# HBV Cure – Definition and New Drugs in Development

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**HBV Cure Meeting**
**November 2016**
**Boston**

# Disclosures for HLA Janssen

**GRANTS**
AbbVie, Bristol Myers Squibb, Gilead, Innogenetics, Janssen, Medimmune, Merck, Novartis, Roche

**CONSULTANT**
AbbVie, Arbutus, Benitec, Bristol Myers Squibb, Eiger Bio, Spring Bank Pharma, Gilead, GSK, Fujirebio, Ionis Pharmaceuticals, Janssen, Medimmune, Merck, Novartis, Roche

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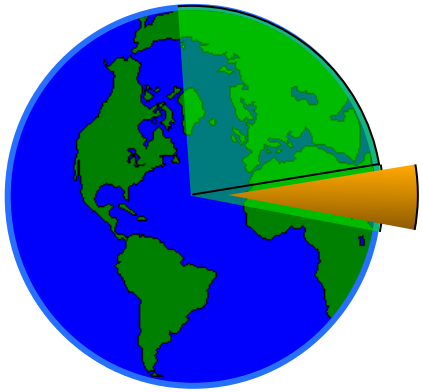
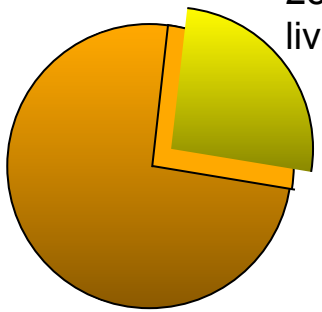
# HBV – A Global Health Problem

2 billion people with evidence of HBV



World population 6 billion



25–40% die of cirrhosis or liver cancer

Approximately 350 million with Chronic HBV (75% in Asia)

***First Line Treatment: Tenofovir, Entecavir and PEG-IFN***
***Majority of patients not diagnosed***

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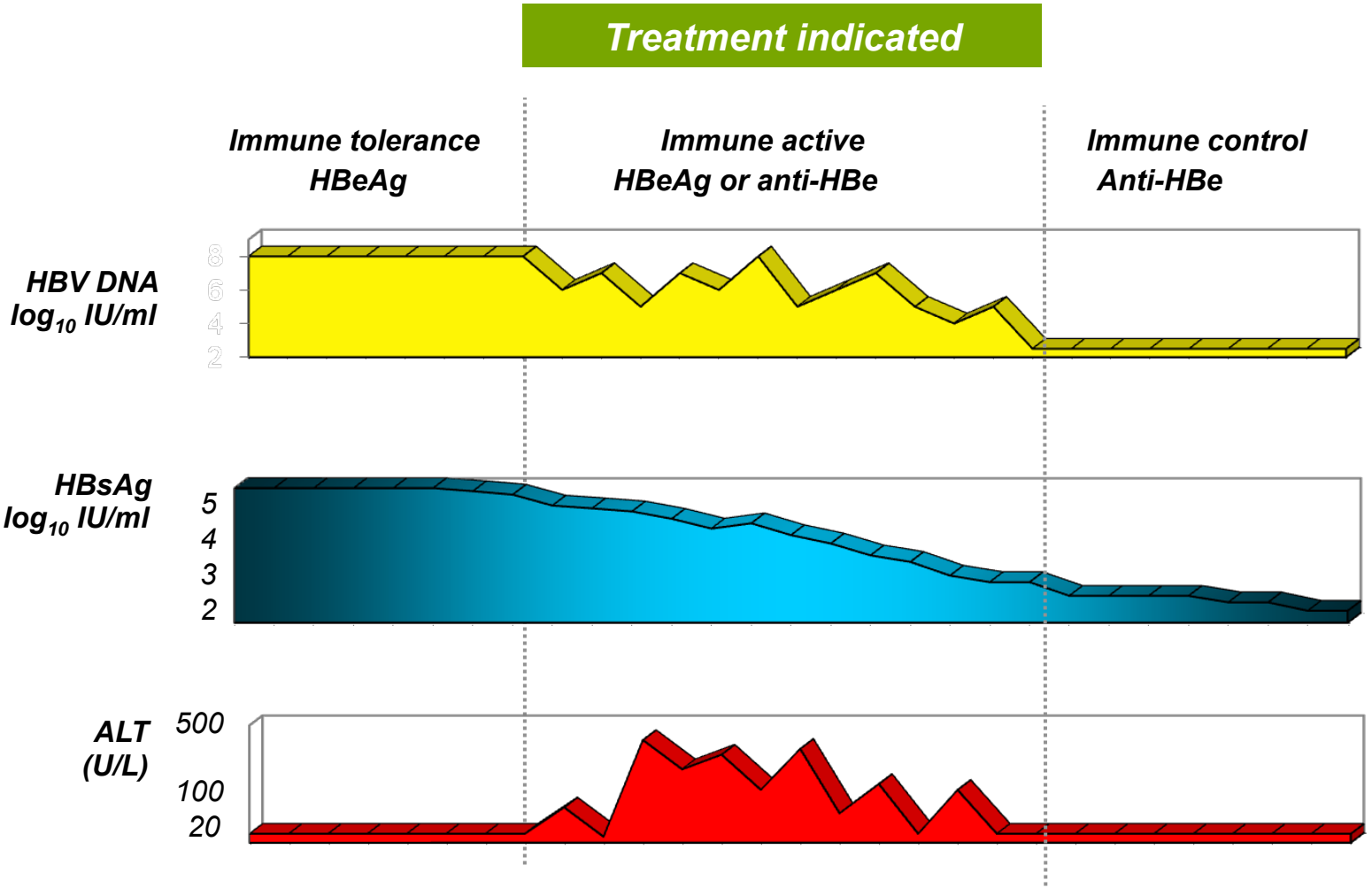
# Natural history of CHB




*New drugs: Is risk/ benefit different depending on therapy, age of patient or phase of disease?*
*Do different phases need different therapies?*

***Janssen, et al. Gut 2012***

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# The decision to treat is historically based on phase of disease and risk of disease progression

| Phase | Immune tolerant | HBeAg-positive CHB | Inactive carrier | HBeAg-negative CHB |
|---|---|---|---|---|
| HBeAg status | Positive | Positive | Negative | Negative |
| HBV DNA | Very high >200,000 IU/mL | >2000 IU/mL | <2000 IU/mL | >2000 IU/mL (fluctuating) |
| ALT | Normal | Elevated | Normal | Elevated (fluctuating) |
| Liver histology | Normal or mild inflammation and limited fibrosis | Inflammation and fibrosis: degree varies | Normal or mild inflammation | Inflammation and fibrosis: degree varies |
| **Disease progression** | Low | **Moderate to high** | No, very low | **Moderate to high** |
| **Treatment** | Not indicated* | **Indicated** | Not indicated | **Indicated** |

**** Treatment indicated in some patients***

*EASL HBV Guidelines, J Hepatol 2012;57:167–185; EASL special HBV conference, J Hepatol 2015;63:1238–1253*

# Key Considerations for Current Treatment Options

- HBV nucleos(t)ides are highly effective and generally well tolerated, but with low rates of successful discontinuation
- Long-term nucleos(t)ide-analogues reduce cirrhosis, liver failure and HCC; safety remains to be determined but appears very good
- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity
- Thus, unlike in HCV drug development there is effective and safe therapy available which suppresses HBV

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# Why is Finite Therapy a Goal for HBV Treatment?

