HBV Roadmap
Update from Recent and EASL Presentations

HBV Forum
pre-EASL 2018

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Disclosures

- See robertgish.com

Introduction

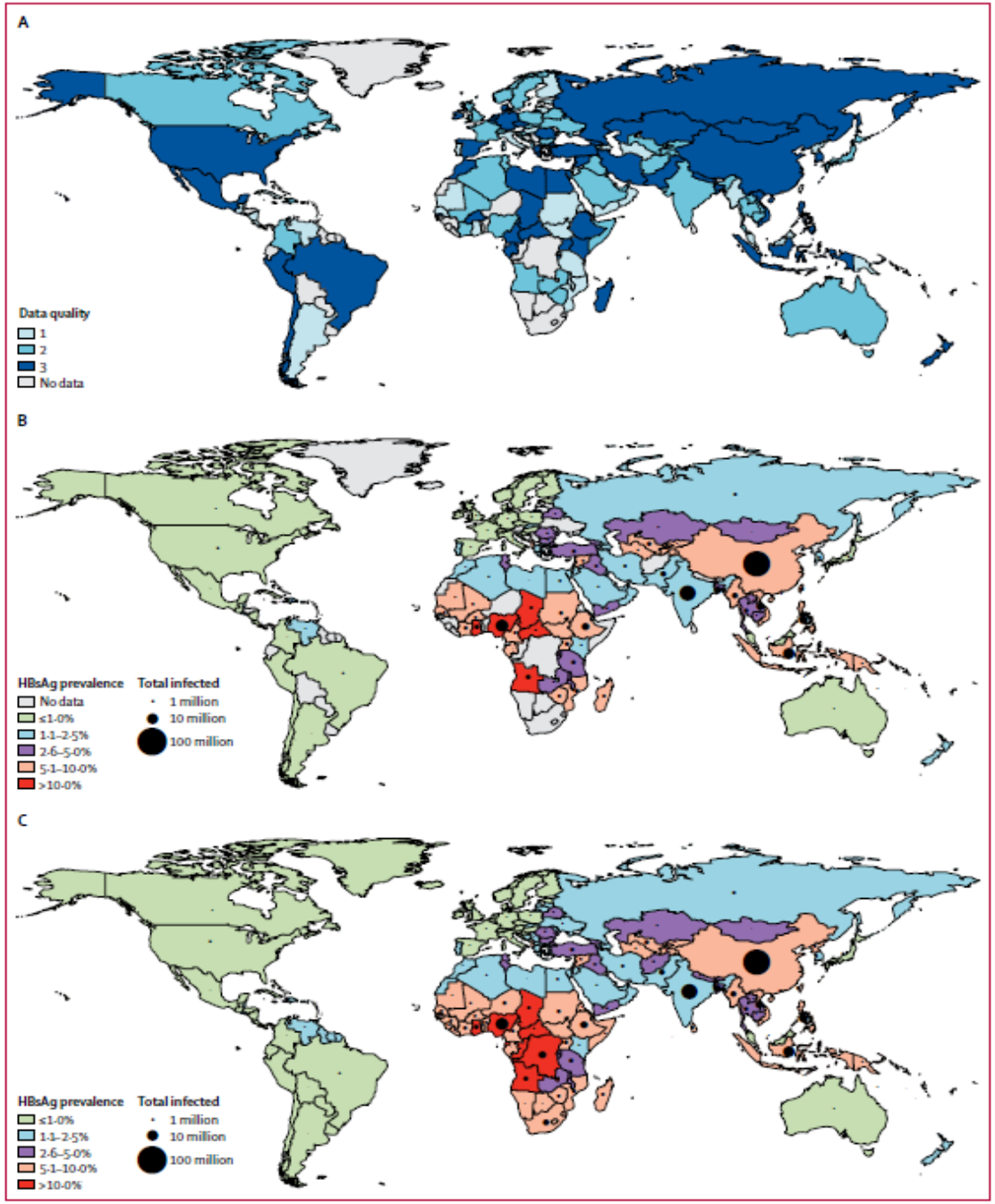
- Aims
  - Understand recent and selected EASL Presentations that will help shape the roadmap to HBV elimination

- Objectives
  - Present data from EASL the may guide drug development and changes and updates in the global HBV elimination program

Where did the 140 M people
with HBV go?

