# Why do we need new HBV treatment and what is our definition for cure?

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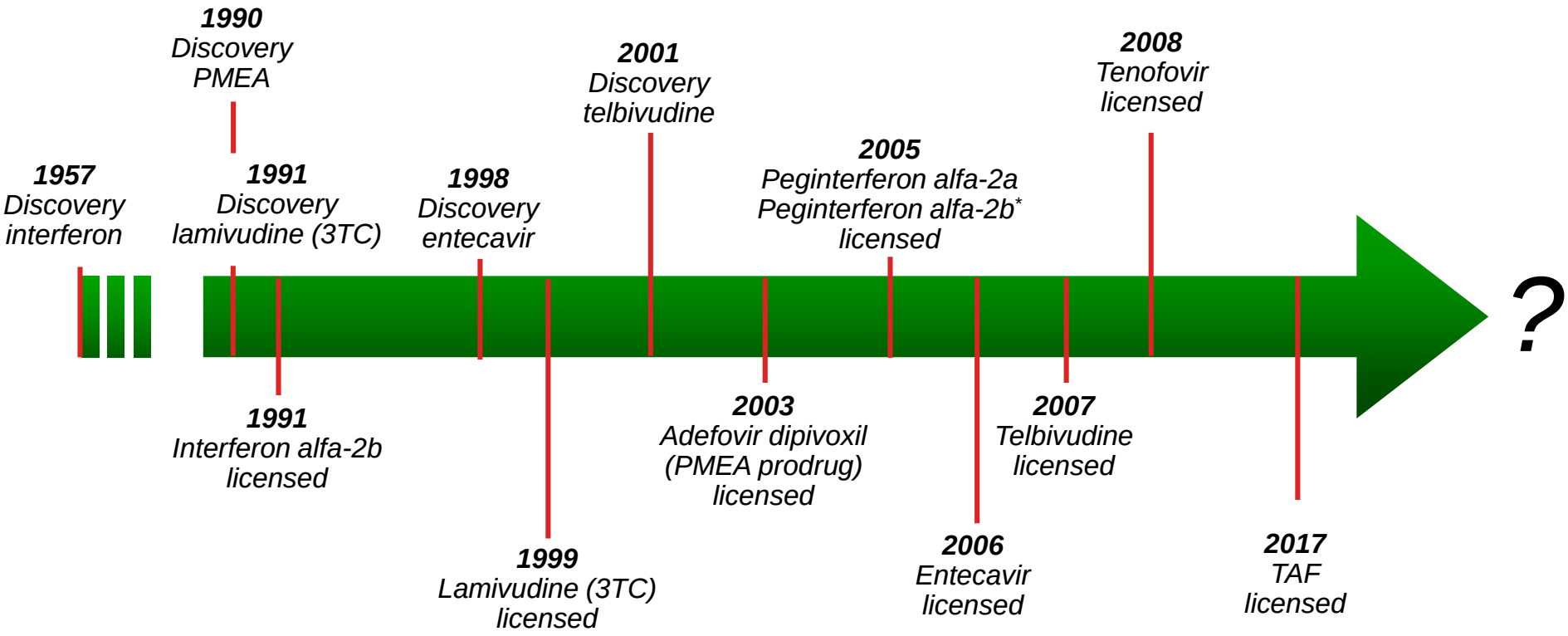
**Hepcure Meeting**
**November 2016**
**Toronto**

# 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, Innogenetics, ISIS Pharmaceuticals, Janssen, Medimmune, Merck, Novartis, Roche

# Advances in HBV treatment




*Adapted from: ClinicalCareOptions.com*

** Specific countries only*

# 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 HCV there is highly effective and safe therapy available which suppresses HBV

# 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*

# 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

- **State achieved where remission of CHB is achieved with improved long term survival**