*Younger patients may find lifelong treatment hard to accept*

*Women who want to become pregnant*

*Patients reluctant to start treatment*

*Working days lost to hospital visits*

*Cost savings to healthcare system*

*Long-term adherence issues*

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# Important Issues for HBV Drug Development

- Low vaccine uptake in adults
- Still many CHB undiagnosed
- Many countries cannot provide long term therapy to patients with CHB
- Unapproved Combination drugs have been studied for HCV, NAFLD and HBV

# What can be considered as a defined cure?

- **Virological cure**
  - elimination of cccDNA
  - lowering or silencing cccDNA
  - Undetectable HBV DNA in serum
  - Off-therapy HBsAg loss

- **Disease cure**
  - No risk of progression to liver faillure or HCC
  - Identifiable by clinical parameters, biomarkers or gene signatures

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# Is HBV Treatment Paradigm Changing?

## Current PARADIGM

- *Indefinite Treatment*
- *Poor off-Rx response*
- *Reduces overall mortality*
- *Reduce but does not eliminate the risk of HCC*
- *Potent NAs :suppresses viral replication but cannot cure the disease*

## New PARADIGM

- *Finite treatment duration*
- *Sustained off-Rx response shift towards endpoint of true immune control &HBsAg seroconversion*
- *No increased risk of mortality and HCC*
- *New HBV treatments with increased chance of curing disease*

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# Defining HBV Cure

## Functional cure

Associated with clinical benefit (disease progression and HCC)

Off-therapy sustained HBV suppression and disease remission

HBsAg serocnversion and cccDNA inactivation/reduction

Risk under immunosuppression

Feasible

## Complete cure

Associated with clinical benefit (disease progression and HCC)

HBsAg seroconversion and cccDNA eradication

Feasibility very uncertain

*Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016*

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# Survey: Surrogate for HBV cure (true/false)

| Best endpoint for HBV cure | |
|---|---|
| HBsAg seroconversion | **61 (92.4%)** |
| HBsAg loss | 43 (65.2%) |
| HBsAg decline | 22 (33.3%) |

***Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group***

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# Approaches to Therapy

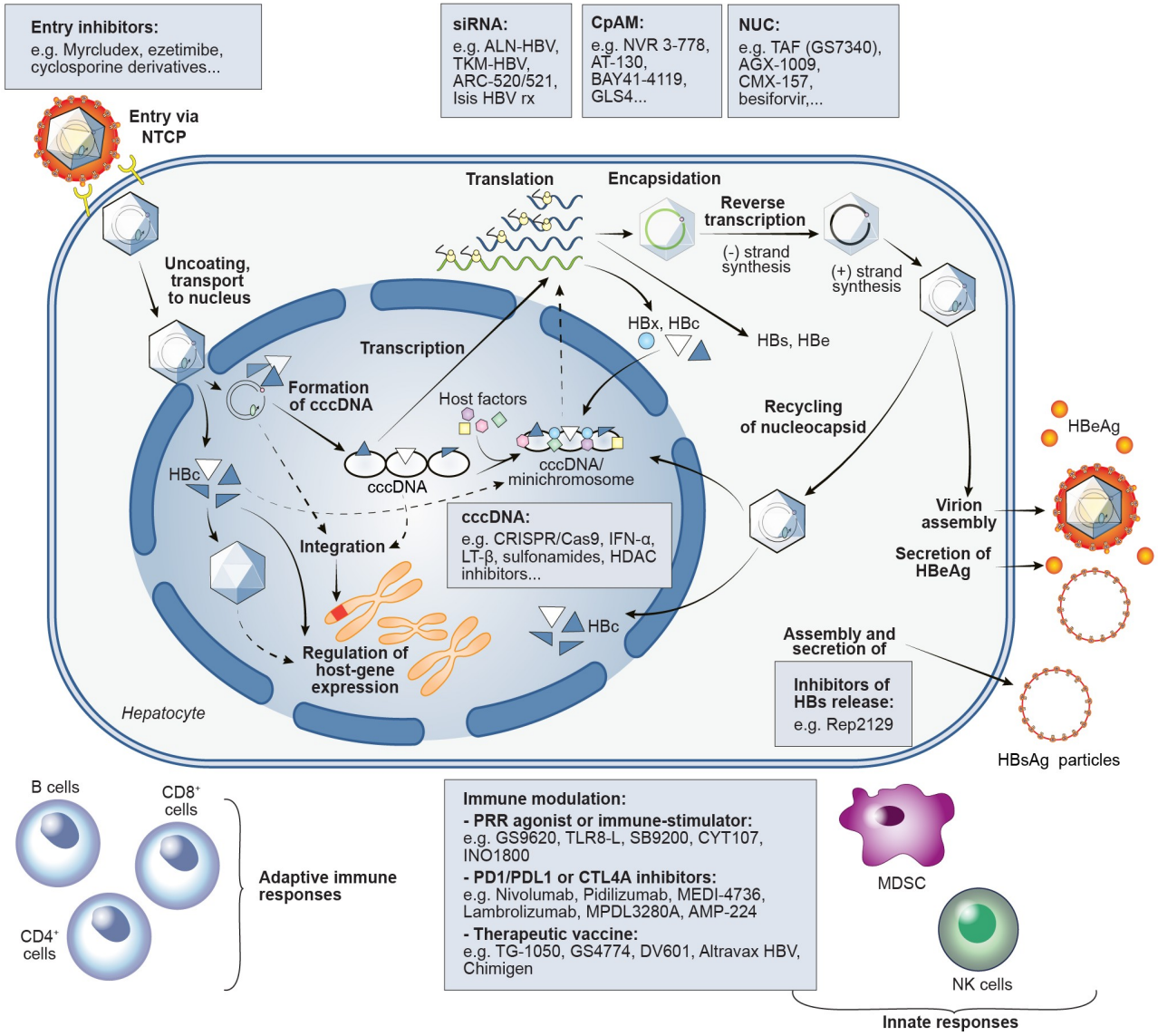
## Viral targets - DAA

- Viral entry
- cccDNA formation/ transcription/degradation
- RNA intermediates
- Encapsidation
- DNA replication
- Assembly
- Release

