Challenges and Opportunities in HBV Cure Drug Development in People Living with HIV and HBV

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Disclosures

- Gilead Sciences, grant to institution

HIV-HBV Co-infection

HBV Prevalence in HIV: 7.4% Globally

Shared Science Towards a Cure

Virus Integration	Cure Research	Translational Science
		
• Chronic Infection and Latency • Reverse Transcription Step	• Combination Immune and Antiviral Strategies • Risks of Viral Rebound and Treatment Interruptions • Risks of Off-Target Effects	• Biomarkers of Cure • Virologic Reservoir Measurement • Immunologic Assessments

Impact of HIV on HBV Disease Progression

- Higher levels of HBV replication (HBV DNA & HBeAg+)[1]
- Higher mortality when compared to HIV or HBV monoinfection[2]
- Higher rate of chronicity[2,3]
  - 20 to 80% as compared to 3-5% in HIV -
  - risk increases with lower CD4 at time of HBV acquisition
- Lower ALT levels[4]
- Faster progression to cirrhosis
- Higher incidence of lamivudine resistance

1. Bodsworth NJ et al. J Infect Dis 1989 2. Thio et al Lancet 2002 2. Bodsworth NJ, et al. J Infect Dis 1991. 3. Hadler SC et al. J Infect Dis 1991. 4. Gilson RJ et al. AIDS 1997.

Loss of HBsAg in HIV/HBV with ART Therapy

Country	N	% HBsAg loss	Predictor	Reference
Zambia	284	10.2 % at 2 years	BL CD4 < 350 OR 4.94 (1.02-23.8)	Chihota et al JID 2020
Germany	359	18% median 4 yrs	Less robust CD4 response associated with non-seroconversion	Van Bremen Liver Int 2020

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Studying HBV/HIV coinfection in first 1-2 years after (HBV) ART initiation may yield important data on viral and immune responses during HBsAg loss

Accelerated HBsAg Loss in Persons with HIV – Opportunities and Challenges

Opportunities

HIV/HBV coinfection offers a naturally enriched population for functional cure studies– seroclearance rates of 10-20% over 5-10 years;

- older PWH with HBV have decades of ART with low qHBsAg values

Immune reconstitution after ART can trigger enhanced HBV-specific T-cell activity, providing a window to intervene with immunomodultory or antiviral agents

Challenges

Loss of HBsAg may be restricted to first few years of ART, low CD4 at initiation

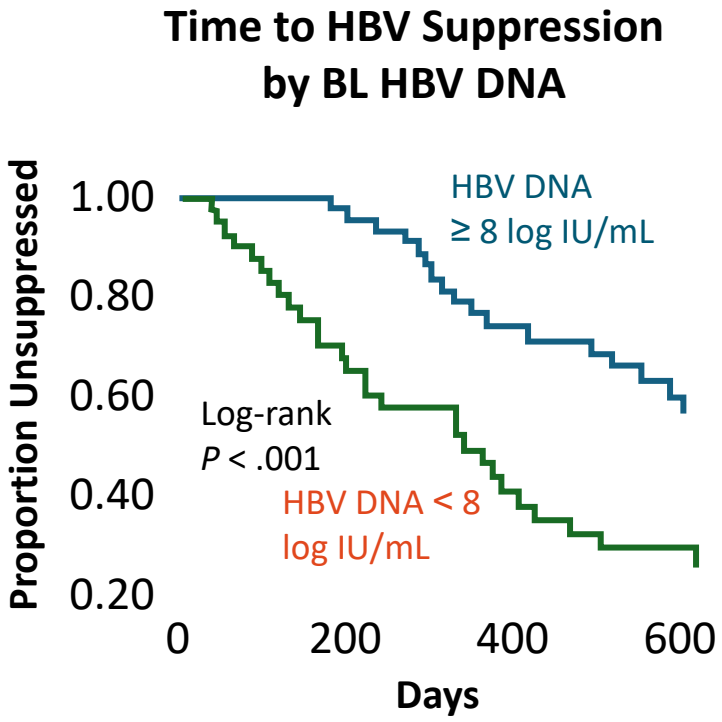
ART only partially restores HBV–specific immunity

Accelerated HBsAg loss may obscure treatment effects of study drug, especially if no placebo

Can results be generalizable to HBV monoinfection?