Current 2018 estimates of HBV
Is 264 M HBsAg +

?2 Billion who are anti-HBc (+)



www.thelancet.com/gastrohep Published online March 26, 2018 http://dx.doi.org/10.1016/S2468-1253(18)30056-6

	Historical prevalence (%)	Modelled prevalence*	HBsAg-positive population, thousands*	Treated/treatment eligible† (%)	Diagnosed (%)‡	HBsAg prevalence in children aged 5 years*	HBsAg-positive population aged 5 years*	Prophylaxis coverage (%)			
								Three-dose vaccination before age 1 year§	Timely birth dose§	HBIG and full vaccination¶	Antiviral treatment of mothers‖
WHO region											
AFRO	9·5%	7·2% (6·2–8·2)	78 166 (68 191–88 606)	33 700/21 356 000 (<1%)	1 486 000 (2%)	3·4% (3·0 to 3·9)	1 046 000 (940 000–1 209 000)	80%	10%	0%	<1%
EMRO	3·0%	2·2% (1·9–3·0)	15 565 (13 041–20 412)	68 900/4 109 000 (2%)	1 000 000 (6%)	0·5% (0·4 to 0·7)	83 000 (71 100–118 000)	85%	26%	7%	1%
EURO	2·0%	1·6% (1·1–2·1)	14 426 (9590–19 965)	268 000/3 940 000 (7%)	2 274 000 (16%)	0·1% (<0·1 to 0·2)	14 800 (10 100–24 300)	82%	72%	14%	3%
PAHO	0·6%	0·4% (0·3–0·6)	3961 (2792–6492)	136 000/1 057 000 (13%)	923 000 (23%)	<0·1% (<0·1 to 0·1)	9200 (7300–16 400)	89%	67%	23%	4%
SEARO	4·0%	3·5% (2·9–4·0)	68 948 (58 382–79 753)	109 000/22 290 000 (<1%)	1 462 000 (2%)	1·5% (1·3 to 1·8)	540 000 (476 000–634 000)	89%	47%	2%	0%
WPRO	7·1%	5·7% (5·1–6·6)	108 672 (97 310–124 304)	3 918 000/40 454 000 (10%)	20 268 000 (19%)	0·5% (0·4 to 0·7)	116 000 (102 000–159 000)	97%	88%	54%	<1%
World Bank region											
High income	1·1%	0·9% (0·7–1·1)	10 307 (8469–12 646)	873 000/35 78 000 (24%)	4 691 000 (45%)	<0·1% (<0·1 to <0·1)	8700 (5800–11 900)	85%	62%	71%	9%
Upper-middle income	4·8%	4·0% (3·5–4·7)	106 829 (93 070–123 656)	3 653 000/38 250 000 (10%)	18 007 000 (17%)	0·2% (0·1 to 0·3)	74 200 (61 700–115 000)	94%	86%	61%	<1%
Lower-middle income	5·3%	4·4% (3·8–5·2)	130 891 (111 825–154 913)	151 000/39 609 000 (<1%)	4 475 000 (3%)	2·0% (1·8 to 2·4)	1 257 000 (1 117 000–1 487 000)	83%	37%	1%	<1%
Low income	8·1%	6·2% (5·3–7·0)	43 695 (38 008–49 538)	85 600/12 586 000 (<1%)	1 635 000 (6%)	1·9% (1·7 to 2·2)	470 000 (422 000–547 000)	87%	3%	0%	<1%
Global	4·9%	3·9% (3·4–4·6)	291 992 (251 513–341 114)	4 762 000/94 043 000 (5%)	28 813 000 (10%)	1·4% (1·2 to 1·6)	1 811 000 (1 607 000–2 162 000)	87%	46%	13%	<1%

HBIG=hepatitis B immunoglobulin. AFRO=Regional Office for Africa. EMRO=Eastern Mediterranean Regional Office. EURO=Regional Office for Europe. PAHO=Pan American Health Organization. SEARO=South-East Asia Regional Office. WPRO=Western Pacific Regional Office. *Data are estimate (95% uncertainty interval). †Treatment eligible reflects the estimated number of HBsAg-positive individuals (diagnosed and undiagnosed) with a high viral load (≥20 000 IU/mL) or with cirrhosis, hepatocellular carcinoma, or liver transplantation, independent of viral load. ‡The denominator in this column is the estimated HBsAg-positive population. §Proportion of all infants. ¶Proportion of infants of HBsAg-positive mothers who received HBIG, first dose of hepatitis B vaccination ≤24 h after birth, and two or more doses of vaccine in the first year of life. ‖Proportion of mothers with a high viral load who received antiviral therapy to reduce mother-to-child transmission.