# 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*

# 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 uncertain

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

# New HBV Treatments

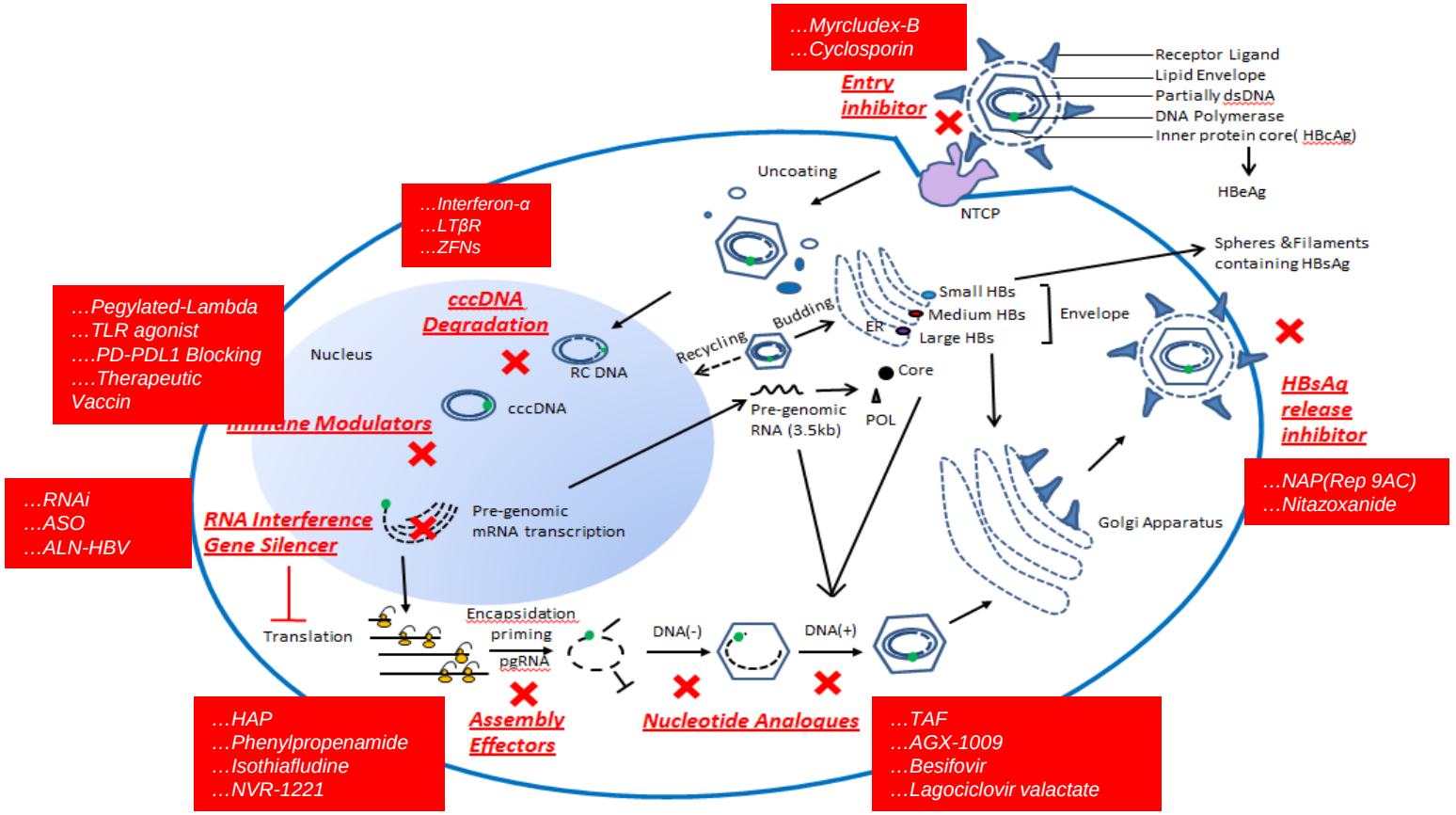
## Virology

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

## Immunology

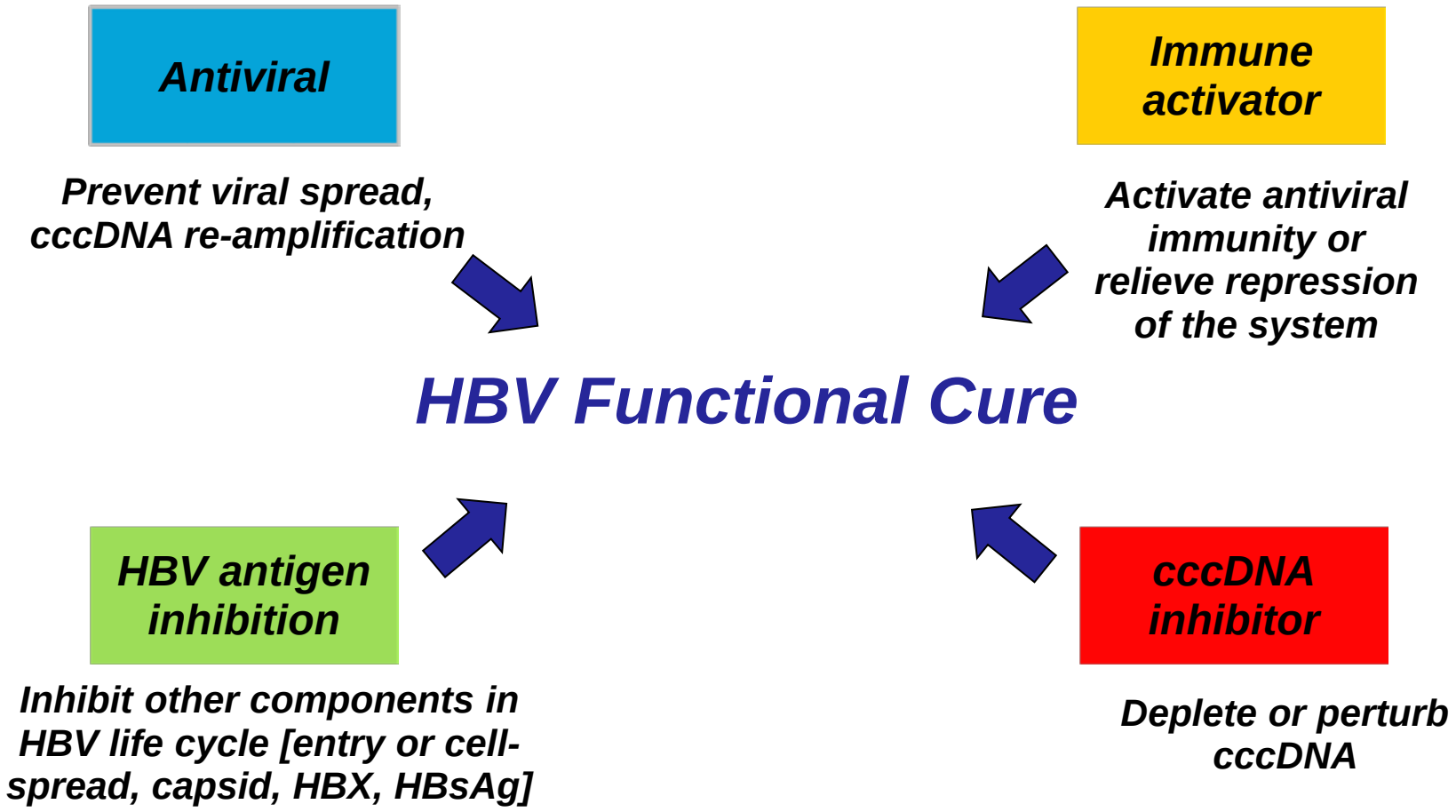
- PEG-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 Blocking

# HBV Life cycle
# Towards New HBV Treatment Targets




*Brahmania and Janssen, Lancet Inf Dis 2016.*