## Immunomodulators

- Innate immune response
  - IFN
  - TLR agonists
  - RIG-I agonists
- Adaptive immune response
  - Anti-antagonists (checkpoint inhibitors)
  - Vaccination

# HBV cure – Compounds in Development




*Testoni & Zoulim, Hepatology 2015; Durantel & Zoulim, J Hepatol 2016*

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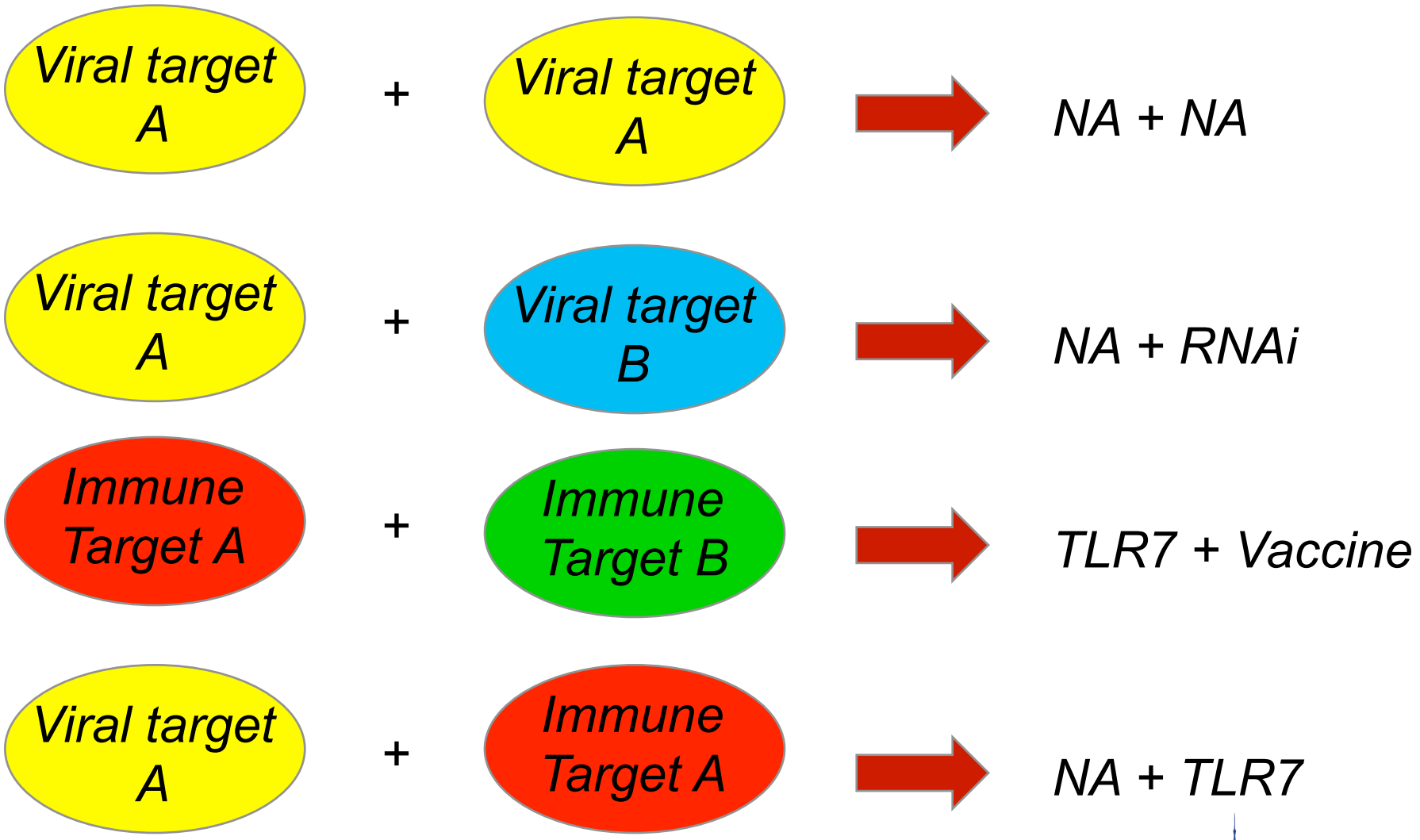
# Combination Approaches

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# Multiple Viral Targets

## Pros

- More profound suppression
- Higher barrier to resistance – not necessary with nucs
- Reduce immuno-suppressive effects of HBV → combo 4
- Safety – in context of nuc suppressive therapy

## Cons

- Same target – only as good as most potent
- May be hard to assess efficacy
- No synergy…or even antagonism?
- Safety

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# Viral + Immune Target

- Appears attractive option
- HBV impairs innate and adaptive immune function
  - Viral replication
  - Viral protein production
- Viral inhibition → improve immune function and responsiveness
- Immunotherapy – the knock-out punch!

# Attractive Combinations

| ***HBV DNA suppression*** | + | ***Viral protein depletion (s, x, core)*** | + | ***Immuno-therapy*** |
|---|---|---|---|---|
| *Nuc* | | *RNAi* | | *TLR/RIG-I agonist* |
| *+/- cccDNAi*<br>*+/- entry inhibitor*<br>*+/- RNAi*<br>*+/- CpAM* | | *Nucleic Acid Polymers*<br><br>*cccDNAi* | | *αPD1/PDL1*<br><br>*Therapeutic vaccine* |

*May not need all 3 'classes'…mix and match*

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# Current endpoints in HBV treatments

| | |
|---|---|
| Biochemical: | ALT normalization |
| Virological: | HBV DNA decline/undetectability |
| Serological: | HBsAg/HBeAg loss/seroconversion |
| Histological: | Reduction of necrosis, inflammation, fibrosis |
| Combined: | Most often HBeAg, HBVDNA and ALT |

# Endpoints: Key considerations

- What surrogate markers of efficacy to monitor success: Immunologic, Virologic, Pathologic?
- Phase 2 or 3 studies
- Primary & secondary endpoints
- Antiviral vs. immunomodulatory drugs
- Treatment naive vs. virally suppressed patients
- Timing of endpoint assessment: on- or off-treatment
- Efficacy criteria for further development of drug

# Clinical trial phases


**20-100 volunteers**

**100-200 patients**

**500-2000 patients**

**Phase 1a**
Safety of single ascending dose

**Phase 1b**
Safety of multiple ascending doses

**Phase 2a**
Optimal dose

**Phase 2b**
Efficacy prescribed dose

Comparison to standard of care

Safety surveillance in 'real-life' patients

Pharmacokinetics & pharmacodynamics

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# Experimental HBV treatment in naive vs virally suppressed patients

## Treatment Naive

Younger

Active Disease

HBVDNA can be used as a biomarker

No resistance

May be more likely to accept finite therapy

## Suppressed

Have safe and effective therapy with reduction of HCC and improved survival

Partial immune restoration may benefit immune modifying therapy

Potentially better protection against flares

May have more objections to accept experimental therapy

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# Endpoint differentiation based on treatment modality?

