WORKSHOP ON DEVELOPMENT OF LONG-ACTING TREATMENTS FOR PERSONS WITH HEPATITIS B

Los Angeles, California
MARCH 18, 2025

leap Long-Acting/Extended Release Antiretroviral Research Resource Program

ABBREVIATIONS

AAASLD American Association for the Study of Liver Diseases
ADV Adefovir
API Active pharmaceutical ingredient
ART Antiretroviral therapy
ARV Antiretroviral
AUC Area under the curve
bis-DHA ETV bis–docosahexaenoic acid entecavir
BMS Bristol Myers Squibb
cccDNA covalently closed circular DNA
CHAI Clinton Health Access Initiative
CHB Chronic hepatitis B
DAA Direct-acting antiviral
DAIDS Division of AIDS (NIH)
DcNP Drug combination nanoparticles
DLD Decompensated liver disease
DDI Drug-drug interaction
DPV Dapivirine
EASL European Association for the Study of the Liver
EDL Essential diagnostics list
ETV Entecavir
EMA or **EMEA** European medicines agency
EML Essential medicines list
ER Extended release
FDA Food and Drug Administration
G/P Glecaprevir/pibrentasvir
HBIG Hepatitis B immune globulin
HepB BD Hepatitis B birth dose
HCC Hepatocellular carcinoma
HCV Hepatitis C virus
HDV Hepatitis delta virus
HIV Human immunodeficiency virus
BsAg Hepatitis B surface antigen
HIC High-income country
HBF Hepatitis B Foundation
IP Intellectual property
ISL Islatrovir
JHU Johns Hopkins University
LA Long-acting
LAI Long-acting injectable
3TC Lamivudine
LEAP Long-acting extended release antiretroviral research program
LMIC Low-middle income country
mAbs Monoclonal antibodies
MPP Medicines patent pool
NA Nucleos(t)ide analog
NHP Non-human primate
NIH National Institutes of Health
PBM Pharmacy benefit manager
PD Pharmacodynamics
PEPFAR President's Emergency Plan for AIDS Relief
PK Pharmacokinetics
PLWHB People living with hepatitis B
PMTCT Prevention of mother-to-child transmission
PPB Plasma protein binding
PQ Prequalification
PrEP Pre-exposure prophylaxis
SC Subcutaneous
SOF Sofosbuvir
TAF Tenofovir alafenamide
TAP Target access profile
TDF Tenofovir disoproxil fumarate
TFV Tenofovir
TLC-ART Targeted long-acting and combination antiretroviral therapy
TLD Tenofovir, lamivudine, and dolutegravir
TLE Tenofovir, lamivudine, efavirenz
TPP Target product profile
U=U Undetectable = untransmittable
WHO World Health Organization
3TC Lamivudine

CONTENT

Where will we LEAP next?

On March 18, 2025, the Long-Acting Hepatitis B Workshop brought together clinicians, researchers, regulatory experts, investors, and business leaders to explore the potential for long-acting therapies to transform hepatitis B treatment. Through a series of expert panels and discussions, participants considered the clinical need, regulatory pathways, business models, and investment strategies critical to advancing the field. The Workshop served as a forum to connect scientific innovation with commercial opportunity, drawing lessons from the success of long-acting therapies in HIV, contraception, and other areas. The Workshop featured keynote overviews, summaries of existing preclinical work, two expert panel discussions, and an investor roundtable. This report summarizes session presentations and major themes from the open discussions.

SESSION 1

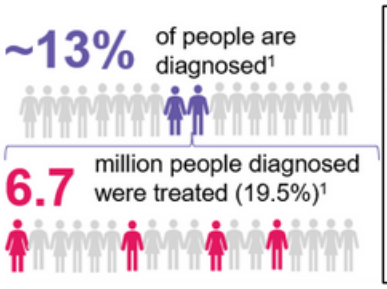
PUBLIC HEALTH & MEDICAL IMPERATIVE FOR LONG-ACTING HBV TREATMENTS

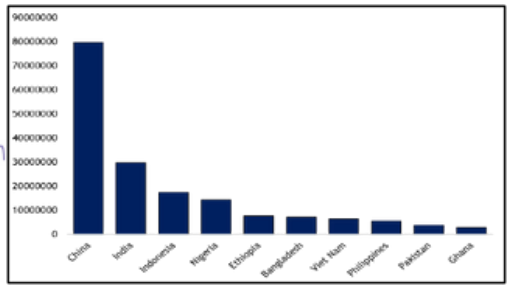
Olufunmilayo Lesi

Team Lead, Global Hepatitis Programme, WHO (Switzerland)

"Public Health and Medical Imperative for Long-Acting HBV Treatments: Global Public Health Significance"

"Hepatitis B elimination is a public-health priority – but progress has been too slow. Long-acting therapies may finally catalyze the momentum we need."





