Take-home messages from Monday 13th January 2020

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ry 2020

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Hepatitis B : first session

therapy of hepatitis B today : HBV suppression

Who to treat? A critical review of the international guidelines ?

New endpoints and biomarkers for treatment of CHB?

Optimal management of CHB patients under NUC ?

Who to treat : critical review of international guidelines

	HBeAg +			HBeAg -		
	HBV DNA UI/mL	ALT	Liver Biopsy Or Fibrosis (NIM)	HBV DNA UI/ml	ALT	Liver biopsy Or Fibrosis (NIM)
AASLD 2018	>20.000	≥ 2x ULN		≥ 2000	≥ 2x ULN	
APASL 2016	>20.000	>2x ULN		>2000	>2x ULN	
EASL 2017	>2000	>ULN	>A1 and/or >F1	>2000	>ULN	>A1 and/or >F1
	>20.000	>2x ULN		>20.000	>2xULN	
WHO	>20.000 *	>ULN *	(>30yo)	>20.000 *	>ULN *	(>30yo)

* All cirrhotic patients regardless HBV DNA or ALT should be treated
NIM: non invasive methods

Terrault NA et al. Hepatology 2018 67; 1560-1599
Sarin SK et al. Hepatol Int 2016; 10: 1-98
Lampertico P et al. J Hepatol 2017; 67: 370-398

Who to treat : critical review of international guidelines

- The development of Guidelines is now a structured process with the global standard being GRADE, relying on systematic reviews to provide the highest quality of evidence
- The WHO and AASLD have structured scoping questions and systematic reviews in their guidelines
- Although there are some differences between AASLD, EASL, APASL and WHO guidelines, in general they are in agreement
- In the future, use of Risk Calculators may simplify selection of patients suitable for therapy
- The goal of current guidelines is to reduce disease progression and mortality, as the likelihood of cure is low but this may change with treatments that can achieve functional cure

New endpoints and biomarkers for treatment of CHB

Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference

	Sterilizing 'cure'	Idealistic functional 'cure'	Realistic functional 'cure'	Attainable Partial functional 'cure'
Clinical scenario	**Never infected**	**Recovery after acute HBV**	**Chronic HBV with HBsAg loss**	**Inactive carrier off treatment**
HBsAg	Negative	Negative	Negative	Positive
Anti-HBs	Negative/Positive	Positive	Positive/negative	Negative
HBeAg	Negative	Negative	Negative	Negative
Serum HBV DNA	Not detected	Not detected	Not detected	Low level or not detected
Hepatic cccDNA, transcription	Not detected Not active	Detected Not active	Detected Not active	Detected Low level
Integrated HBV DNA	Not detected	Detected?	Detected	Detected
Liver disease	None	None	Inactive, fibrosis regress over time	Inactive
Risk of HCC	Not increased	Not increased	Declines with time	Risk lower vs. active hepatitis