# HBV Curative Regimen?



# How to assess treatment efficacy
## Endpoints: The ideal biomarker...

- Predictive (visible early, and indicative of, clinical outcome)
- High specificity
- High sensitivity, also correlation with severity
- Reflective of durable response
- High reproducibility
- Non-invasive/accessible
- Rapid/simple
- Inexpensive

*Biomarkers Definitions Working Group, 2001*

# 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 |

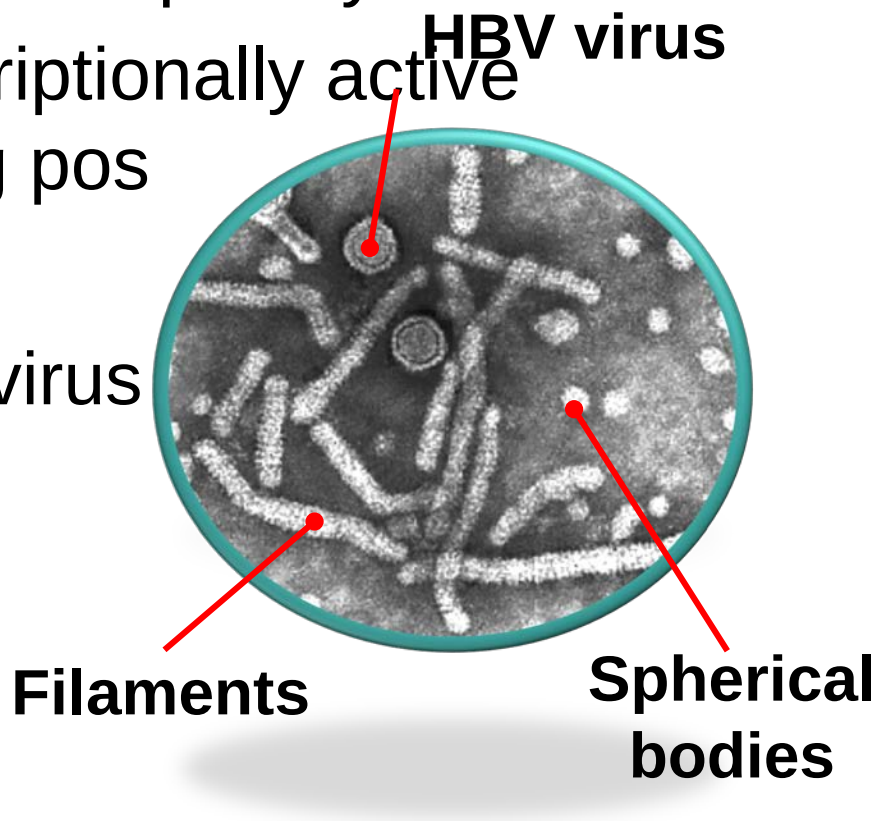
# Virological Markers to Follow CHB Patients