Table 3: 2016 estimates of HBsAg infection prevalence, treatment, and prophylaxis, by WHO or World Bank region

Modeling is key: Polaris

Razavi, H., S147 (THU-057),
S148 (THU-058), S149 (THU-059),
S153 (THU-065), S153 (THU-067),
S154 (THU-068), S155 (THU-069),
S164 (THU-088), S165 (THU-089),
S169 (THU-097), S172 (THU-103),
S174 (THU-107), S176 (THU-111),
S193 (THU-145), S308 (THU-397)
Razavi-Shearer, D., S164 (THU-088),
S165 (THU-089), S169 (THU-097)
Razavi-Shearer-Spink, D., S147 (THU-057),
S148 (THU-058), S153 (THU-067),
S154 (THU-068), S155 (THU-069)

Screening and Diagnostics

First Level: The Patient

- POC/Rapid tests
  - Serologic tests <1$
  - PCR at 18$
- Policy
  - All adults?
  - Selected at risk ?
  - HBsAg only
  - Full panel
    - Anti-HBc, anti-HBs, HBsAg

Second Level: Drug Development

- qHBV RNA
  - Is this pgRNA
  - Integrants?
- HBV RNA sequencing
  - cccDNA
  - Integrants
- qHBcrAg
- Various particles, empty
- qHBeAg
- Anti-HBs, type and quant
- q-anti-HBc
- Deep sequencing of RNA in liver tissue
- Liver biopsy information on treatment
- FNA cell aspiration
- qHBxAg

Vaccination

- 2 dose vaccines
- Do we need anti-HBs to be protected?
- 12 hour birth dose
  - Do we need Nucs?

POLARIS OBSERVATORY

THU 097

Table 1. Changes to vaccination coverage needed to meet WHO targets in 5 year olds

Country	Base			WHO		
	3D Coverage (2014)	Treated Mothers (2014)	BD Coverage (2014)	BD Coverage (2025)	3D Coverage (2025)	Treated Mothers (2025)
Burkina Faso	91.0%	0.0%	0.0%	99.0%	99.0%	80.0%
Burundi	95.0%	0.0%	0.0%	74.3%	98.0%	52.5%
Cameroon	87.0%	0.0%	0.0%	99.0%	99.0%	85.0%
Central African Republic	23.0%	0.0%	0.0%	99.0%	99.0%	99.0%
Chad	46.0%	0.0%	0.0%	74.3%	85.8%	74.3%
Ethiopia	77.0%	0.0%	0.0%	95.0%	96.0%	75.0%
Gabon	70.0%	0.0%	0.0%	99.0%	99.0%	65.0%
Gambia	96.0%	0.0%	96.0%	99.0%	99.0%	99.0%
Kenya	81.0%	0.0%	0.0%	81.0%	81.0%	0.0%
Madagascar	73.0%	0.0%	0.0%	99.0%	99.0%	50.0%
Malawi	91.0%	0.0%	0.0%	91.0%	91.0%	0.0%
Nigeria	66.0%	0.0%	54.0%	***99.0%	99.0%	85.0%
Rwanda	99.0%	0.0%	0.0%	99.0%	99.0%	0.0%
Senegal	89.0%	0.0%	0.0%	99.0%	99.0%	80.0%
Uganda	95.0%	3.0%	0.0%	99.0%	99.0%	70.0%
Tanzania	97.0%	0.0%	0.0%	99.0%	99.0%	50.0%
Zimbabwe	91.0%	0.0%	0.0%	99.0%	99.0%	75.0%
Average	80.4%	0.2%	8.8%	91.7%	96.5%	62.0%

CDA FOUNDATION

Achieving World Health Organization Targets for Hepatitis B in Infant
s and 5-year olds by 2030: Results from 17 WHO AFRO Countries Nde eet all

