

Long-acting HBV treatments: setting the stage

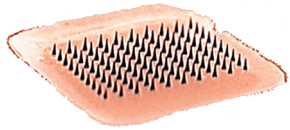
David Thomas, MD, Johns Hopkins Medicine

NIH - LEAP, <https://www.longactinghiv.org>

Overview of long-acting anti-HBV treatments

- Define long-acting
- Describe use cases/TPP
- Examples of products
- Challenges

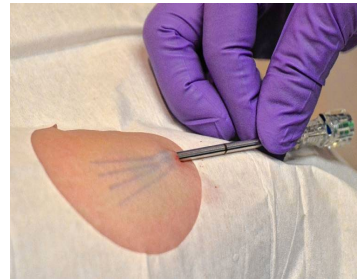
Definition: long-acting (LA) means weeks/months of bioavailability



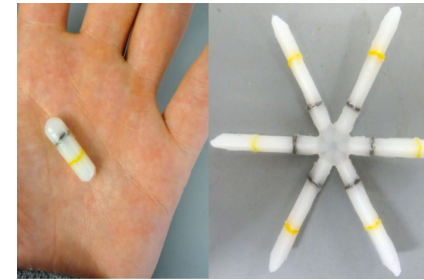
PATCH



INJECTION



IMPLANT



ORAL/INDWELLING
PILL

- Small molecule (eg, cabotegravir)
- Biologic (peginterferon, monoclonal antibodies)

Goals of Long-Acting HBV Therapies (Target Product Profiles)

HBV, sustain care/prevent

- Replace daily nucleoside/tide for up to 294 million persons
- Pair with coming anti-RNA, pegIFN
- Pair with LA anti-HIV
- Use in pregnancy to prevent mother-infant transmission

Long-acting treatments may help eliminate hepatitis B when birth dose vaccination does not occur

- Maternal tenofovir prevents perinatal HBV transmission
 - With birth dose vaccine when HBV DNA > 200,000 IU/ml
 - ? When birth dose not received
- Universal treatment of HBsAg positive pregnant women
- Like HIV prep, long-acting injection may be preferred esp in settings where birth dose vaccination is unlikely
- ?preferences of persons living with HBV not known

Multiple long-acting anti-HBV compounds are in development

- E-CFCP, a 4' modified NRTI, inhibits HBV in cell culture and mice after intragastric inoculation
- ETV hot melt extrudate coated tablets were toxic in rodents
- ETV prodrug mCMQ657 has long bioavailability in dogs
- Long-acting 3TC protide effective in cell culture
- TAF/TFV-DP

Higashi-Kuwata J Hepatol 2021; Henry European J Pharm Sci 2019; Chatterjee et al personal communication; Wang Nanomedicine 2020

Tenofovir prodrug as a long-acting HBV treatment

- Multiple TAF implants tried for HIV in animal models
 - Biodegradable polymer, polyurethane tube, refillable pump, silicone tube*
 - Efficacy to prevent SHIV
 - Local reactions sometimes severe (e.g., polyurethane tube)
 - ? Hepatocyte concentrations