Current CHB Antiviral Therapies

Parameter	NA therapy (since 2008)	peg-IFNα (since 1995)
HBV DNA suppression	Significant	Moderate
HBsAg suppression	Minimal	Moderate
Impact on cccDNA and integrated HBV DNA	Insufficient (potential impact on integrated HBV DNA with long-term NA therapy)	Insufficient (potential impact on cccDNA)
Immune activation	No	Yes
Clinical impact	• Can lead to decreased liver inflammation • Can reverse liver fibrosis and decrease risk of cirrhosis, HCC, liver-related death	
Tolerability	Generally well tolerated	Side effects and multiple contraindications limit its use
Duration of treatment	Long-term therapy (10+ years) for most patients globally	48-96 weeks
Limitations	• Relapse typical after discontinuation • Residual risk of liver-related complications	• Sustained decrease in HBV DNA in only 20-25% patients

Global Burden of CHB

- 254 million people worldwide living with CHB infection (2022 data)
- 1.5 million new infections/year
- 820,000 deaths annually from cirrhosis and HCC
- 15-40 % untreated develop cirrhosis, liver failure, or HCC
- 10 countries: 2/3 of global burden (Stockdale et al., J Hepatol 2020)
- 12 million people have HDV co-infection (globally under-monitored)
- New HCC cases projected to rise > 50 % by 2040 (Rumgay et al., J Hepatol 2022)

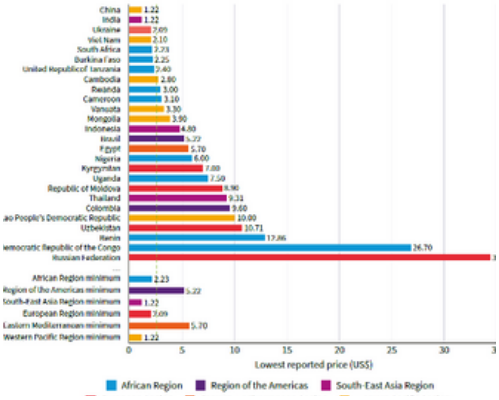
Impact model: 2.85 million lives saved + 2.1 million cancers averted if targets met by 2030

Barriers Despite Available Generic Treatment for Effective Control

- Variable cost and access to HBV diagnostics
- High out-of-pocket expenses
- Inadequate policy, funding, lack of awareness

2024 Expanded WHO Treatment Guidelines

- National guidelines, strategies, and plans
- Financing and pricing
- Product inclusion in national EML, EDL
- Product registration
- IP
- Decentralized product availability
- Procurement and supply
- Local production
- Expanded eligibility for treatment (from 8-15 % → > 50 %), earlier treatment
- Increase HBsAg capture
- Applicable to all settings (with/without DNA facilities)
- Addresses children & pregnant women
- Importance of HDV testing



Lowest reported monthly treatment price of TDF 200mg (30 tablets), WHO-focus countries for viral hepatitis response, 2023

Four Urgent Actions to Restore Momentum

(1) Scale up testing + treatment to reduce mortality
(2) Reduce disease incidence, including HepB BD
(3) Increase access to affordable drugs and diagnostics
(4) Strengthen country surveillance including mortality tracking and outcomes

Case Studies

China: New guidelines treat all adults with detectable DNA; > 20 M people to start treatment by 2028

Malawi: > 1 M pregnant women screened for HBV since 2023; universal TDF prophylaxis ongoing

Looking Ahead – The Promise of Long-Acting Therapies

- Improved adherence, reduced pill burden
- Lower resistance risk, health-system costs
- Reduced transmission, stigma (especially for PMTCT)
- Simplified service delivery

Key Takeaways

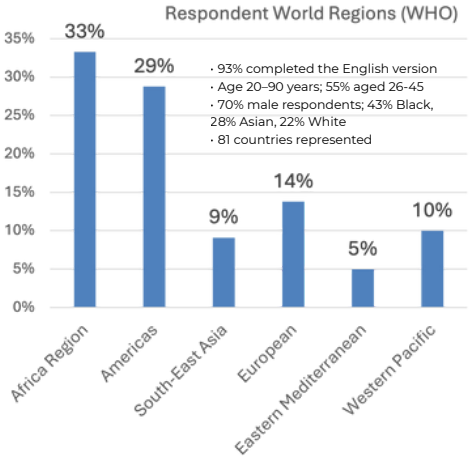
- CHB remains a major public-health priority
- Treatment scale-up critical for population-level impact
- Long-acting formulations can address adherence and access gaps
- Advocacy and multi-sector partnerships are key

Chari Cohen

President, Hepatitis B Foundation

"Perspectives of People Living with Hepatitis B on Long-Acting Treatments"

"This was our first effort to hear directly from people living with hepatitis B about their views on long-acting treatment."



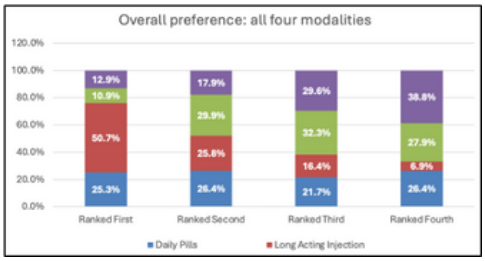
First Global Survey of PLWHB

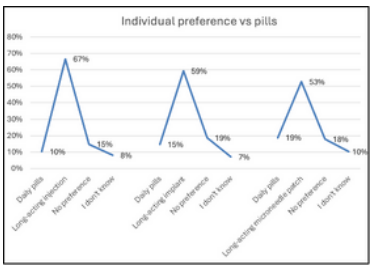
- Mixed-methods, IRB-approved (global quantitative survey + planned follow-up focus groups), closed in early 2025
- Likert survey of 49 questions across four domains (16 weeks via Qualtrics): demographics, treatment experience, challenges with daily therapy, and preferences for three long-acting delivery routes – injectables, implants, microneedle patches
- Developed collaboratively with clinicians, behavioral scientists, patient advocates to ensure cultural accuracy and plain-language accessibility
- Available in five languages (English, Spanish, Mandarin, Arabic, and Tagalog)
- Recruitment through Hepatitis B Foundation networks, global listservs, newsletters, and social media
- Eligible participants were adults ≥18 years self-reporting CHB

Current Treatment Experience

- 29% diagnosed within 5 years; 66% in clinical care; 54% currently taking medication, mostly first-line antivirals (TDF)
- 43% reported embarrassment filling prescriptions; 58% worried about being stigmatized for taking pills
- Reported challenges:
  - o Cost (15%)
  - o Psychological burden/daily reminder (15%)
  - o Remembering doses (13%)
  - o Side effects (11%)
- Adherence high overall: 70% rarely or never missed doses, but 13% missed >1/week, often due to busyness, forgetting, or out-of-stock at pharmacy

"More than half [of respondents] said they would be willing to receive an implant if it worked as well as pills."