Cornberg M et al. J Hepatol 2019, epub

New endpoints and biomarkers for treatment of CHB

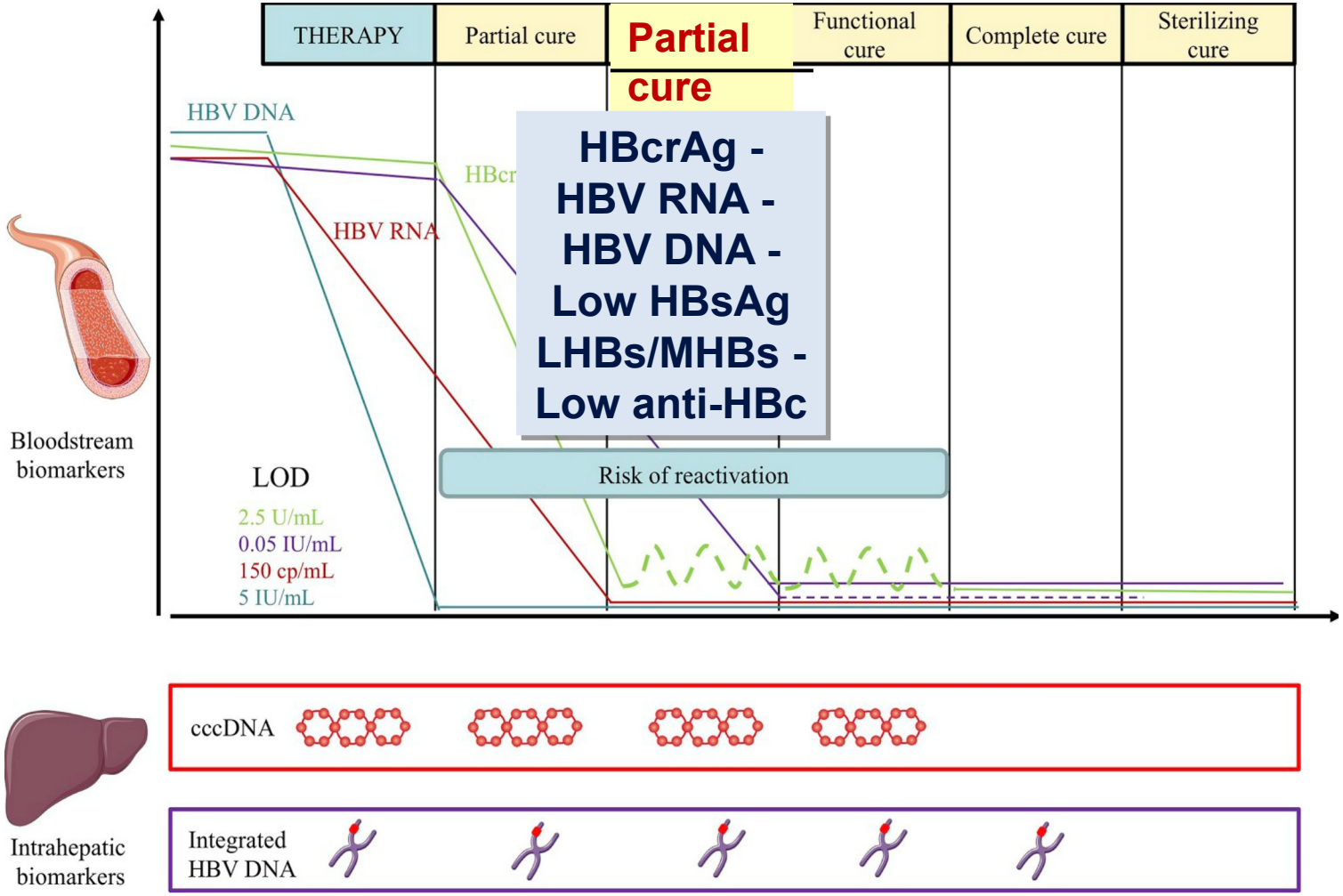
	Sterilizing 'cure'	Idealistic functional 'cure'	Realistic functional 'cure'	Attainable Partial functional 'cure'
Clinical scenario				**Inactive carrier off treatment**
HBsAg				Positive
Anti-HBs				Negative
HBeAg				Negative
Serum HBV DNA				Low level or not de-tected
Hepatic cccDNA, transcription				Detected Low level
Integrated HBV DNA				Detected
Liver disease				Inactive
Risk of HCC				Risk lower vs. active hepatitis

New HBV biomarkers – for a more refined characterisation of the activity of the infection and risk for adverse outcomes