In principle, rather not:

- All HBV treatments aimed at common clinical goal
- Association with clinical endpoint is essential

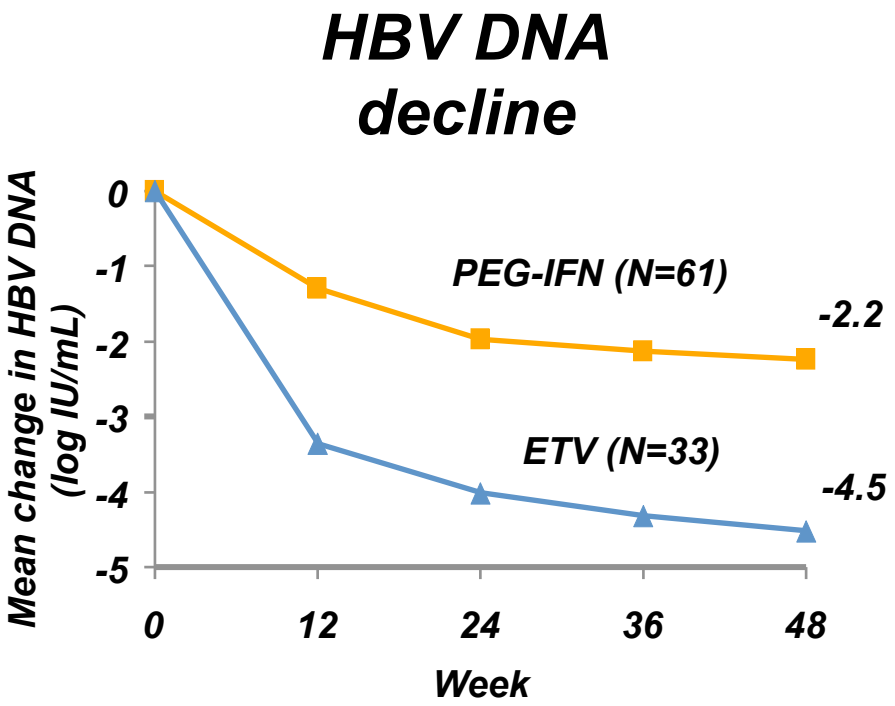
But:

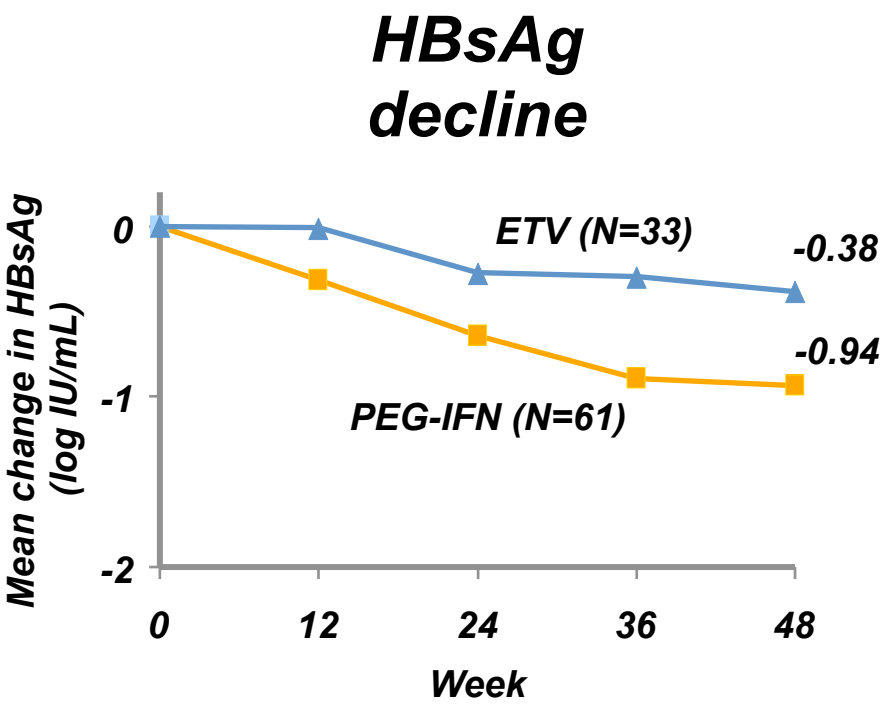
Different mechanism of action → different response durability

- HBsAg loss with immune modifying treatment vs. viral treatments such as RNA interference

Different validated endpoints could be used for different treatments in phase 2 studies (proof of concept) also because drugs with different MOA and endpoints could potentially be combined into one regimen