LA Formulation Preferences

LA type	Prior experience?	Willing to take if same efficacy?	Duration/ Frequency	Join Clinical Trial?	Pros	Cons
Injection	47% (excluding vaccines)	81% (75% would self-inject)	6-month most preferred	68% yes	Fewer side effects, improved efficacy, freedom from daily reminders, and privacy	Possible reduced efficacy, side effects, clinic visits, pain (fear of injections low)
Implant	10%	55% (54% prefer biodegradable self-dissolve)	6-12 months	47% yes	—	Pain/discomfort, visibility, the need for insertion/removal (stigma)
Microneedle Patch	—	50%	—	47% yes	—	Effectiveness, side effects, visibility, skin irritation

Next Steps

- Correlational analyses by region, age, treatment status
- Compare with prior HIV/HCV studies
- Assess specific perspectives in more depth, language-specific differences, feedback
- Consider more surveys, focus groups

Jordan Feld

Professor of Medicine, R. Phelan Chair in Translational Liver Disease Research, Toronto Centre for Liver Disease, University of Toronto

"Long-acting HBV Treatment Target Product Profile – Medical Perspective"

"Long-acting therapy [is] … an important parallel track to pursue – not an alternative one."

TPP

- LA injection
- ETV or TFV (TAF > TDF)
- Dosing interval >3 months

Regional Considerations

Economic Status	Implementation Considerations
HIC	To address preferences including avoiding daily pill fatigue, stigma ; limited pharmacy access (rural or institutional environments)
LMIC	Simplified "test and treat" approaches, potentially essential for meeting WHO elimination goals

Clinical Opportunities for LA Therapy

- CHB infection (primary): improve adherence + reduce stigma (HIV experience suggests ≥3-6-month dosing optimal for uptake)
- Perinatal prevention where access to HepB BD or HBIG is limited
- Immunosuppression: prevent HBV reactivation in patients receiving chemotherapy or biologics (HBsAg+ or anti-HBc+)
- Complicated regimens and co-infection (HIV, HDV): "one-and-done" HBV injection for durable protection during other antiviral treatments
- Immune-tolerant individuals (younger) with high viral loads but minimal liver damage who are reluctant to start lifelong pills (LA therapy could improve adherence, reduce transmission, maintain suppression)
- Post-transplant recipients: Important for people receiving HBV core antibody-positive donor organs where reactivation risk is high
- Low-risk/minimal drug reactions, except bone and kidney toxicity (TAF/TDF prolonged systemic exposure), teratogenicity/weak HIV activity (ETV)

CHB Cure Regimens?

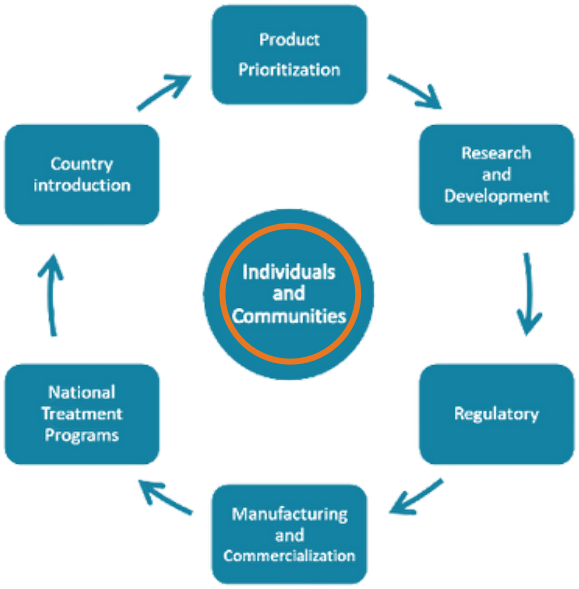
- Combination strategies essential to future curative regimens (siRNA, cccDNA-targeting/editing, mAbs/other immunotherapies)
- Diverse pharmacological properties, mechanisms of action may complicate LA formulations (TAF may be best backbone)
- Supplemental preventive use (HBV PrEP): could protect vaccine non-responders and unvaccinated close contacts (pending further safety and acceptability studies, not clear if U=U will apply)

Paul Domanico

Global Health Research Fellow,
Clinton Health Access Initiative

"Considerations for Catalyzing a Long-Acting HBV Treatment Market"

"The bar should be high; "good enough" won't do."



1 Patients and caregivers Community Advisory Boards Civil society	Patient-centered care. Equity. "Nothing for us without us"
2 WHO committees. Ministry and National Treatment Programs. WHO and national guidelines	Priorities. TPP & TRP. Addressable markets.
3 Academia, governments Clinical trials networks Pharma: innovator/generic	Drugs / Regimens Evidence
4 WHO PQ, SRAs, NRAs	Clinical Evidence. Quality-assurance
4 Pharma: innovator/generic Public:Private Partnerships	Market strategies: Products licensed, developed, scaled, distributed, & optimally priced.
6 Local and Regional KOLs. Healthcare and Community HC workers	Real-world evidence Awareness. System strengthening. Training
7 Ministries. Guideline committees. Procurement agencies	Patient-centered care. Equity. Roll-out & monitoring strategies. Access pricing.