Cornberg M et al. J Hepatol 2019, epub

New endpoints and biomarkers for treatment of CHB

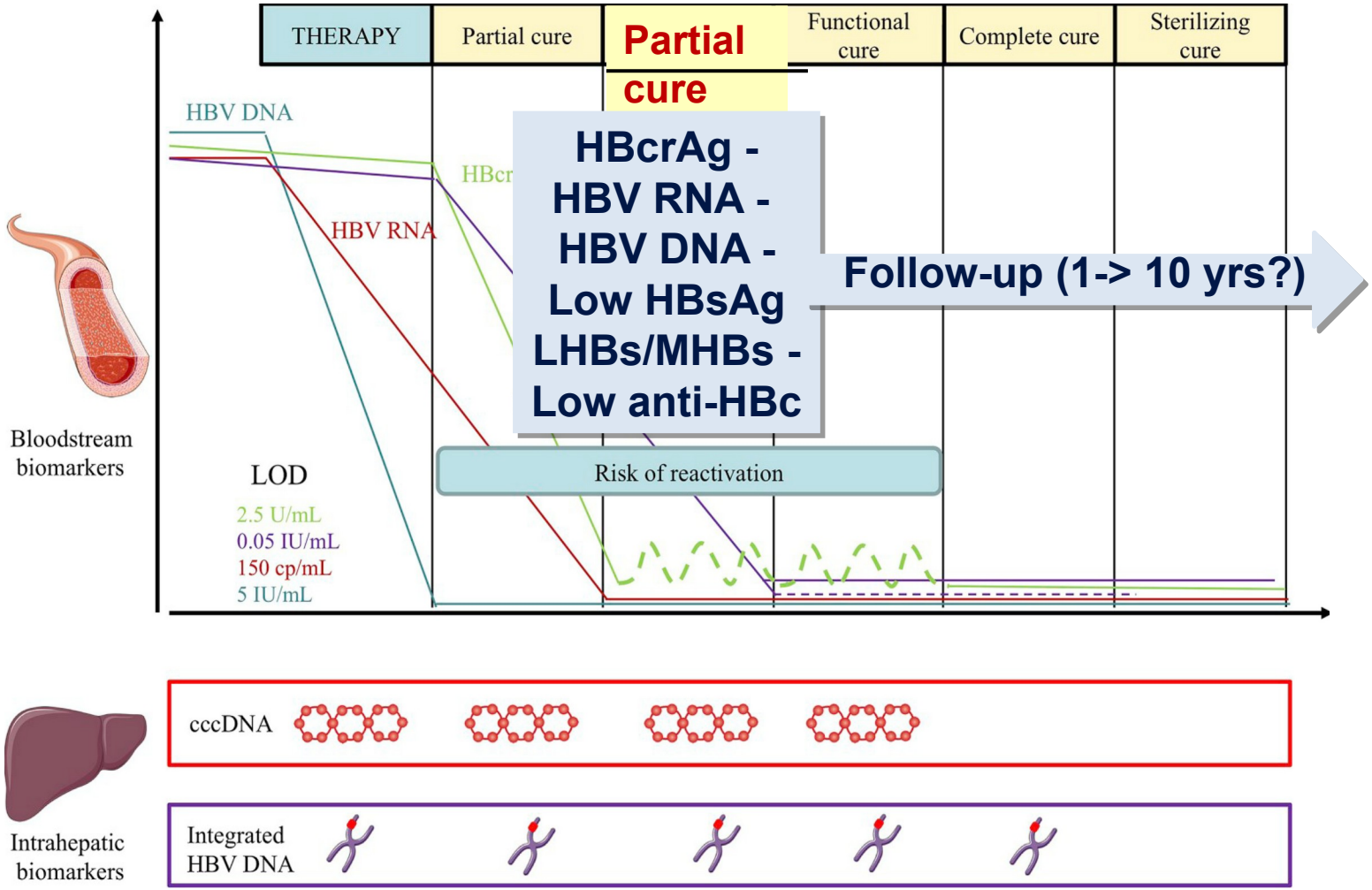
Classification of HBV-cure with new biomarkers



Charre C et al. Antiviral Res 2019; 169: 104553

New endpoints and biomarkers for treatment of CHB

Chance for transition into a true functional or even complete cure stage after having achieved a partial cure?