| | | |
|---|---|---|
| **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

# Serum HBsAg Quantification

- HBsAg loss associated with better outcome
- Reflects number of infected hepatocytes
  - Association with transcriptionally active cccDNA level in HBeAg pos
- Easily measured in serum
  - Produced in excess of virus particles
  - Standardized assays available




*Chan et al. Clin Gastro Hepatol 2007; Volz et al. Gastro 2007; Werle-Lapostolle et al. Gastro 2004*

# Endpoints: Key considerations

- 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

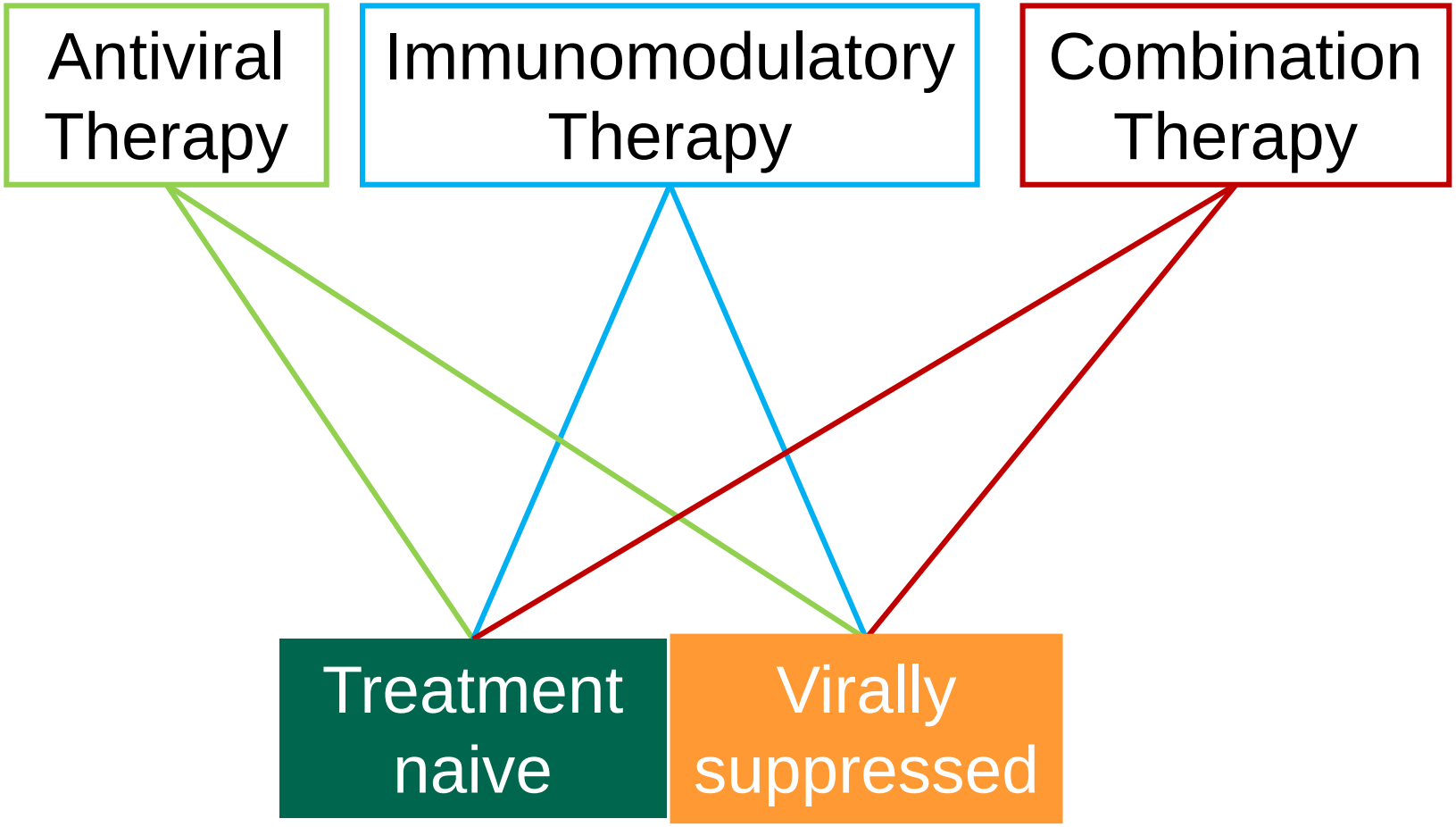
Pharmacokinetics & pharmacodynamics