Linkage to care

- HBV treatment
- Screening for stage of liver disease
- Surveillance for HCC and liver disease progression

Treatment

- Will we treat all HBsAg(+) regardless of HBV DNA status ?
- Current is Nuc suppression until HBsAg loss
  - <10% at 5 year
- New selected treatments to follow

Summary of response to NAP-based combination therapy on-treatment and during follow-up

REP 301 / REP 301-LTF

Suboptimal REP 2139-Ca + pegIFN
(only 15 weeks in combination)
HBeAg negative treatment naïve
chronic HBV / HDV co-infection

Patients entered into trial		12
End of treatment HBsAg response	> 1 log below baseline	9
	< 1 IU/mL	6
	<0.05 IU/mL	5
HDV RNA response	> 5 log below baseline	12
	target not detected	11
Patients currently completed treatment and ≥ 1.5 years of follow-up		**11**
HBsAg ≤ LLOQ		4 (3 @ FW2Y)
HBV DNA < LLOQ		6 (5 @ FW2Y)
HDV RNA target not detected		7 (6 @ FW2Y)

REP 401

REP 2139-Mg/REP 2165-Mg + TDF + pegIFN
(48 weeks combination)
HBeAg negative treatment naïve
chronic HBV infection

Patients entered into trial		40 (20 with NAPs following 24 weeks of pegIFN)
End of treatment HBsAg response	> 1 log from baseline	36
	< 1 IU/mL	27
	< 0.05 IU/mL	23
Patients currently completed treatment and ≥ 12 weeks of follow-up		**33**
HBV DNA < 1000 IU/mL (repression)		25 (75%) (6 @ FW48)
HBV DNA < LLOQ (remission)		22 (65%) (5 @ FW48)
HBsAg < LLOQ		16 (2 @ FW48)

Assembly Biosciences “Capsid Inhibitors” CpAMs - 2018 Roadmap

ABI-H0731 (1st Generation CpAM)

- Potent, selective and pangenotypic
- Derived from novel chemical series
- Phase 1a (volunteers) completed
  - Good safety and oral exposure
  - T½ of ~24 hr and minimal accumulation with repeat dosing
- Phase 1b (patients) ongoing
  - Good safety and efficacy exhibited
  - Interim data being presented at EASL (poster LB-012)
  - Phase 2a studies to initiate 3Q18

ABI-H2158 (2nd Generation CpAM)

- Enhanced potency and PK
- Derived from distinct and novel chemical series
- Phase 1a to initiate 4Q18

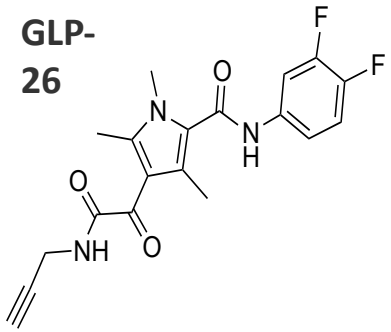
cPAMs, Capsid Core Inh

- Block assembly
- Missassembled
- Expedite degradation
- Block cccDNA regeneration

- But these Compounds will not stop HBsAg production

New class of non nucleoside inhibitors glyoxamide-pyrrolamides (GLP)

GLP-26



Patent# **WO2017156255 (A1) – Elimination of Hepatitis B Virus with Antiviral Agents.**

HepAD38 system

- ✓ Inhibits HBVDNA replication – $EC_{50/90}$ = 3/30 nM
- ✓ Inhibits HBeAg secretion – EC_{50} = 3 nM
- ✓ Reduce cccDNA amplification by 1.3 log at 1 µM
- ✓ Active in human primary hepatocytes