# HBeAg (+) patients: More HBsAg decline with PEG-IFN than ETV

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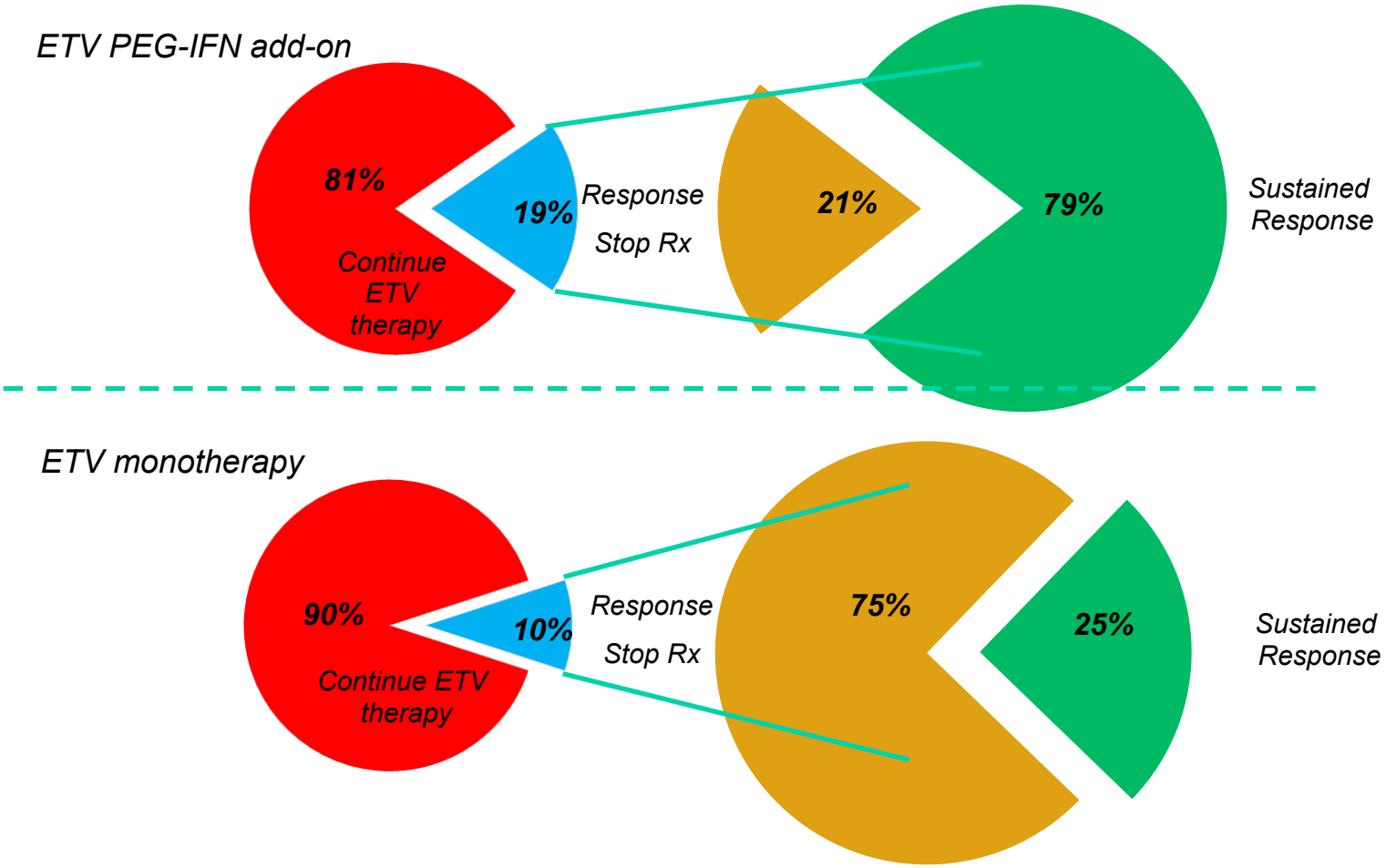
*Reijnders et al. J Hepatology 2011*

# Sustained Response: ETV Peg-IFN add-on vs. ETV ARES Study




***Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL***

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***Brouwer et al. Hepatology 2015***

# Endpoint differentiation based on clinial study phase?

## Phase 2a, b

Proof of concept

Dose finding

Safety very important

On- and off-treatment efficacy

## Phase 3

Aim is functional cure

Comparison to standard treatment

Sustained response off-treatment

# Survey: Primary efficacy endpoints for phase 2/3 trials aimed at virologic cure

| | Antiviral therapy | | Immunomodulatory therapy | |
|---|---|---|---|---|
| | **Phase 2** Rank | **Phase 3** Rank | **Phase 2** Rank | **Phase 3** Rank |
| **Serum HBV DNA undetectable** | **1** | **2** | **1** | **2** |
| **Sustained decrease in HBsAg level by >1 $\log_{10}$ IU/mL off treatment** | **2** | **3** | **3** | 4 |
| **HBsAg negative** | **3** | **1** | 5 | **1** |
| Maintained decrease in HBsAg level by >1 $\log_{10}$ IU/mL on treatment | 4 | 5 | 4 | 7 |
| Anti-HBs positive | 5 | 4 | 6 | **3** |
| Restoration of T cell response to HBV antigens | N/A | N/A | **2** | 5 |

***Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group***

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# Survey: Prediction of HBsAg loss

Assuming HBsAg loss is reliable surrogate for cure what is the desired response in phase 2 and 3 studies on antiviral and immune therapies to move to the next phase?

| Antiviral & immunomodulatory therapies | | |
|---|---|---|
| | **Phase 2** | **Phase 3** |
| HBsAg level decrease by >1log$_{10}$ IU/mL in >50% participants | **31 (47.0%)** | 12 (18.2%) |
| HBsAg loss in >10% participants | 18 (27.3%) | 21 (31.8%) |
| HBsAg loss in >30% participants | 17 (25.8%) | **33 (50.0%)** |

***Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group***

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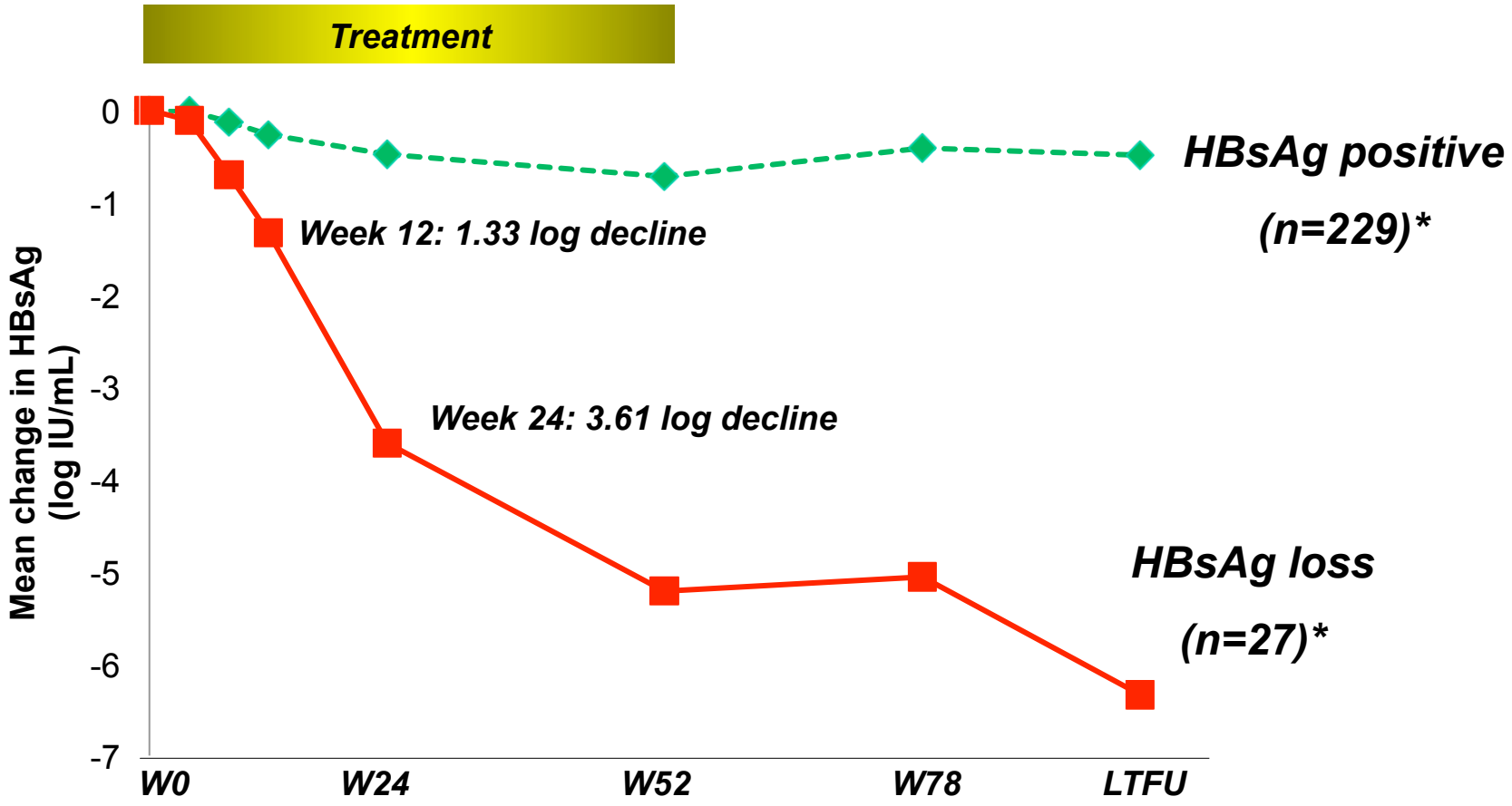
# HBeAg positive CHB: PEG-IFN α-2b
# HBsAg decline in those who achieve HBsAg loss