# 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***

# Primary endpoint catered to treatment modality and patient group?



# Experimental 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

# 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:

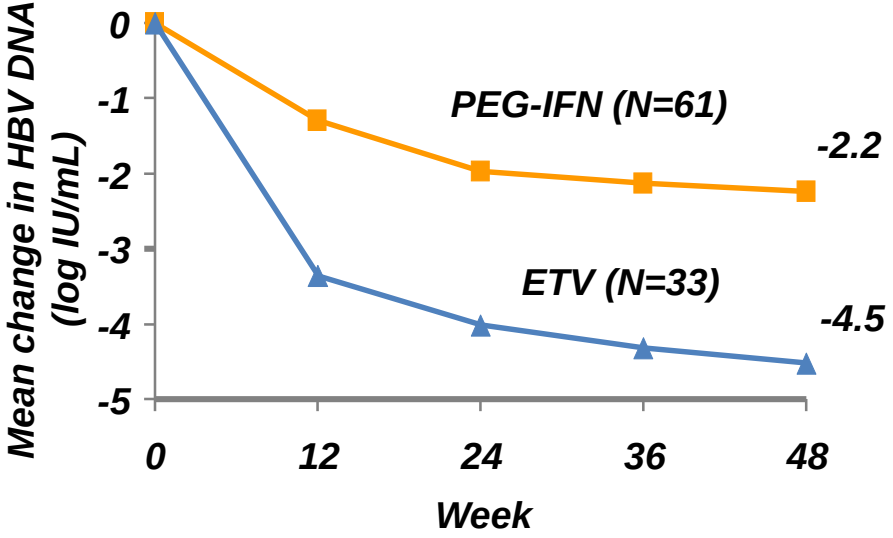
Different mechanism of action → different response durability

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

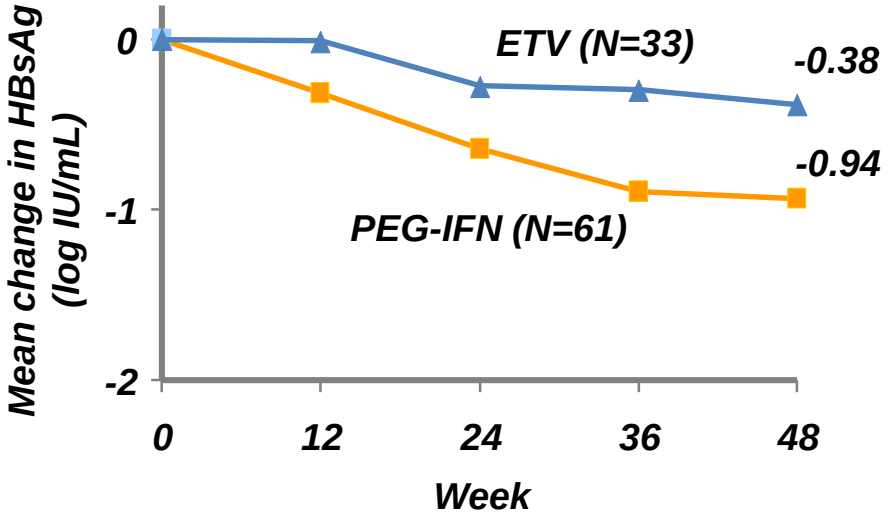
Different validated endpoints could be used for different treatments in phase 2 studies (proof of concept) also because drugs with different MOA and endpoints could potentially be combined into one regimen