Modified according to Charre C et al. Antiviral Res 2019; 169: 104553

Optimal management of CHB under NUC

- **proper assessment** before starting therapy
- **selection of the most appropriate NUCs** for treatment, particularly in special populations
- switching to TAF when there are risk factors for TDF use
- **adequate HCC surveillance**, regardless of the type of NUC
- **Finite therapy duration** : further study investigating potential predictive factors of achieving HBsAg loss after stopping therapy

State of the art lecture

New EASL recommendations for the management of occupational liver disease

Take Home Message

- Collecting the occupational history is crucial. Patients must be assessed by a multidisciplinary team.
- Acute liver disease is rare compared to chronic liver injury. There are many sensitizing cofactors.
- Liver angiosarcoma is clearly associated with high exposure to vinyl chloride (in the past only), HCC is possible, cirrhosis is unlikely.
- Hepatitis and cholestasis are the dominant occupational lesions, often obscured by comorbidities such as alcohol and metabolic steatohepatitis.
- The unmet needs : availability of specific tests of toxicity.

Unmet Needs and Future Research

- A step forward in improving safety in the workplace is collecting cohort data from **occupational exposure registries** including clinical, biochemical and follow-up information in order to obtain incidence figures of hepatotoxicity and trends in re (emerging) OLD.

- The **development and quantification of sensitive and specific biomarkers of liver damage** caused by toxicants that may help in fine-tuning of differential diagnosis, without the need for histological examination of the liver.Could provide clues to prognosis.

- Advancements in the field of biomarkers would allow more effective **risk stratification** algorithms, while providing **mechanistic insights** that would help the development of safe and effective treatments.

EASL CPG on OLD J Hepatol 2019

Clinical case

Approach to the patient with CHB and decompensated cirrhosis

HB DECOMPENSATED CIRRHOSIS DUE TO HBV

HBV unknown HBV known but not being treated	Intervention

Chronic progression of active HBV
HBV flair as a result of:
• E-antigen seroconversion
• Treatment of HCV
• Cancer chemotherapy
• Treatment of immune disease
  ▪ High dose corticosteroids
  ▪ Calcineurin inhibitors
  ▪ Biologic agents
	Start or restart oral HBV treatment
	Stop inciting agent:
	• Chemotherapy
	• Immune suppressive agent
	• PEGINF
	Consider for transplant if liver function does not improve

• •	

HB DECOMPENSATED CIRRHOSIS NOT DUE TO HBV

HBV inactive HBV suppressed on treatment	Intervention
Progression of another liver disease Acute alcoholic hepatitis Acute non-HBV hepatitis Drug induced liver injury • Cancer chemotherapy • Check-point inhibitors	Treat or continue treating HBV Treat the inciting agent Stop the inciting agent Consider for transplant if liver function does not improve

Hepatitis B : second session

therapy of hepatitis B tomorrow : HBV cure

Can we cure HBV with novel direct antivirals?

Boosting innate and adaptive immunity for HBV cure ?

