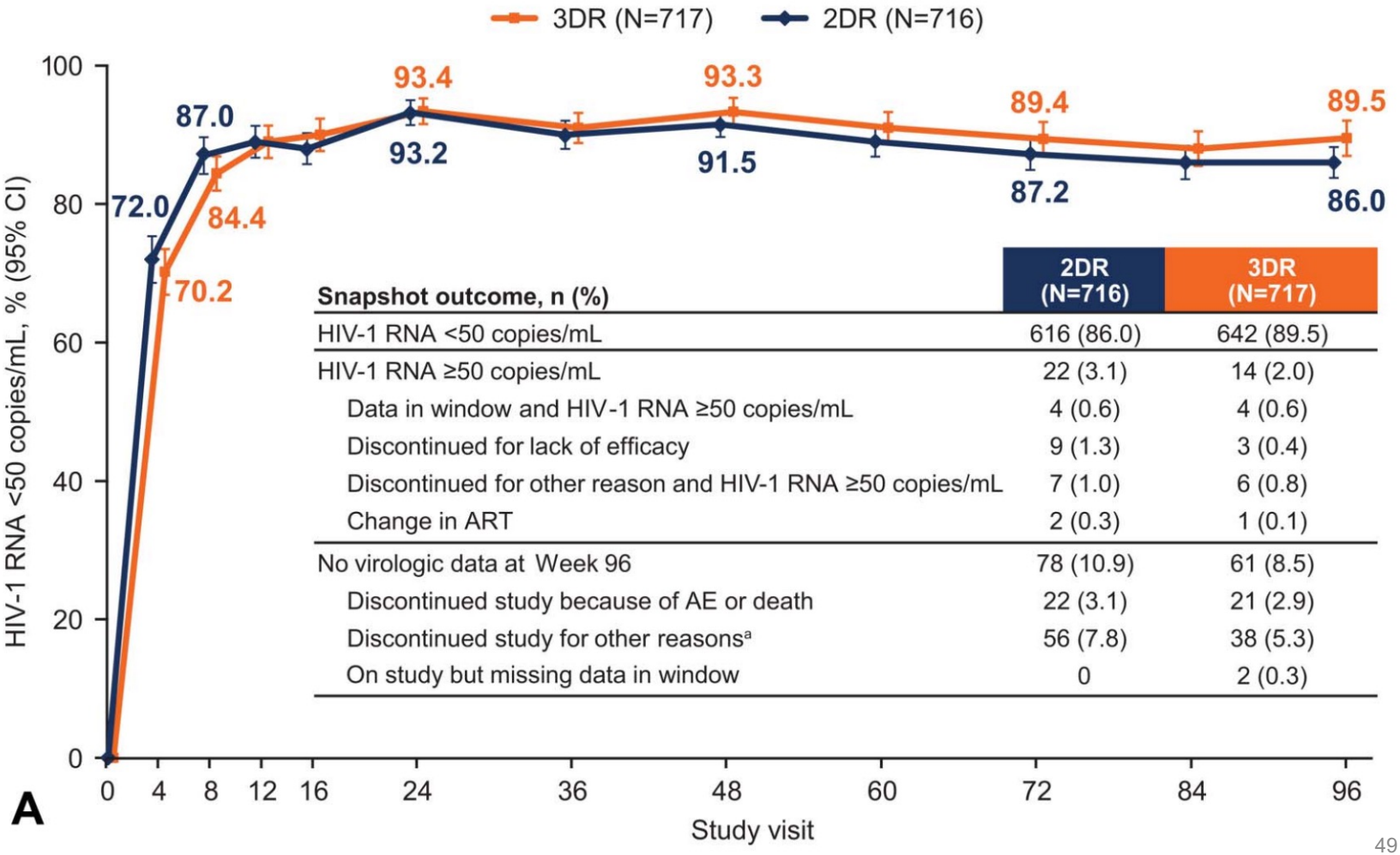
Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study)

Kin Seng Liem ,[1,2] Scott Fung,[1] David K Wong,[1] Colina Yim,[1] Seham Noureldin,[1] Jiayun Chen,[1] Jordan J Feld,[1,3] Bettina E Hansen,[1,4] Harry L A Janssen[1]

Gut

Liem, Gut 2019

GEMINI Trial: Non-inferiority of 2-drug (3TC/DTG) and 3-drug (TDF/FTC/DTG)



Snapshot outcome, n (%)	2DR (N=716)	3DR (N=717)
HIV-1 RNA <50 copies/mL	616 (86.0)	642 (89.5)
HIV-1 RNA ≥50 copies/mL	22 (3.1)	14 (2.0)
Data in window and HIV-1 RNA ≥50 copies/mL	4 (0.6)	4 (0.6)
Discontinued for lack of efficacy	9 (1.3)	3 (0.4)
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	7 (1.0)	6 (0.8)
Change in ART	2 (0.3)	1 (0.1)
No virologic data at Week 96	78 (10.9)	61 (8.5)
Discontinued study because of AE or death	22 (3.1)	21 (2.9)
Discontinued study for other reasons[a]	56 (7.8)	38 (5.3)
On study but missing data in window	0	2 (0.3)

Cahn, JAIDS 2020