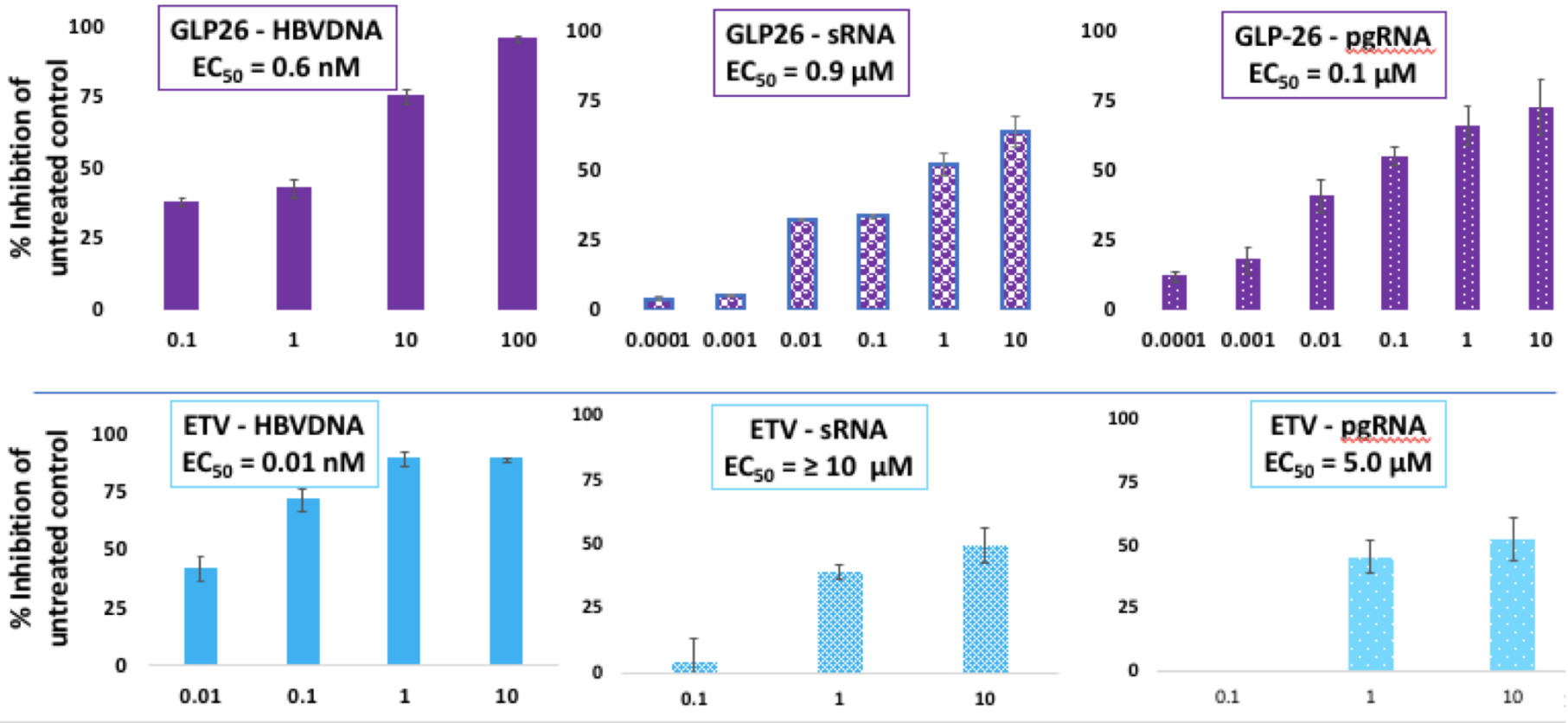
In vivo

- ✓ Long stability ($T_{1/2}$ >24 h) in dog and human plasma
- ✓ Good stability ($T_{1/2}$ = 7.6 h) in human liver microsomes
- ✓ Long half life in mice after oral administration (> 6 hr)

EASL, 2016 L Bassit et al.,

MultiTargeted HBV Therapy in Action

Figure 1. GLP-26 Inhibits HBVDNA, Surface (sRNA) and pregenomic RNA (pgRNA) in HBV-Infected HepG2-NTCP Cells