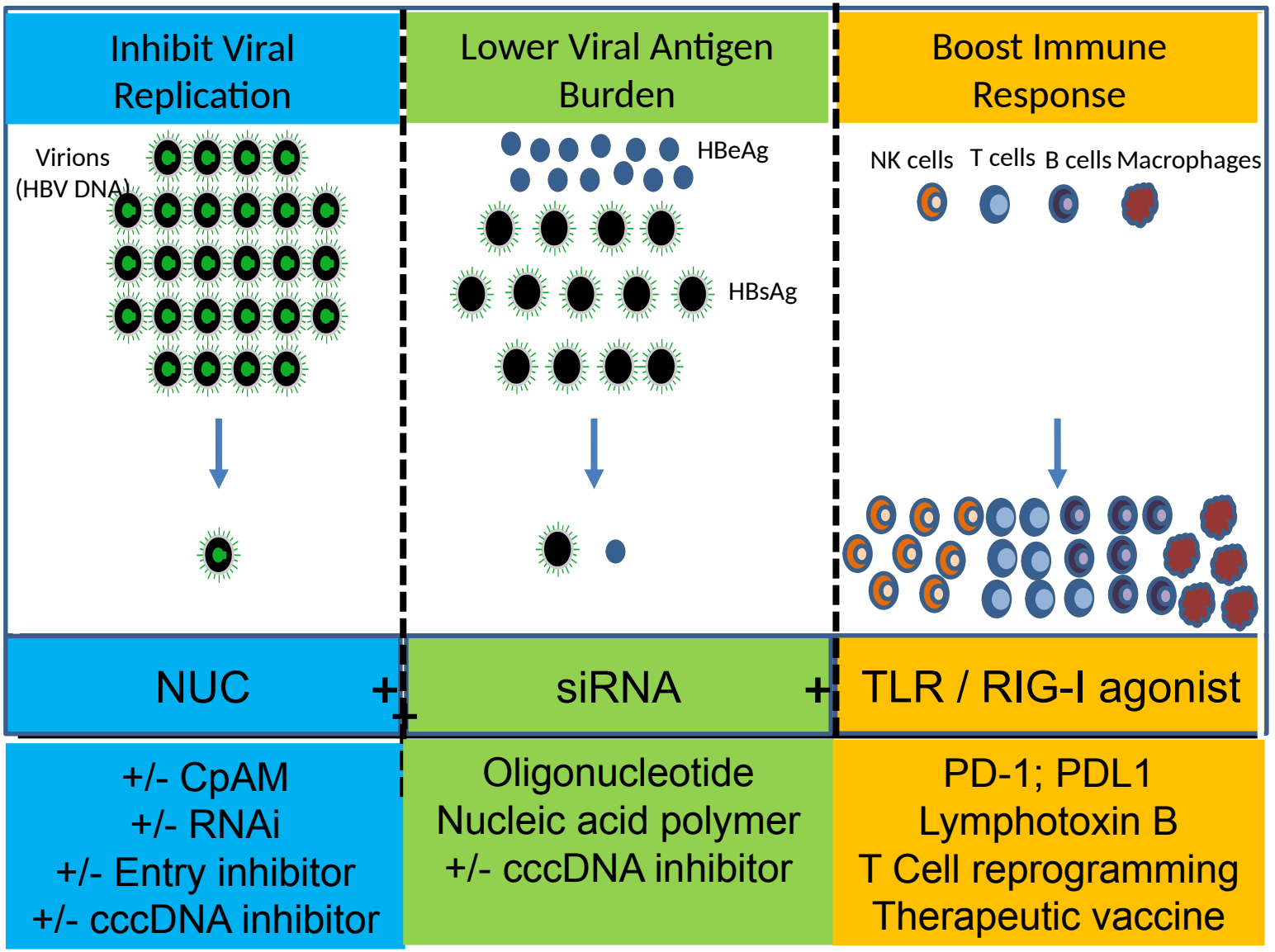
Will we need novel combinations to cure HBV infection ?

Can we cure HBV with novel direct antivirals?

Cure of HBV infection with direct acting antivirals

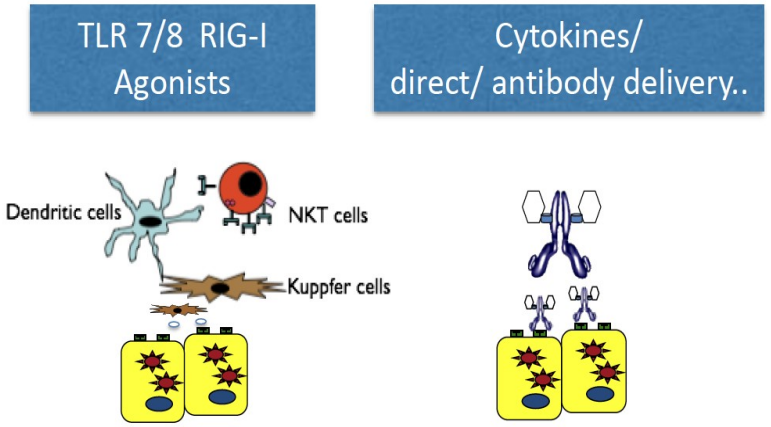
- **Curing infected hepatocytes**
- **With pre- and post- cccDNA targets**
  - Accelerate the kinetics of cccDNA decay
  - Combination therapy likely required
  - Duration of treatment will depend on the rate of hepatocyte turn-over
  - Major issue: cccDNA half-life, number of infected cells, infected hepatocyte half-life ?
- **Direct targeting of cccDNA**
  - Cytokine-mediated degradation
  - Nuclease-based gene editing
  - Small molecules
  - Still a long way to go: specificity, safety profile, delivery issues…
- **Will this be sufficient or will we need combinations with immunomodulatory approaches ?**