"We cannot rely on TDF-like workhorses forever; they are a foot in the door."

Patient-Centered Product Principles

- Market size is very different from (much larger than) target market, addressable market (10 countries with 70% HBV burden), or actual market
- Lived experience must anchor both TAP and TPP
- Enormous care population – LA HBV treatment formulations must be safe, simple, scalable
- 6-month minimum dosing

What's Needed to Transform Care?

- Safety + efficacy across comorbidities, populations, lifespan
- Work alongside existing care touchpoints
- Overcome testing hurdles

	2020	2022	2030 targets
Diagnosed*	10%	13.4%	90%
Treated*	2%	2.6%	80%
Deaths	0.82 million	1.10 million	310,000
New infections	1.5 million	1.23 million	170,000
* % Global Burden			

Key Takeaways

- HBV LA market could eventually rival the HIV LA market if products are cost-effective for ministries, transformational for patients, and profitable enough for manufacturers
- >6-month dosing key threshold for a viable long-acting HBV product
- Success depends on clarity of goals, patient-centered design, early alignment among governments, donors, industry
- Sustainable market must balance transformation + feasibility: creating drugs transformational enough to change care while realistic enough to scale

Arnab Chatterjee

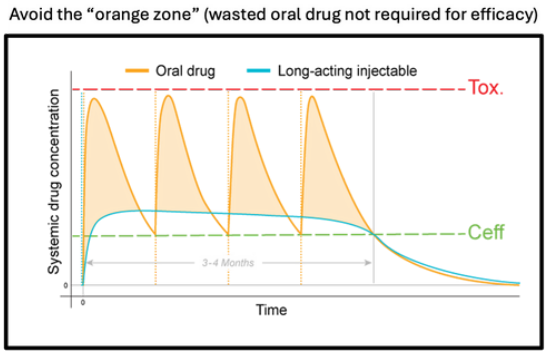
Vice President, Medicinal Chemistry, Calibr-Skaggs Institute for Innovative Medicines

"ETV Prodrug for LAI"

"Our guiding principles are to use excipients and formulation systems already approved for injectables, minimizing regulatory risk and ensuring wide availability."

Calibr-Skaggs Institute

- Independent 501(c)(3) translational research institute within Scripps Research
- Focuses on bridging the valley of death between preclinical discovery and clinical development
- ~ 35% of portfolio supports global health initiatives in partnership with AbbVie, Merck, Gilead, the Gates Foundation, and Medicines for Malaria Venture



Calibr's LA Platform

· Advanced 14 novel drugs > clinic, including several LAIs for HIV, malaria, TB

· Links synthetic chemistry, excipient design, formulation engineering – cross-disciplinary model uncommon in industry but key to affordable innovation

· Target a production cost of < $1 per month of coverage

· Simple ester modifications + oil-based depot formulations: oral agents > LAIs

ETV Prodrug Development

· ETV is an excellent anchor for HBV therapy due to its potency (IC_{50} ≈ 0.5 nM), low clearance, low protein binding

· Problem: Parent ETV's high melting point (~298 °C) + rapid clearance

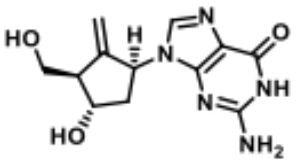
· Solution: Synthesize > 30 ETV prodrugs (esters and carbonates) to optimize solubility and release kinetics

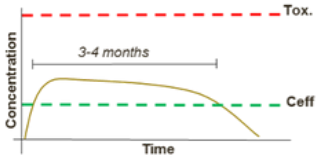
Success Stories

Malaria: LA atovaquone (MMV371) prodrug achieved > 2 months of coverage in rats

HIV: LA islatravir (GS-1614) prodrug extended antiviral exposure from days to 3-6 months (now in clinical trials with Gilead)

Calibr LAI Workflow





0.5 nM IC50, low PPB (13%), low clearance;100 x more potent > 3TC & ADV

Product Development Pathways

· Develop prodrugs or enhanced formulations of existing chemical matter, in some cases enabling accelerated registration via the FDA 505(b)(2) regulatory pathways

· Generate novel chemical matter, obtaining patent protection and freedom to operate through combination of formulations, novel chemical structures

ETV Pro-Drug Candidate	Modifications/Properties	Features
CBR109	SAIB vehicle	Extended exposure, flatter PK curve (rats)
CBR261	castor oil solute	Improved solubility, longer plasma persistence
CBR540	bis-DHA ETV (long-chain omega-3 fatty acid diester)	Multi-week coverage, low C_{max} (therapeutic levels maintained > 1 month)

Marc Baum

President & Senior Faculty Member,
Oak Crest Institute of Science

TAF & Other Implants

"We achieved our primary objectives: the trial demonstrated the first ultra-long-acting, single-application HIV prevention product to sustain drug release for up to one year in humans."