** At End-Of-Follow-Up or Long-Term Follow-Up*

*Baseline Mean HBsAg 4.5 log*

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***Sonneveld et al. Hepatology 2011***

# Survey: When should primary efficacy endpoints be assessed in phase 2/3 trials aimed at HBV virologic cure?

| | Antiviral therapy | | Immunomodulatory therapy | |
|---|---|---|---|---|
| | Phase 2 | Phase 3 | Phase 2 | Phase 3 |
| Month 6 off treatment | **30 (45.5%)** | **42 (63.6%)** | **33 (50.8%)** | **44 (66.7%)** |
| Month 6 on treatment | 25 (37.9%) | 4 (6.1%) | 8 (12.3%) | 14 (21.2%) |
| Month 12 off treatment | N/A | 14 (21.2%) | N/A | 5 (7.6%) |
| Month 12 on treatment | 11 (16.7%) | 6 (9.1%) | 24 (36.9%) | 3 (4.5%) |

***Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group***

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# New Virologic and Host Markers Endpoints?

## Current

### *Virologic Markers*

- HBV DNA (q, non q)
- HBsAg (non q)
- HBsAg (q)
- HBeAg

### *Host Markers*

- Anti-HBs (q/non q)
- Anti-HBc (q/non q)
- IgM and IgG
- Standard liver tests
- Imaging

## Experimental

### *Virologic Markers*

- HBcrAg (q)
- cccDNA (q)
- Integrated DNA (q)
- HBV RNA

### *Host Markers*

- PD1, Tim3, CTLA4 expression (q) on HBV-specific CD8 T cells by Flow cytometry
- CD127 on HBV-specific T cells by Flow cytometry/ functional assays
- Cytokines (q)
- HBsAg epitopes

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# New Kits on the Block

- Further standardization and validation of tests needed
- Association with clinical outcome is preferred or needed for further use
- Of interest to dissect mechanism of response in treatments targeting host and virus

# HBV cure - Remaining challenges

**Basic science**

- cccDNA biology
- Regulation of HBV specific immune response

**Translational issues**

- Standardized assays for cccDNA quantification and epigenetics
- Clinical immunology assays
- Studying viral integration

**Clinical trials, drug evaluation, new conceptsTx**

- New regulatory path
- Re-defining patient populations, virus characteristics, etc.
- New endpoints linked to cure and treatment strategy
- Combination of investigational drugs
- Safety: major issue (NUCs are safe !)

**Revill et al, Nature Reviews Gastroenterol Hepatol 2016**

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# Conclusions

- NA are effective, safe and not so easy to replace
- Shift towards endpoint of true immune control, functional cure and HBsAg seroconversion
- New Viral agents: HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development
- Direct ccc-DNA inhibition may be needed but is difficult to reach
- Immune modification: TLR/RIG-I agonist, therapeutic vaccination, PD1-PDL1 blocking in development
- Combination therapy most likely needed!
- The science is the ‘easy part’…getting these agents into people, doing the right trials and getting them approved is a whole other story…

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# Conclusions

- Quantitative HBsAg and HBVDNA will probably be the most important biomarkers used for endpoint in phase 2 and 3 studies
- Endpoints are different in naive vs suppressed patients
- Endpoints may not have the same meaning for different drugs
- For proof of concept (phase 2) studies different validated endpoints can be used for different compounds depending on their MOA, also to allow future combination therapy

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# *SPARES*

# Other Questions for HBV Cure studies

- Which patients should and can we treat with new drugs?
  - Should patients be already suppressed on nucs?
  - Is risk/ benefit different depending on therapy, age of patient or phase of disease?
  - Do different phases need different therapies?

# Conclusions

Endpoint selection will differ between phase 2 and 3 studies:

## Phase 2

- Response can be assessed on- and off-treatment
- HBsAg decline >1 log, HBsAg loss, HBVDNA decline >1 log or HBVDNA undetectable

## Phase 3

- Response should be assessed at least 6 months off-treatment
- HBsAg loss/seroconversion **and** HBVDNA undetectable
- More definite endpoint reflecting functional cure of HBV infection

# Viral Targeting Combos

- Targeting different steps in viral lifecycle may lead to greater/even complete suppression of replication
- May still require long-term therapy to clear existing infected hepatocytes…especially if a leak persists
- Given safety & potency of nucs…logical choice to combine with newer agents
- But could combine any 2 or more viral targeting agents – challenging studies (safety, monotherapy for each, different companies…)
- **Key issue**: need *assays to detect low level replication below current LOD to determine efficacy*