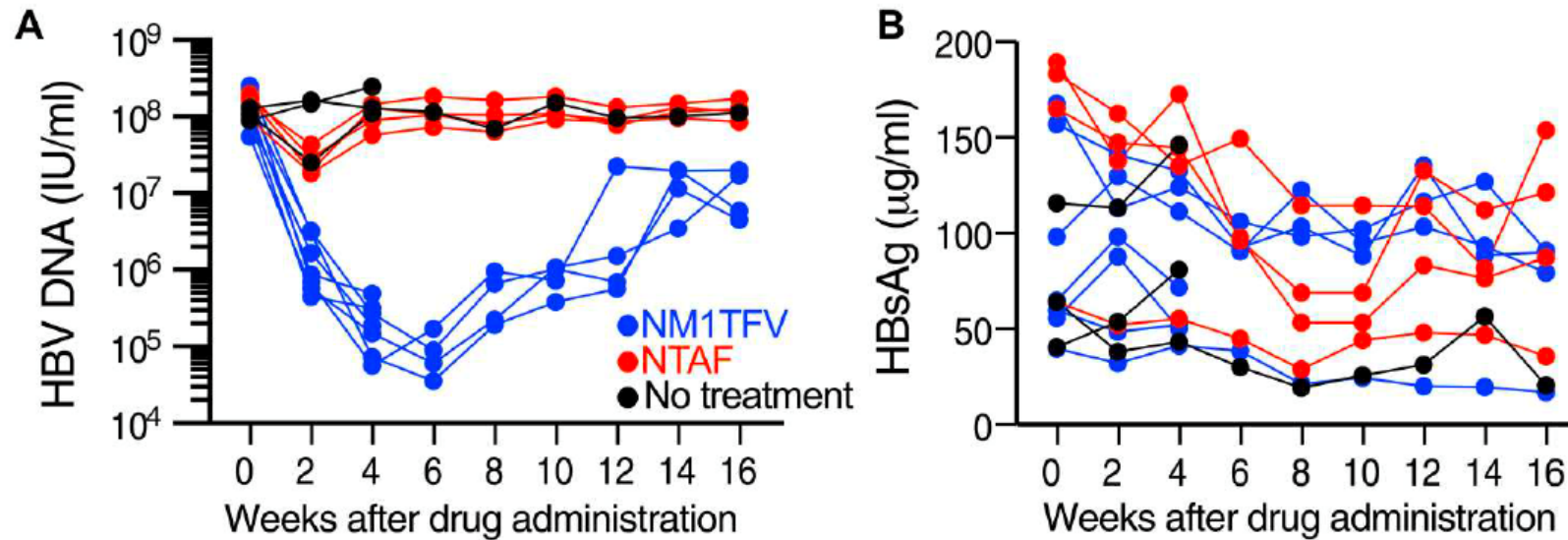
* In clinical trials

Thomas, Kiser, and Baum CID 2022; Chua J Control Release 2018; Gunawardana M Antimicrob Agents Chemother 2015; Johnson LM Pharmaceutics 2019; Pons-Faudoa FP, Adv Ther 2021; Schlesinger E Pharmaceutical research 2016; Simpson SM, Pharmaceutical research 2020; Su JT Antimicrob Agents Chemother 2020; Zane D Microbiol Spectr 2021; Weld and Flexner, Curr Opinion HIV AIDS 2020

Tenofovir prodrug as a long-acting HBV treatment

- Implants
- Injections
 - Water-in-oil emulsion of BIC and TAF as 229 nm spheres
 - TLC-ART 101 lopinavir, ritonavir, lamivudine and TFV nanoparticles
 - TFV protides (NM1TFV) created using docosanol ester to mask alanyl isopropyl ester in TAF to make lipophilic
 - Sustained TFV and TFV-DP concentrations in liver 56 days
 - Anti-HBV efficacy in in vitro, humanized mice and transgenic mice

NM1TFV suppressed HBV blood DNA level after IM injection of transgenic mouse without substantial change in HBsAg



There are challenges to develop LA treatments

- Unclear perspectives of persons living with HBV
- Unclear market/donor commitment
- Production costs and cold chain
- Prolonged toxicity
- Regulatory questions
- Patent and licensing agreements
- Different pharmacology (eg aqueous solubility)

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Long-acting treatments for hepatitis B