Incomplete HBV Suppression Common in PLWH

- Retrospective cohort study in US of 133 patients with HIV/HBV coinfection and HBV viremia
- Tenofovir-based ART initiated; HBV DNA measured at 1 yr
- 54% (95% CI: 46% to 63%) had incomplete HBV DNA suppression at 1 yr
  - Incomplete suppression associated with BL HBV DNA level > 8 IU/mL (adjusted OR: 3.21; 95% CI: 1.39-7.43)



Hafkin. J Viral Hepatitis. 2014;21:288.

HBV Virologic Failure Associated with Increased Risk of HCC; even with ND HIV!

TABLE 1. Risk of HCC Associated With Time-Updated HBV DNA Level and Time-Updated Detectable HIV and HBV Status Among Persons Coinfected With HIV/HBV Who Had Quantitative or Qualitative HBV DNA Assessed in the NA-ACCORD (1995-2016) (n = 5,316; 87 Incident HCC Events Identified)

Characteristic	No. Exposed*	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Time-updated HBV DNA						
Undetectable	3,656	44	22,692	1.9 (1.4-2.6)	Reference	Reference
Detectable	3,364	43	12,850	3.3 (2.4-4.5)	1.87 (1.22-2.85)	2.22 (1.42-3.47)
Time-updated detectable HIV and HBV status‡						
Undetectable HIV and HBV	3,494	42	19,164	2.2 (1.6-3.0)	Reference	Reference
Detectable HIV, undetectable HBV	1,881	2	3,529	0.6 (0.07-2.0)	0.29 (0.07-1.21)	0.27 (0.06-1.14)
Undetectable HIV, detectable HBV	2,835	27	8,510	3.2 (2.1-4.6)	1.55 (0.95-2.52)	1.77 (1.07-2.92)
Detectable HIV and HBV	2,480	16	4,340	3.7 (2.1-60)	1.93 (1.07-3.49)	2.21 (1.17-4.18)

Incomplete HBV Virologic Suppression: Opportunities and Challenges

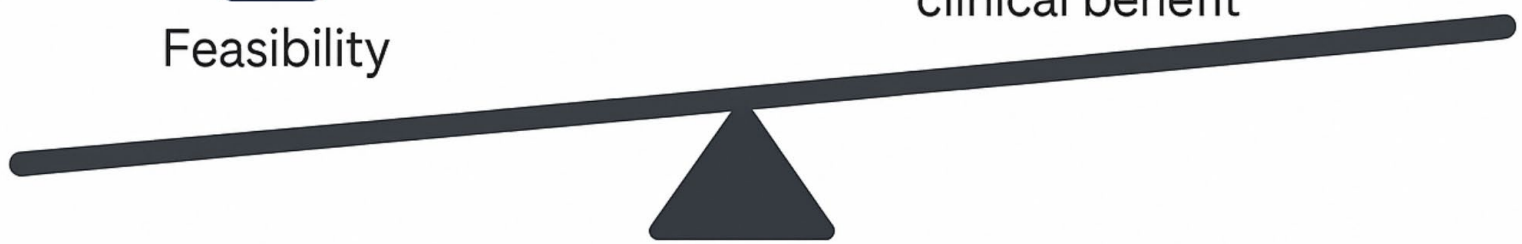
Opportunities

Identifies Subgroup for Intensification Strategies

Feasibility

Challenges

HBV DNA is not an adequate primary endpoint in add-on superiority trials Nrtls achieve substantial suppression, so small additional reductions in HBV DNA may not translate to clinical benefit



Clinical Trial Design Questions

Trial Population

Lack of HBsAg screening

qHBsAg thresholds for greater ART durations?

HBeAg negative or positive?

Nadir CD4 Threshold?

Region and HBV Genotype

Design

Placebo Arm?

Time within 3 years of ART or later?

Feasibility in varying geographic areas?

Liver biopsies/FNA?