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

***HBV DNA decline***

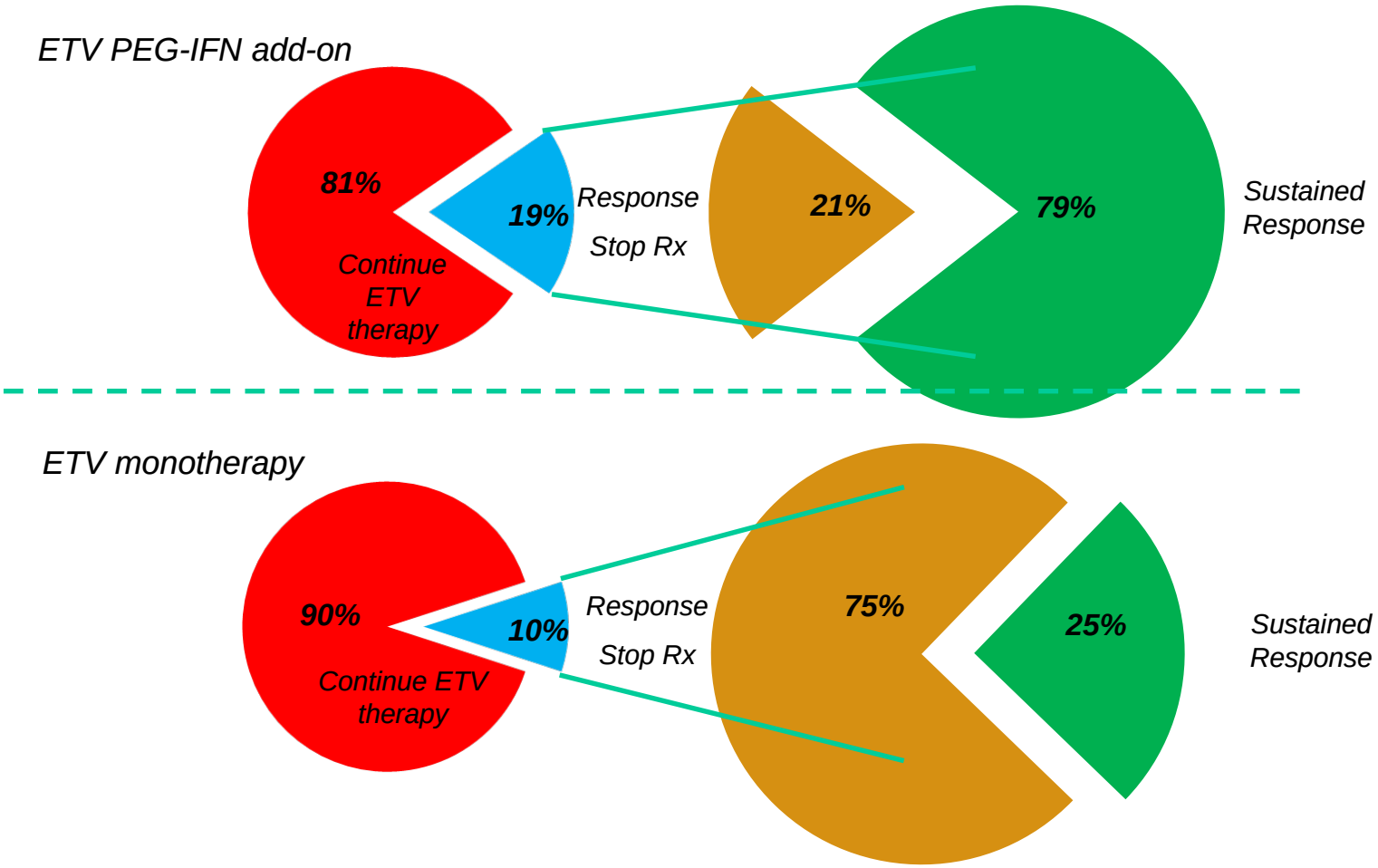



***HBsAg decline***




*Reijnders et al. J Hepatology 2011*

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




*Brouwer et al. Hepatology 2015*

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

# 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

# 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)

# New Kits on the Block

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

# Conclusions

- NA are effective, safe and difficult 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 agonist, therapeutic vaccination, PD1-PDL1 blocking in development
- Combination therapy most likely needed!

# Conclusions

- Quantitative HBsAg and HBVDNA will 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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