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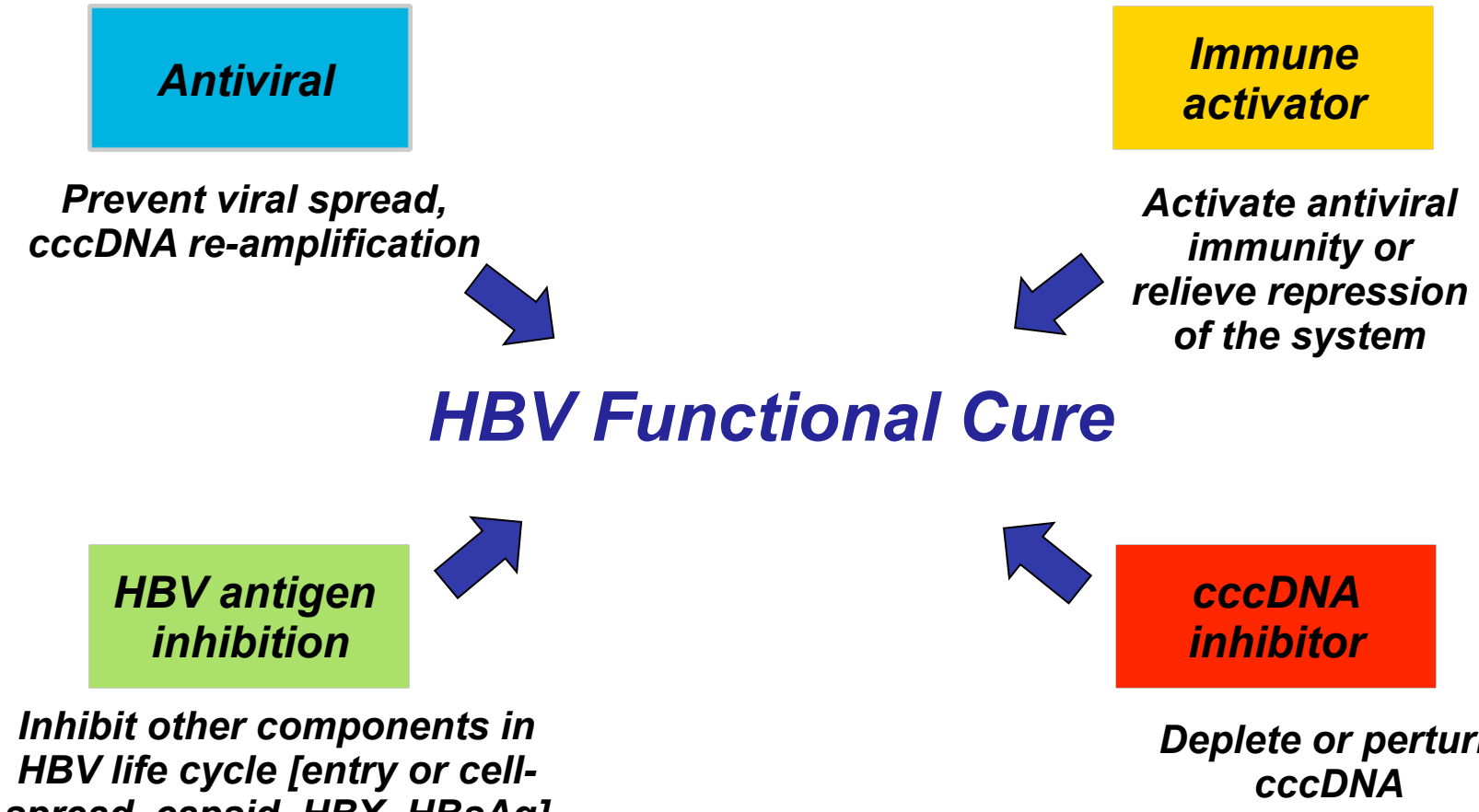
# HBV Curative Regimen?

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# Summary

- Multiple promising therapeutic approaches
- Combining tools to:
  1. Improve viral suppression to ‘plug the leak’ and prevent replenishment of cccDNA
  2. Promote immune clearance
- Combination improved antiviral + immunotherapy +/- viral protein depletion
- The science is the ‘easy part’…getting these agents into people, doing the right trials and getting them approved is a whole other battle…

# Chronic HBV: a Dynamic and Heterogeneous Disease

- Phases neither clear nor distinct
- Varying levels of HBsAg even in inactive
- Immunologic status between stages fluid
- A high level of HBV-DNA integration and clonal hepatocyte expansion in young patients even immune tolerant indicating that possible hepatocarcinogenesis even in patients with early stage CHB

# Virological Markers to Follow CHB Patients

| | | |
|---|---|---|
| **HBV DNA** | Applicable to both HBeAg + and HBeAg-<br><br>Not really indicative of sustained immune control | Standardized assays available |
| **Quantitative HBeAg** | Applicable only in HBeAg +<br><br>More indicative of sustained immune control | Commercial assays not currently available |
| **Quantitative HBsAg** | Applicable to both HBeAg + and HBeAg-<br><br>Most indicative of sustained immune control | Standardized assays available |

Immune control: HBeAg neg and low HBVDNA

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# New HBV Treatments

## Virology

- Entry inhibitors
- cccDNA Degradation/Silencing/Elimination
- RNA interference (RNAi)/Gene silencing
- Assembly (Nucleocapsid) inhibitors
- New Nucleos(t)ide Analogues

## Immunology

- PEG-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 Blocking

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# Other Potential Viral and Immunologic Endpoints in Phase 2 and 3 Studies

## Viral

- Hepatitis B core-related antigen (HBcrAg)
- HBV RNA in serum
- (Quantitative) cccDNA in liver/blood
- HBsAg epitope mapping

## Immunologic

- HBV-specific T & B-cell response
- T-lymphocyte markers
- Expression of inhibitory molecules (PD-1, Tim-4, CTLA4)
- Quantitative anti-HBs
- Anti-HBc (IgM/total)