Drug Drug Interactions

Management of hepatotoxicity

HBV Treatment Interruptions

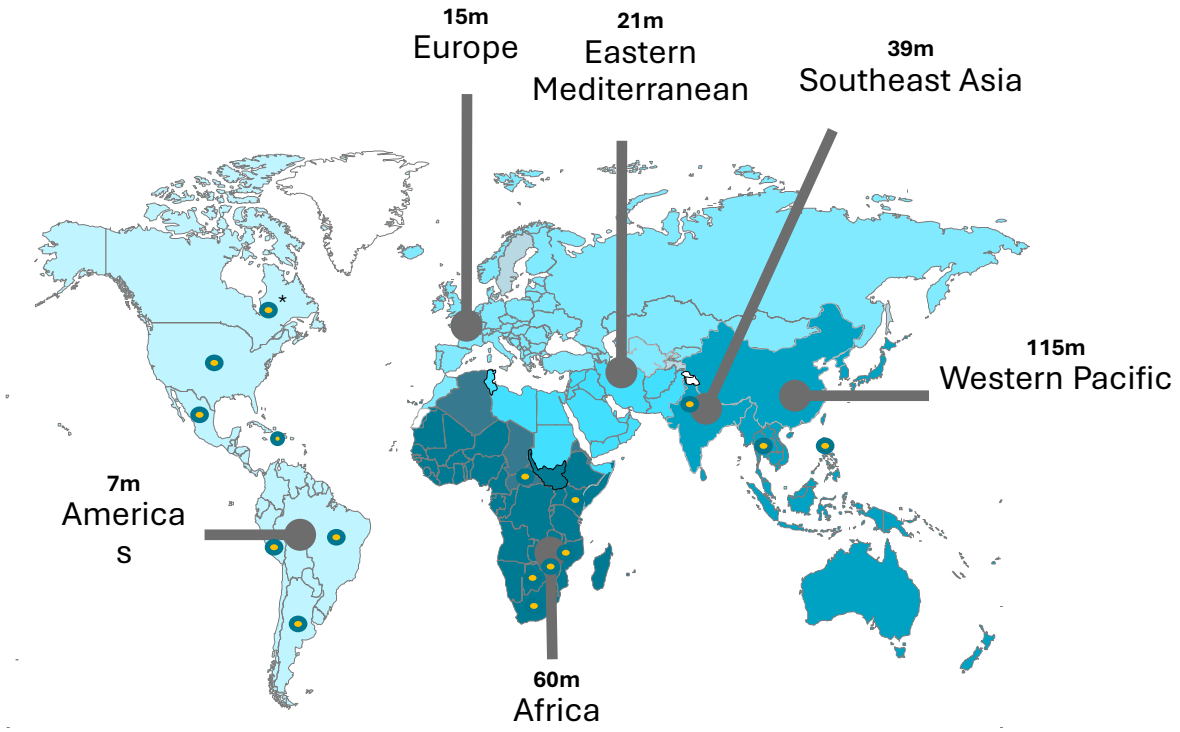
How do we handle HBV treatment interruptions?

- Role of XTC-sparing and long acting formulations

Predictors of rebound HBV viremia?

ACTG and HBV: Shared landscape

<u>ACTG sites:</u>
Brazil, Peru, Argentina, Haiti, Mexico



<u>ACTG sites:</u>
Kenya, Malawi, Zimbabwe, Botswana, South Africa, Uganda

India, Philippines, Vietnam, Thailand,

WHO. Global hepatitis report, 2017.
*protocol specific site: Toronto, Canada

Learning from HIV

- Community Engagement
  - How do we incorporate lessons learned from the community living with HIV re: engagement in clinical trials, advocacy
- Viral Reservoir Dynamics and Rebound
  - What can we learn from the depth of the characterization of the HIV reservoir?
  - Latency Silencing Agents
  - Analytical Treatment Interruptions
- Immune Response and Immunotherapies
  - What can we learn from immunotherapies in HIV?
  - Role of immune response and hepatic flares

Long-acting injectable therapy for HIV and HBV rx -sparing HIV therapy

- Long-acting injectable ART regimens (e.g., **cabotegravir + rilpivirine**) have **no activity against HBV**.
- Increasing use of TDF/TAF/XTC sparing regimens for HIV therapy
- Provide option for evaluating finite therapies in HIV/HBV coinfection
  - Risk of HBV flare with NA withdrawal
- No long-acting HBV therapy available