Preclinical Data

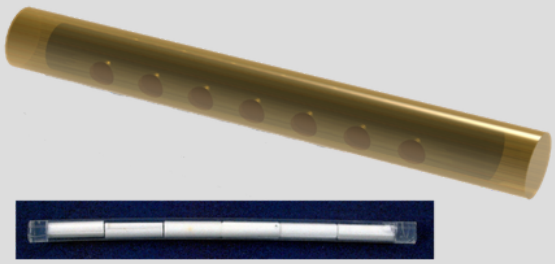
• Good local tolerance across species at <1 mg/day TAF; variability in release rates highlights the need for better predictive models
• High apparent bioavailability suggests efficient delivery; supports a target dose of 0.25 mg/day, unprecedented among ARVs

- Gunawardana et al. Front Pharmacol 2020
- Gunawardana et al., Sci Rep 2022
- Gunawardana et al., Pharm Res 2022

CAPRISA Trial (South Africa)

• First-in-human trial evaluated safety, acceptability, and pharmacokinetics of the Oak Crest TAF implant in women (Gengiah et al., BMJ Open 2022)
• 48 weeks; randomized 4:1 active vs. placebo with either one or two implants per participant
• Single implants: Generally well tolerated; 2/3 completed 48 weeks
• PK modeling validated < 0.5 mg/day should maintain protective intracellular TFV-DP levels

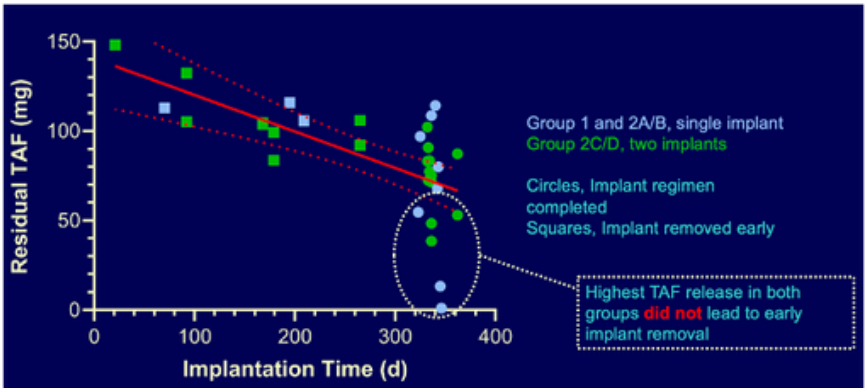
Oak Crest Silicone Reservoir-type Implant



Gunawardana et al., AAC 2015

TAF Implant Design

• Cylindrical rod (40 mm × 2.5 mm for human use) made from medical-grade materials
• Controlled drug release occurs through precisely engineered orifices, rather than diffusion
• Loaded with compacted microtablets of nearly pure TAF with trace lubricant



Benson Edagwa

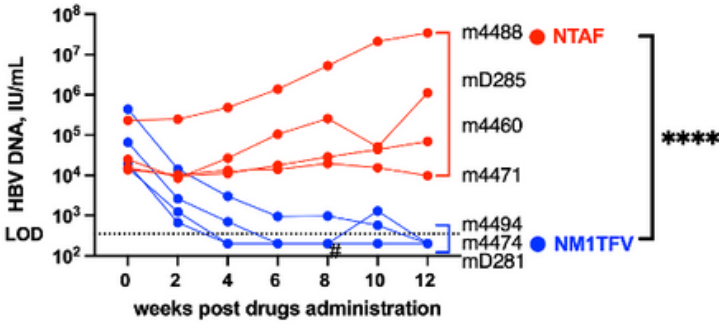
Professor, University of Nebraska Medical Center
Community Pride of Nebraska

"Long-Acting Tenofovir Prodrug Formulations"

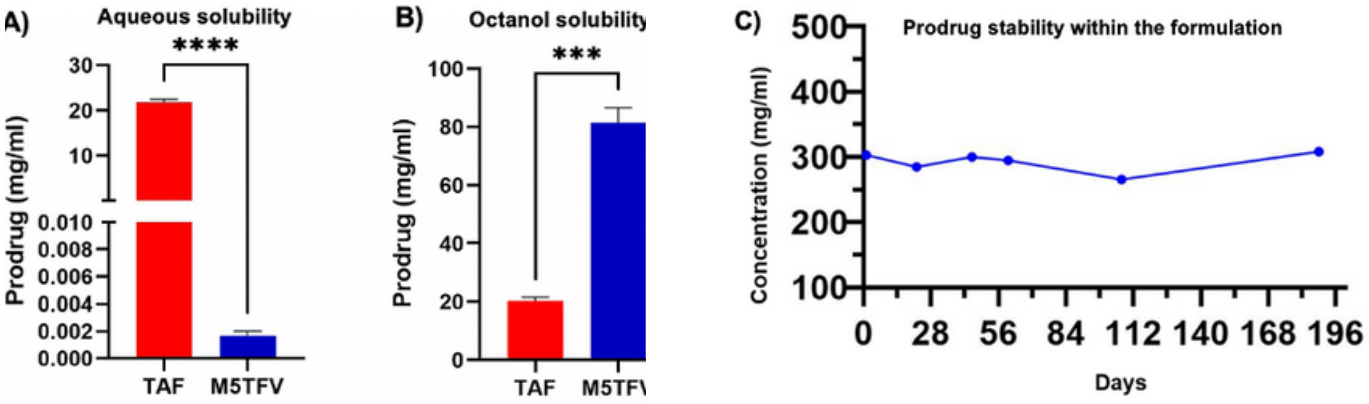
"While TAF works well orally, it is not ideal for long-acting depot-based applications.".