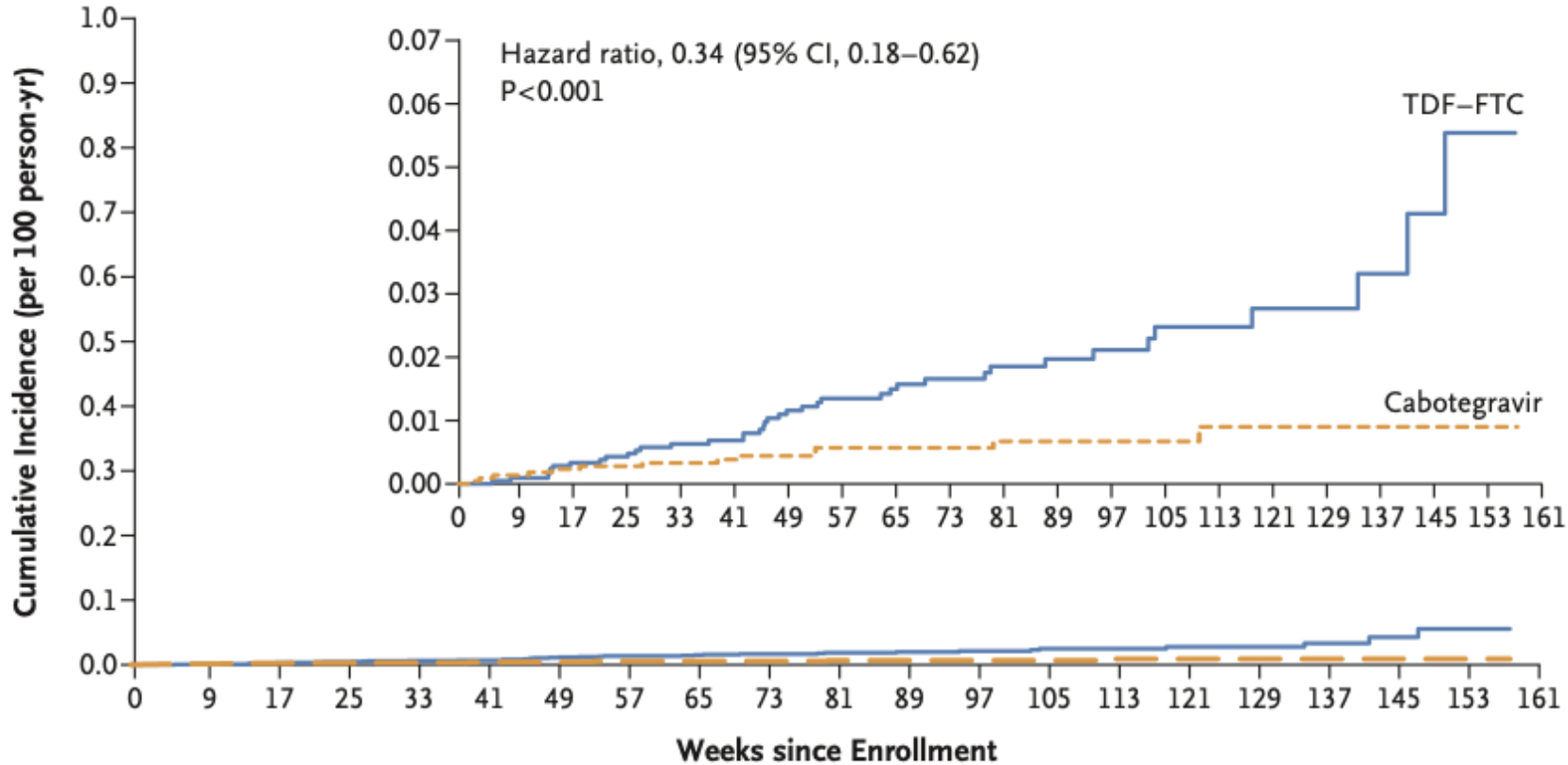
- Strong public health justification for HBV
- Enormous potential contributions to public and individual health
- Critical to understand perspectives (children and pregnant women)
- Critical to make case for development and de-risk for pharma
- “We would still have smallpox if we gave out a prescription for the vaccine”

Hepatitis Extended Release Long Acting Injectable/Implantable Medication (HEP ELIM) Research Group

- HBV – Marc Baum and Jen Kiser
- HCV- Andrew Owen, Steve Rannard
- LA/ER consortium – Ethel Weld, Charlie Flexner, Sue Swindells
- Epidemiology – Shruti Mehta, Sunil Solomon, Ethel Weld
- Clinical – Mark Sulkowski, Dave Thomas
- Benson Edagwa, L Poluektova
- DAIDS - Carl Dieffenbach and Peter Kim
 - CFAR - 5P30AI094189
 - LEAP - R24AI118397
- **Unitaid-Longevity (Owens)**
- Clinton Foundation – Paul Domanico, Christian Ramers, Sean Regan
- Arnab Chatterjee Scripps
- Coalition for Global Hepatitis Elimination (J Ward, N Gupta)

Unitaid: Longevity, Centre of Excellence in long-acting therapeutics <https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/>; US NIH/LEAP <https://www.longactinghiv.org/>; MPP <https://medicinespatentpool.org/>; Treatment action group <https://www.treatmentactiongroup.org/>

Cabotegravir Injections Prevent HIV Infection Better Than Pills



No. at Risk

TDF-FTC	2281	2132	2081	2019	1913	1765	1624	1494	1295	1132	965	817	644	517	401	311	231	150	85	33	0
Cabotegravir	2280	2138	2091	2031	1920	1776	1633	1489	1315	1124	957	798	644	503	401	318	243	173	111	42	0

Entecavir as long-acting HBV treatment

- ETV hot melt extrudate coated tablets in rodents
- >180 days of continuous release
- High local toxicity and teratogenic
- More success with modifications (eg A Chattergee, mCMQ657 in dogs)