Summary

- Accelerated HBsAg loss in PWH – ideal patient population to evaluate HBV cure?
- Incomplete HBV Virologic Suppression offers opportunities for add-on therapy
- Clinical Trial Design in HIV-HBV have Unique Considerations
  - Population
  - How to manage treatment discontinuations
  - Hepatotoxicity Management

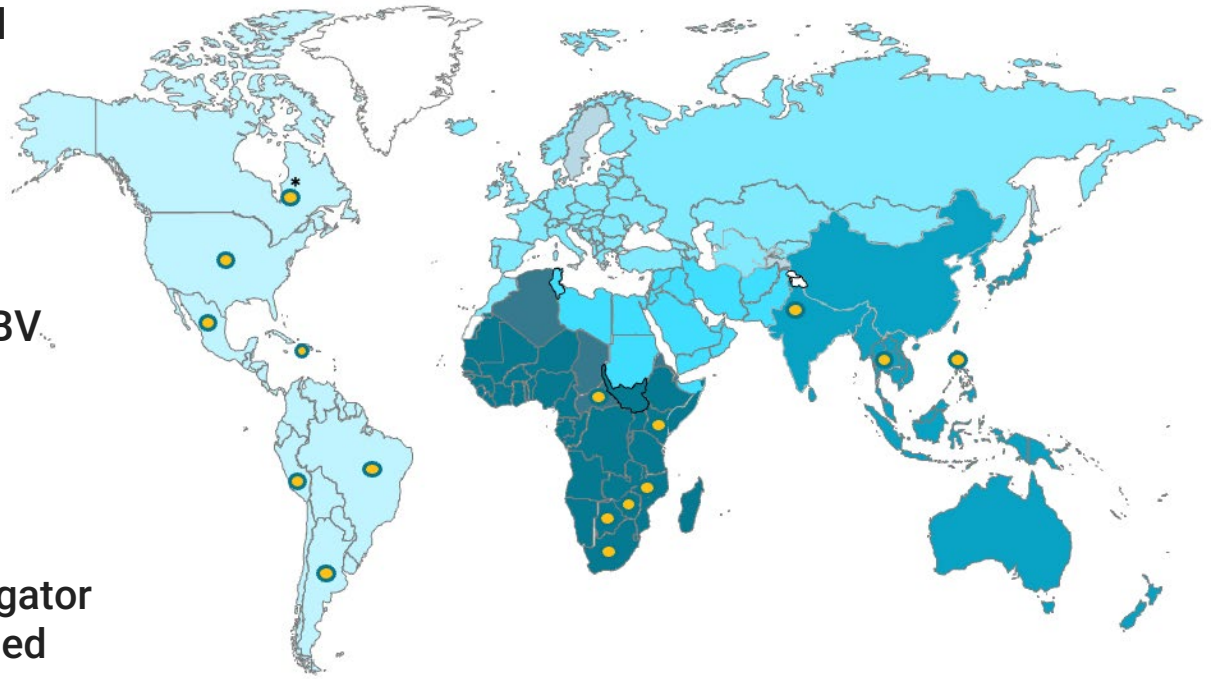
Additional Slides

HBV Clinical Trial Engagement: Results of Spring 2022 Site Survey 46% Respondents non-US

83% Ever Conducted HBV studies

89% Interested in HBV Studies

82% Investigator Identified



10-100+

Range of no. of participants at site with HIV/ HBV or HBV monoinfection

35 responses, 16 non-US

ACTG's unique opportunity to contribute to HBV cure research

- **Patient population**

  HIV co-infection

  Partnership with international sites including South America, Africa, Asia
- **History of collaboration with multiple companies**
- **Development and mentorship of junior and/or ex-US researchers**
- **Translational research**

  Parallels to HIV cure agenda
- **Behavioral sciences**

  Acceptability of cure research, patient-related barriers
- **Community engagement**

HBV Cure Questions in Observational Cohorts:
Determinants and Predictors of HBV Cure

What are biological determinants of HBV functional cure?