Limitations of TAF & Design Rationale

- TAF has fewer toxicities than TDF but is less stable and has reactive breakdown products
- Chemical redesign targeted non-ionizable, stable analogs to eliminate intermediates causing local irritation
- Aligns with the WHO 2030 elimination goals by addressing adherence, access, and affordability



M1TFV: first-generation prodrug achieved complete HBV DNA suppression for up to 3 months in humanized liver mouse models; healthy hepatocyte engraftment



M5TFV: second-generation pro-drug engineered for simpler synthesis, lower cost, greater chemical stability; predicted 2 years stability at room temperature; equivalent antiviral potency and durability to M1T

Rodney Ho

Professor of Pharmaceutics,
University of Washington
Director, TLC-ART Program

"Long-Acting Tenofovir for People with Hepatitis B"

"LA TAF and TLD formulations may finally offer a scalable, durable, and practical solution for treating and preventing both HIV and hepatitis B worldwide."

Platform and Product Pipeline

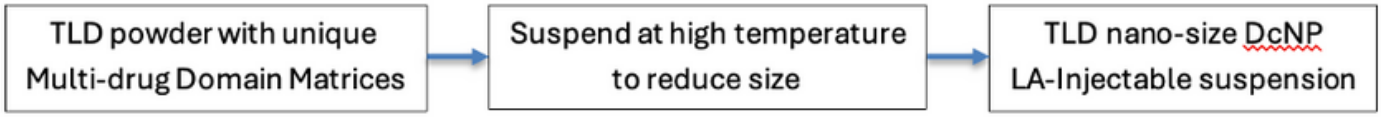
Drug combination nanoparticle technology (DcNP) co-formulates otherwise incompatible active compounds using lipid excipients.

Global Outlook

- HBV co-infection affects 5-10% of people with HIV; current LA HIV regimens lack HBV coverage
- LA single SC injection could replace ~30 pills/month

TLC-ART Program

- NIH- and UNITAID-supported initiative developing LA TFV-based formulations for HIV and HBV
- Began with LA HIV therapy, adapted for HBV where burden is greatest
- Once-monthly dosing appears feasible for TFV + 3TC + DTG (NHP data); regulatory success could enable longer intervals
- Need to consider PK and PD in context of decompensated liver disease (DLD)
- Partnerships with generic drug makers could ensure a steady, affordable supply of TFV + prodrugs



Perazzolo et al., AIDS 2023

Product	Propose Treatment Indication	Research	Preclinical	IND-ES	Clinical
	HIV Treatment				
TLC-ART 101	Long-acting HIV treatment	■	■	■	■
TLC-ART 301	Long-acting HIV treatment	■	■	■	
TLC-ART 302	Long-acting HIV treatment	■	■		
TLC-ART 201	Long-acting HIV treatment	■			
	HBV Treatment				
TLC-ART 303	Long-acting HBV treatment	■			

- HIV-HBV co-infection: TLC-ART 301 (next-gen LA TLD (TFV + 3TC + DTG)); achieved monthly dosing (NHP data))
- CHB: TLC-ART 303 (TFV/TAF-only product; favorable PK; no injection-site reactions (NHP data))

David Thomas
Professor of Medicine, JHU

Paul Domanico
Global Health Research Fellow, CHAI

"Regulatory Considerations for Long-acting HBV Treatments"

"LA HBV drugs have the potential to transform global implementation of HBV treatment strategies."

- Both FDA and EMA recognize the transformative potential of LA HBV delivery systems, but emphasize data-driven dosing, safety, PK profiles
- Two FDA HBV development pathways: chronic suppression or finite therapy (FDA 2022: Chronic HBV infection: developing drugs for treatment - guidance for industry)

Practical Clinical Development Strategies

Leverage prior safety and efficacy data, potentially allowing for accelerated or equivalence-based regulatory review:

- LA formulation of an existing approved drug
- Conversion of an existing prodrug into an LA version

FDA CHB Drug Guidelines for Industry

Regulatory Considerations

Equivalence	Establish exposure-response data to extrapolate LA efficacy, PK, PD, Cmin (or AUC) focus for dosing, personal and cultural preferences
Safety	Local + systemic toxicity (drug + non-drug components), drug-drug interactions, chronic vs curative, monitor Cmax and transition to oral when needed, special populations (pregnancy)
Impact	Balance efficacy with ease of use, model public health outcomes


Mila Maistat Lobna Gaayeb

Policy and Advocacy Manager Head of Scientific & Medical Affairs

Medicines Patent Pool

"Access to Viral Hepatitis Treatments in LMIC Through Access-oriented Voluntary Licensing"

"Expanding timely generic entry is central to access."

Why Generics?

- Most essential medicines are patented
- Only originator versions exist until patent expiry
- Prices remain high
- No or limited access in LMICs
- Public health voluntary licenses enable generic entry for viral hepatitis medicines

MedsPal.org

MEDICINE	BRAND NAME	PATENT EXPIRY MAIN PATENT (SECONDARY PATENTS)
Tenofovir disoproxil fumarate (TDF)	Viread ®	2017 (2018)
Tenofovir alafenamide (TAF)	Vemlidy ®	2032
Daclatasvir	Daklinza®	2027 (2030)
Sofosbuvir	Sovaldi ®	2024 (2028/2032)
Sofosbuvir/ledipasvir	Harvoni ®	2030 (2033)
Sofosbuvir/velpatasvir	Epclusa®	2031 (2034)
Glecaprevir/pibrentasvir	Maviret ®	2031 (2035)
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi ®	2033 (2034)

MPP – Voluntary Licenses & Tech Transfer

- Created by Unitaid in 2010: negotiates non-exclusive voluntary licenses with patent holders to expand access to essential medicines in LMICs
- Model ensures competition, technology transfer, quality through WHO prequalification + stringent regulatory approval
- Royalties paid by generic manufacturers to patent holders; MPP takes no royalties
- Partnerships span HIV, viral hepatitis, TB, COVID-19, LA therapeutics, several noncommunicable diseases
- More than 40 billion doses have been supplied under MPP licenses to 148 countries