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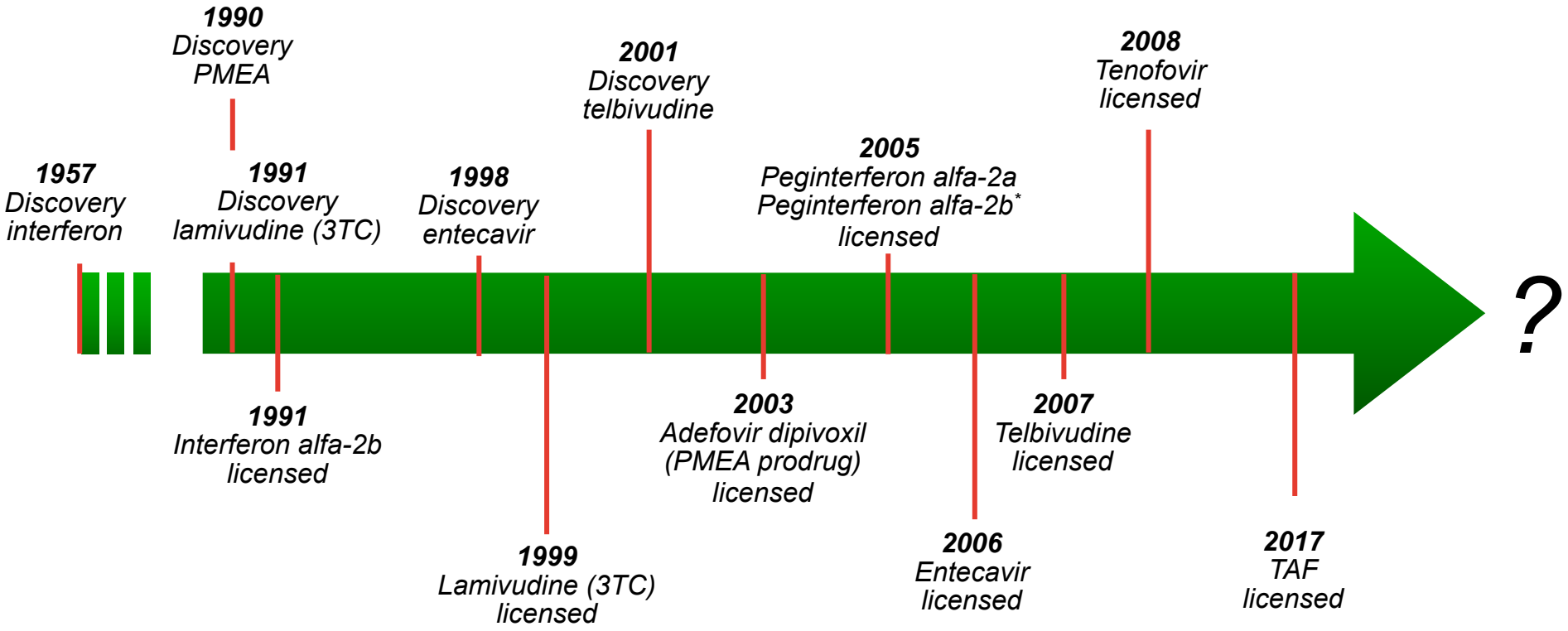
# Advances in HBV treatment




*Adapted from: ClinicalCareOptions.com*

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** Specific countries only*

# Current HBV treatments

- PEG-IFN for few patients, effective in some
- ETV/TDF for most CHB patients, very effective (>95%)
- IFN-NUC for selected patients, TAF available in 2017
- Prevention of clinical decompensation, improvement of portal hypertension, HCC the only complication
- Excellent 5-yr overall and liver-related survival
- New strategies/drugs needed to reduce HCC and to improve HBsAg loss rates

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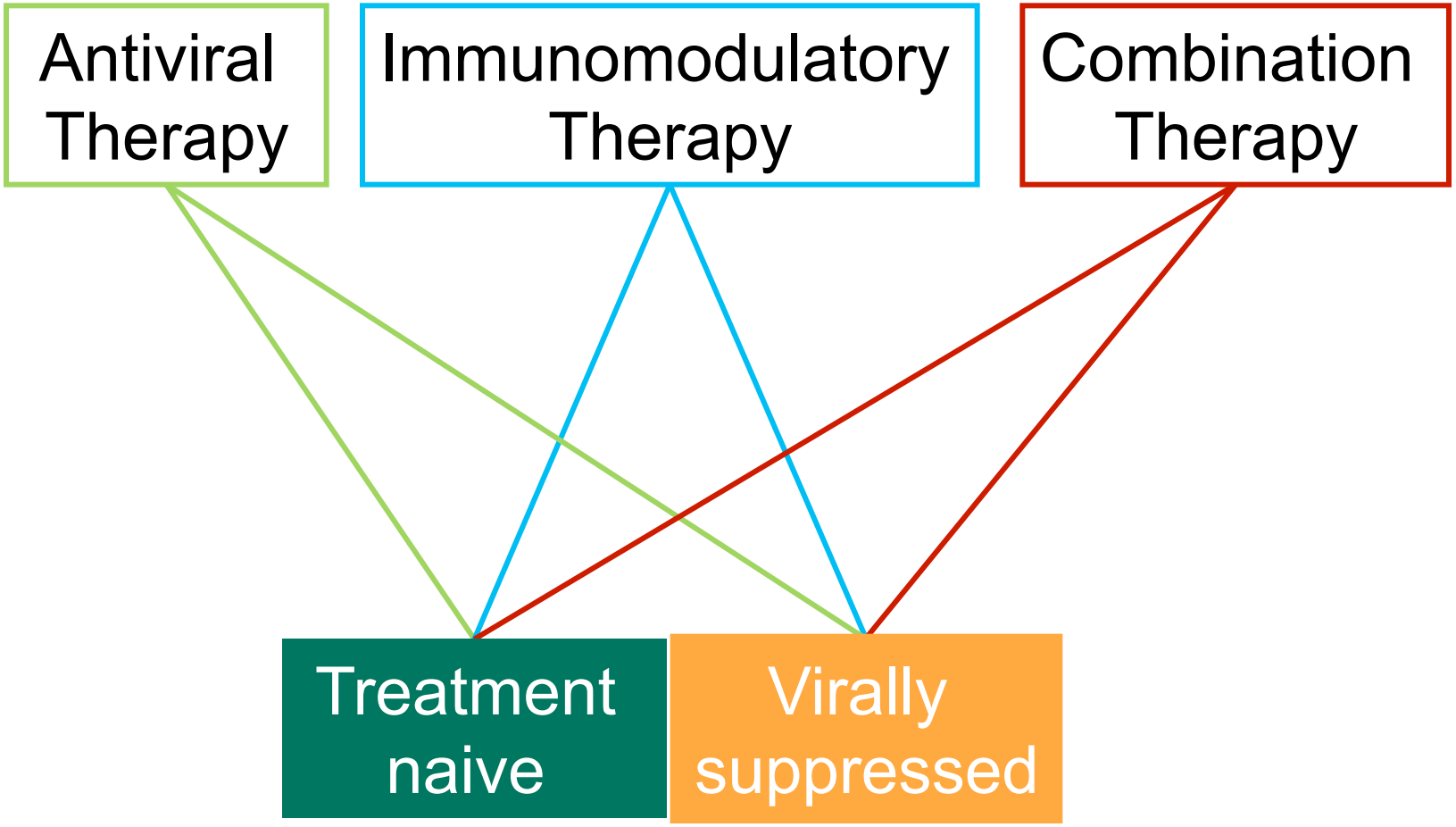
# Primary endpoint catered to treatment modality and patient group?

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