- Demographic, sociocultural, behavioral, diet (e.g., aflatoxin)
- Comorbidities (metabolic), coinfections (HDV, schisto)
- Viral (HBV genotype, HBV DNA, HIV RNA)
- Genetics, adaptive/innate immunity

How do these determinants differ in people with HIV?

What factors predict cure with current, new HBV therapies?

- Above factors + biomarkers? How differ in people with HIV?

Hepatitis Flares in HIV-HBV coinfected patients starting HBV active HAART (TICO trial substudy)

- TICO Trial substudy:
- 36 antiretroviral naïve HIV/HBV in Thailand randomized to receive:
  - TDF vs LAM vs TDF + LAM as part of an Efavirenz-based HAART
  - 8 (22%) cases with Hepatic Flares (ALT > 5 X ULN or > 200 within 12 weeks) → 1 died from LF (3%)
  - Predictors of flares:
    - High HBV DNA
    - High ALT
    - Low CD4
  - Pathogenesis of flares: Probable Immune Restoration Disease by cytokine substudy:
    - T cell and NK activation markers ↑↑↑
    - Markers of IFNγ induction (IL-18) and activity (MCP-1) ↑↑↑

Crane et al *Hepatology* 2009, *JID* 2009.

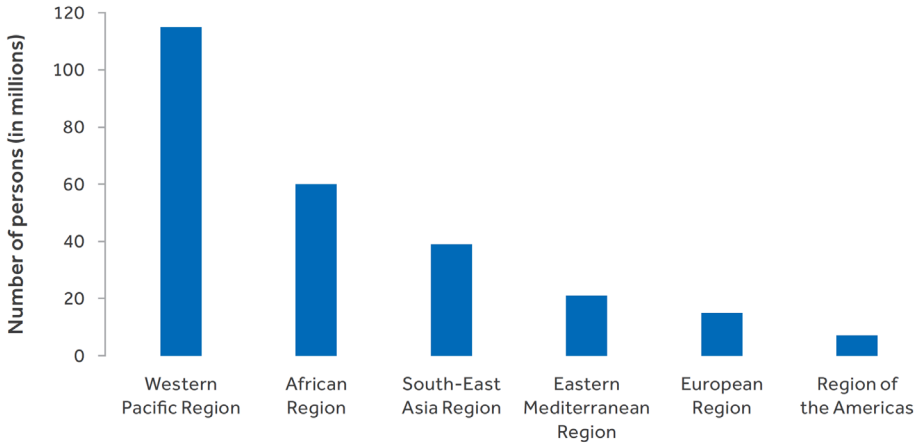
Opportunities and Challenges

- IRB
  - Novel agents, procedures (FNA, liver biopsy, leukapheresis, PBMCs)
- Other regulatory
- Pharma-specific- Drug Labeling, Importation?
- Site Activation, Lab Activation
  - MTAs, other issues?
- Recruitment-
  - Where are you recruiting from?
  - Engagement with community?
  - Screening HBsAg?

Global Status of HBV Infection

- 2015--257 million people living with chronic HBV infection;
  - 68% in African and Western Pacific regions
- **7.4% of persons with HIV also have HBV coinfection (2.7 million persons)**
- Hepatocellular cancer (HCC) is 3rd most common cause cancer mortality globally
  - HBV → 40% of liver cancers

HBsAg Prevalence in General Population



WHO Global Hepatitis Report. 2017, GBD Report 2016.

Critical Differences Between HIV and HBV

HIV	HBV
No successful immune response that results in HIV clearance	Successful immune response which results in HBV clearance in some patients
Latent Phase During Replication	No Latent Phase During Replication
No Vaccine	Effective Vaccine
HIV template is integrated provirus	HBV DNA template is cccDNA episome

Functional Cure May Be More Attainable with HBV

HBV Virologic Failure

- Meta-analysis of 23 studies (550 HBV/HIV coinfected) with follow-up of 3 years
- Overall proportion of HBV DNA suppression was
  - 57.4% at one year
  - 79.0% at two years
  - 85.6% at three years
- Notably, HBV virologic failure occurs despite ND HIV viral loads

Price PLOS One 2013, Boyd Hepatology 2014