Bassit EASL 2018

More on Combination THerapy

SCIENTIFIC PROGRAMME / THURSDAY 12 APRIL 2018

Parallel session: HBV cure: Pre-clinical studies	South 4
	Chairs: Julie LUCIFORA, *France* Stephen LOCARNINI, *Australia*
16:00-16:15 PS-025	**Combinatorial RNAi/vaccination therapy for chronic hepatitis B achieves long-term functional cure in preclinical mouse model** Thomas MICHLER, *Germany*
16:15-16:30 PS-026	**Novel and potent HBV capsid modulator reduces HBeAg and cccDNA in core site directed T109I mutant in HepNTCP cells** Leda BASSIT, *United States*
16:30-16:45 PS-027	**Preclinical antiviral drug combination studies utilizing novel orally bioavailable investigational agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, a HBV RNA destabilizer** Nagraj MANI, *United States*
16:45-17:00 PS-028	**Combination treatment of a TLR7 agonist RO7020531and a capsid assembly modulator RO7049389 achieved sustainable viral load suppression and HBsAg loss in an AAV-HBV mouse model** Lu GAO, *China*

Single>Combination Treatment

- Nuc +/- INF
- Nuc (INF) + iRNA
  - Arrowhead, ARB, Alnylam, GSK
- Nuc + anti-sense
- Entry Inh (Myr) + Capsid (Assembly, Enanta, many others), MABs
- CRISPR-Cas9 + Capsid
  - Others in class TALENS, editing
- iRNA + Capsid + immuneM?
- Drugs with multiple targets? GLP (Emory)
- DAA: RIG-I SB on encapsidation?
- cccDNA:
  - Breakdown
  - Edit
  - Stop synthesis

- RNA destabilizer (ARB)
- TLR7 + Capsid Inh (RO)
- Customized T-cell therapy
- Selective immunomodulation
  - Springbank RIG-I

- Release inhibitors ++?
  - REP compounds
- Immunomodulators +++?
  - Vaccine (Alnylam, Transgene, China groups, VacciTECH, others)

- Cellular targets +++ ?
  - FXR agonists (Enyo)
- PD1 PDL1 + ????
- HBxAg target
- RNA-ase H target

Special Populations

- Co-infection with HDV, HCV, HIV
- Dialysis
- Nuc suppressed
- ALT <20 in women
- ALT <30 in men
- All HBsAg+ patients
- Transplant patients
- Anti-HBc+, OBI, HBsAg mutants
- Immune suppressed

Need for partnership

- High need (3-4 partners)
  - Entry inhibitors
  - Release inhibitors
  - FXR
  - Therapeutic vaccines
  - TLR -8
  - T cell manipulation
  - Nucs
  - PEG Inf
- Need more data
  - Anti-Sense RNA/DNA
  - CRISPR-Cas9
  - T-cell and other new immune technology
- Moderate need (1-2 partners)
  - RIG –I Stim
  - iRNA
  - Capsid, pCAM
- Not going forward?
  - PD1 PDL1 antagonists

Goals of new combination therapy

- Oral >> SQ >> IV
- Treatment ≤ 12 months
- sAg loss > 20% 50% with sustained DNA suppression, or "no go"
- sAg loss from both cccDNA and integrants
- AE profile <10% higher than Nucs
- AE profile < << INF
- Planned global price gradient
- Treat all patients who are HBsAg+

Endpoints

- HBsAg >0.5 log early
- HBsAg> 3 log by 3-6 months
- HBsAg loss 20-40% in < 1 year
- qHBeAg in HBeAg(+) patients
- Fall qHBV RNA
  - Type of RNA
- Clear HBsAg from integrants
- HBxAg
- qHBcrAg
- q-cccDNA, tissue, blood?

Safety

- Do NAPS lead to sAg accumulation?
- Do cPAMS lead to core accumulation?
- iRNA: is there effect of gRNA, breakdown of iRNA, effect of RNA long term polyNuc?
- PDL1 and PD1: autoimmune
- Combination therapy too early, before full tox profiles finished
- Immune - Immune collaborations?

Action items

- Accelerated birth dose vaccine programs (<12hours) eliminate cold chain, eliminate Nuc for mother, eliminate HBIG
- Robust screening algorithms
- Funding
  - GAVI for birth dose !
  - Govt
  - WHO
  - CDC and equivalents

- Accelerated
  - Diagnostic Test Approval
    - Applies to therapeutics
  - Drug development
    - Regulatory
    - Corporate
    - Investors
- Large companies have libraries
- Small companies need polygamy
- Minimize lawyers
- Production of drug/technology is it scalable

Recognition of the Real Roadmaps

- ICE HBV
- ANRS
- CEVAP
- WHO
- CDC
- HBV Forum
- Many others

Questions