Nearly $2 billion in health system savings have been estimated from MPP-enabled procurement

Availability of Generic HBV and HCV Treatments

Parameter	HBV Access	HCV Access
Drugs	ETV, TFV, TDF, TAF	DAC, DAC/SOF, G/P
Patent Status	ETV, TDF now off-patent globally	DAC patents withdrawn by BMS; AbbVie G/P licensed royalty-free
Licensing Partners	Gilead (for TDF, TAF) via MPP license	BMS (DAC, DAC/SOF); AbbVie (G/P) via MPP licenses
Countries Covered	TAF license covers 117 countries	DAC and DAC/SOF supplied to 38-48 countries; G/P license covers 96 countries
Manufacturers	Multiple sublicensees (e.g., Laurus, Lupin) with stringent regulatory approvals	Multiple generic producers under MPP and WHO PQ frameworks
Supply Volume	~3 million packs of TAF 25 mg supplied to 18 countries (11 LMICs, 7 UICs)	4.8 million packs DAC (~1.6 million treatments) and 517,000 packs DAC/SOF (~172,000 treatments)
Price Benchmarks	Generic TDF available for < $30 per patient-year via public procurement	WHO benchmark for DAC/SOF: ~ $60 for 12-week course
Program Impact	MPP-Gilead license enabled rapid manufacturer entry, lower prices, and secure supply	Generic competition lowered DAA prices, expanded access across LMICs
Regulatory / Quality	WHO PQ and stringent regulatory approvals ensure quality	WHO PQ for first generic G/P (2022); others in development
Therapeutic Guidance	Core antivirals for HBV management and prevention	G/P: pan-genotypic, WHO/AASLD/EASL-recommended 8-week regimen, safe in renal impairment

Looking Ahead

- LA frontier presents new opportunities for equitable access
- MPP holds non-exclusive worldwide licenses with Tandem Nano for LA G/P and with the University of Washington for long-acting TLD (first LAI HBV candidate subject to a public-health oriented voluntary license)

Key Takeaways

- Generic access in LMICs essential to reach elimination goals; treatments otherwise unaffordable
- Quality-assured generics for HBV and HCV available in most LMICs through MPP and bilateral licenses
- Affordable drugs alone not enough; access and delivery systems crucial
- Treatment uptake remains low in many LMICs due to weak programs, limited funding, no screening, and costly diagnostics
- Unclear demand discourages generic manufacturers from investing or scaling production
- Availability of low-cost generics helps governments plan and launch national treatment programs
- Oral G/P for HCV offers a major opportunity for LMICs, especially in genotype 3 regions; long-acting G/P could be transformative

Charles Flexner

Professor of Medicine, JHU

Overcoming Roadblocks to the Development of LA-HBV Formulations: Lessons from HIV Drug Development"

Historically, nearly every successful global health intervention – from contraceptive implants to antivirals – has had commercial-sector origins or partnerships."

HIV therapy began as a high-income market product but now reaches most people in LMICs through generic licensing, partnerships, and political will.

Three Hollywood-Inspired Models for LA Antiviral Drug Development

Model	Description	Key Lesson for HBV
Do the Right Thing	The one-pill, once-daily TLD (TDF + 3TC + DTG) regimen transformed HIV treatment: an expensive U.S. product (~$27K/year) became affordable in LMICs (~$74/year) through generic licensing and PPPs	Global access succeeds when licensing and affordability align with ethical leadership (PEPFAR)
Lassie Come Home	Merck's veterinary anti-parasitic ivermectin (still in widespread veterinary use) funded eradication of river blindness in humans	Dual-market or cross-subsidy models could make HBV drug access sustainable
Field of Dreams	The DPV vaginal ring – developed entirely by nonprofits – saw minimal uptake despite approvals, showing the limits of purely nonprofit development	Partnership with commercial sectors is essential to achieve scale and sustainability

Key Takeaways

- Profitable high-income market can sustain affordable access in LMICs
- Dual-indication drugs (HIV + HBV) may expand markets + strengthen investment incentives
- Global partnerships (public, private, and philanthropic) are essential for translation, scale
- Aligning ethics, economics, and practicality is key to sustainable access: "If we build it wisely, they really will come."

SESSION 4 PANEL DISCUSSION ON LA HBV TREATMENTS

The Investment Case for Long-Acting HBV Treatments

The session explored economic and strategic realities affecting LA HBV development. Discussion centered on balancing ultra-low generic oral prices with the promise of improved adherence, reduced stigma, and reactivation prevention. Panelists agreed that payer and investor confidence depends on demonstrating measurable outcomes – such as higher rates of durable suppression or reduced HCC risk – rather than convenience alone. Other themes included IP and patent timing, viable entry pathways through niche indications or HIV-first strategies, and the need for voluntary licensing and public-private partnerships to enable access in LMICs. The consensus: long-acting HBV will advance only with a clear value proposition, credible evidence base, and a scalable delivery model.

What is the ultimate clinical goal for long-acting HBV drugs – functional cure, sterilizing cure, or sustained control?"

What Problem will LA HBV Actually Solve?

- Convenience alone will not drive adoption or investment
  - Persistent stigma from daily pills and infection visibility
  - Inconsistent adherence, especially in HIV/HBV co-infection
  - Reactivation risk during immunosuppression + cancer chemotherapy
- Need a consistent, LA suppressive therapy that can act as the antiviral backbone within finite (defined endpoint), combination-cure regimens

How Can Value Be Demonstrated?

- Regulators may approve based on virologic endpoints, but payers demand proof that deeper or more durable suppression reduces clinical events like HCC or cirrhosis, or at least a credible modeled scenario
- LA HBV therapies prove their value if they help difficult-to-treat patients achieve and maintain viral suppression (no detectable HBV DNA), show fewer viral blips over time, prevent HBV reactivation during immune suppression

How Do Price Realities Shape Strategy?

- LA HBV therapy cannot be priced like U.S. TAF to achieve widespread adoption – the economics simply don't fit the size of the global HBV population
- U.S. generics (TDF, ETV) ≈ $100/year
- Premium pricing requires clear value or niche differentiation
- Because pharmacy benefit managers (PBMs) favor high-rebate products and payers demand measurable outcome benefit, pricing leverage for new HBV therapies is limited

What Are the Lowest-Risk Entry Paths?

- Preventing HBV reactivation in patients receiving immunosuppressive or chemotherapy treatments
- Target HBeAg+ partial responders + HIV/HBV coinfection
- HIV-first route: integrate LA TDF in HIV combos, then extend to HBV
- Apply LA NAs as suppressive backbones for finite curative regimens (siRNA/ASO, checkpoint inhibitors or T-cell–based immunotherapies under exploration for functional cure)

"The big question is demonstrating value over cheap, safe, resistance-free generic nukes."

Remaining Challenges

Scientific feasibility vs. market reality	• LA HBV formulations technically achievable: chemistry, formulation, but delivery advances have outpaced commercial incentives • Economic case remains bottleneck in high-income markets, where oral generics cost about $100/year • New products must demonstrate measurable clinical or operational advantages, not just convenience, to gain reimbursement or investor support
Delivery infrastructure in LMICs	• ~ 70% of global HBV burden in LMICs • Delivery capacity + program funding are rate-limiting steps • Products must meet real-world delivery needs
Patient value is real but rarely reimbursed	• LA options could reduce stigma + daily reminders of disease, improving adherence and quality of life • Yet quality-of-life and reduced stigma relief rarely translate into reimbursement unless tied to measurable health outcomes

Design Features for Adoption

- ≥6-month dosing optimal; shorter intervals add limited value
- Weekly/monthly LA orals may reduce stigma and improve adherence
- Optimal features: low risk of DDIs, safe for use in pregnancy and adolescents, easy to administer in primary-care settings, stable at room temperature to enable delivery in LMIC

IP Insights

- Long-term business case for LA HBV depends heavily on patent and exclusivity strategy
- Base TAF patent (chemical structure) limits direct competition, but new patents for LA delivery methods (LAIs or implants) can extend exclusivity and make the R&D investment worthwhile
- LA combinations: Pairing a known antiviral with a novel delivery or new mechanism (siRNA, immune modulator) can qualify as a new, protectable product, effectively resetting patent life
- Products entering the market near patent-expiry generic erosion must be tied to a clearly novel mechanism or delivery innovation to justify premium pricing and not be perceived as costly reformulations of generics
- Together, these IP factors determine whether companies have sufficient incentive to pursue LA HBV formulation

"U.S. payers repeatedly tell us they won't pay for convenience or compliance alone; they want hard outcomes."

Long-Acting Oral or Injectable – or Both?

- Weekly/monthly orals are familiar and reduce stigma
- LAIs align with desire for simple, low-burden treatment, reducing daily pill fatigue, adherence lapses, and stigma from visible medication use
- Both must demonstrate value beyond convenience

What Will It Take for Broad LMIC Adoption?

- Voluntary licensing (MPP), competitive procurement can reduce costs
  - When voluntary licenses or generics are available, multiple manufacturers can bid to supply national programs
- Uptake depends on national program funding, registration, and actual demand
- LMIC delivery requires simple logistics: easy to store and transport, little or no refrigeration needed, and includes basic testing tools so non-specialist health workers can deliver care

Investors + payers want a clear, succinct value thesis showing how LA HBV product uniquely addresses a clinical or operational gap, not just convenience.

- Demonstrate a stepwise, lower-risk path to market: begin with small, high-need niches (e.g., reactivation prophylaxis), gather real-world evidence, then expand to broader chronic HBV indications once safety and efficacy are established
- Need a long-term IP plan that supports continued investment and product expansion

"What does the business case look like: by population and geography? If the goal is suppression (not cure), development doesn't necessarily take a decade, but you need a crisp value thesis."

What Evidence Should the Field Prioritize?

- Need evidence that better viral suppression from LA HBV drugs actually leads to better long-term health outcomes, especially lower rates of HCC, cirrhosis
- Modeling important to quantify how LA HBV treatments could improve adherence, reduce missed doses, and ultimately lower long-term costs in ways that matter to payers and health systems
  - Especially useful for groups outside large pharma
  - LEAP's modeling group supports demand + impact projections
- Pragmatic implementation evidence in reactivation + co-infection settings

Key Takeaways: Challenges to Meet

High-Income Markets	• Demonstrate deeper and more durable viral suppression in hard-to-suppress groups • Provide validated evidence or strong modeled links connecting suppression to improved outcomes (e.g., reduced HCC or cirrhosis risk) • Establish clear role in finite cure regimens
LMICs	• Deliver transformative product profile that simplifies care, improves adherence, scales effectively within existing health systems • Build access pathway from the beginning: using voluntary licensing, competitive procurement, early coordination with global access partners

Long-Acting/Extended Release
Antiretroviral Research Resource Program