Pathways to Achieving Functional Cure

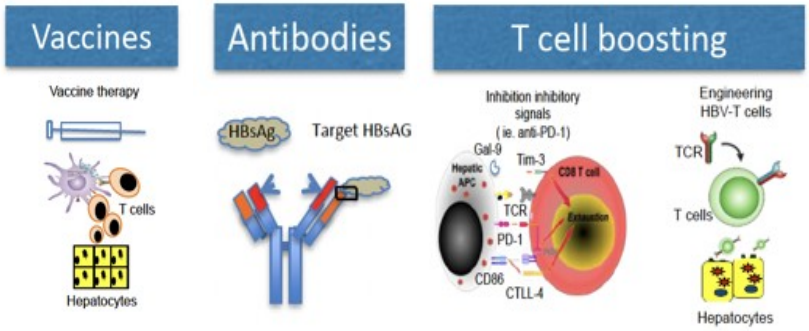


Boosting innate and adaptive immunity for HBV cure – M Levrero

Activation of Intrahepatic Innate Immunity



Restoration of HBV-specific Immunity



- CHB is characterized by defects in the intrahepatic innate immune responses, NK cells impaired in their anti-viral capacity, deeply dysfunctional HBV-specific T cells and the expansion of functionally defective HBsAg-specific atypical memory B cells

- Multiple approaches aimed to activate the intrahepatic innate immunity and to restore HBV specific adaptive immunity are actively pursued

IFN-alpha remains the only therapy that increases functional cure

Why Immune therapies didn't (so far) work?

- Immune therapy could be an important asset for HBV cure but patients selection is crucial

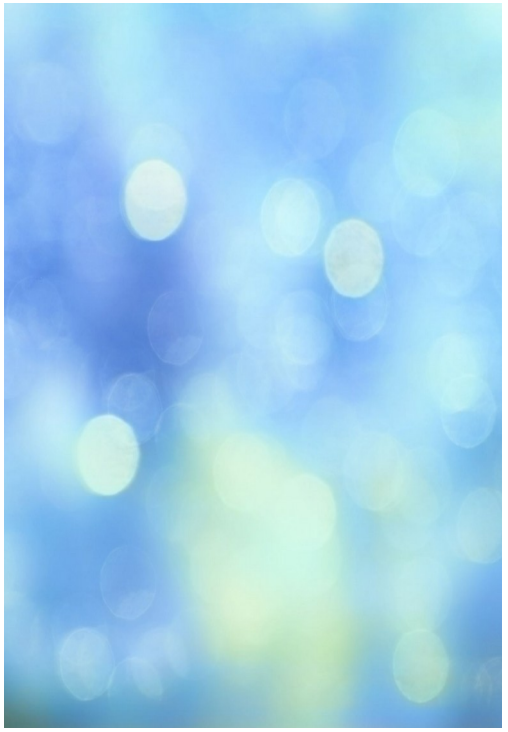
- Immune therapies need to be personalized in relation to the immune profile of disease and not only to virological parameters

Will we need novel combinations to cure HBV?

Synergistic mechanisms need to incorporate a decrease in HBV transcription, loss of cccDNA or altered epigenetic regulation of cccDNA and immune modulation or immunologically stimulated hepatocyte cell turnover.

Nucleoside analogue suppressed patients being included in many current trials. Trials are progressing to combination therapy as additive or synergistic effects are sought.

These trials will provide important insights into the biology of HBV and perturbations of the immune response, required to effect HBsAg loss at different stages of the disease.



State of the art lecture

Hepatitis E: what is the real issue ?

The issue of hepatitis E in 2020

- Incidence is high and rising
- Role of subtype (3f)
- There is a risk of transmission by transfusion
- Neurological disorders are frequent
- Treatment of acute hepatitis E with ribavirin in immunocompetent patients
- Second line treatment of chronically infected patients

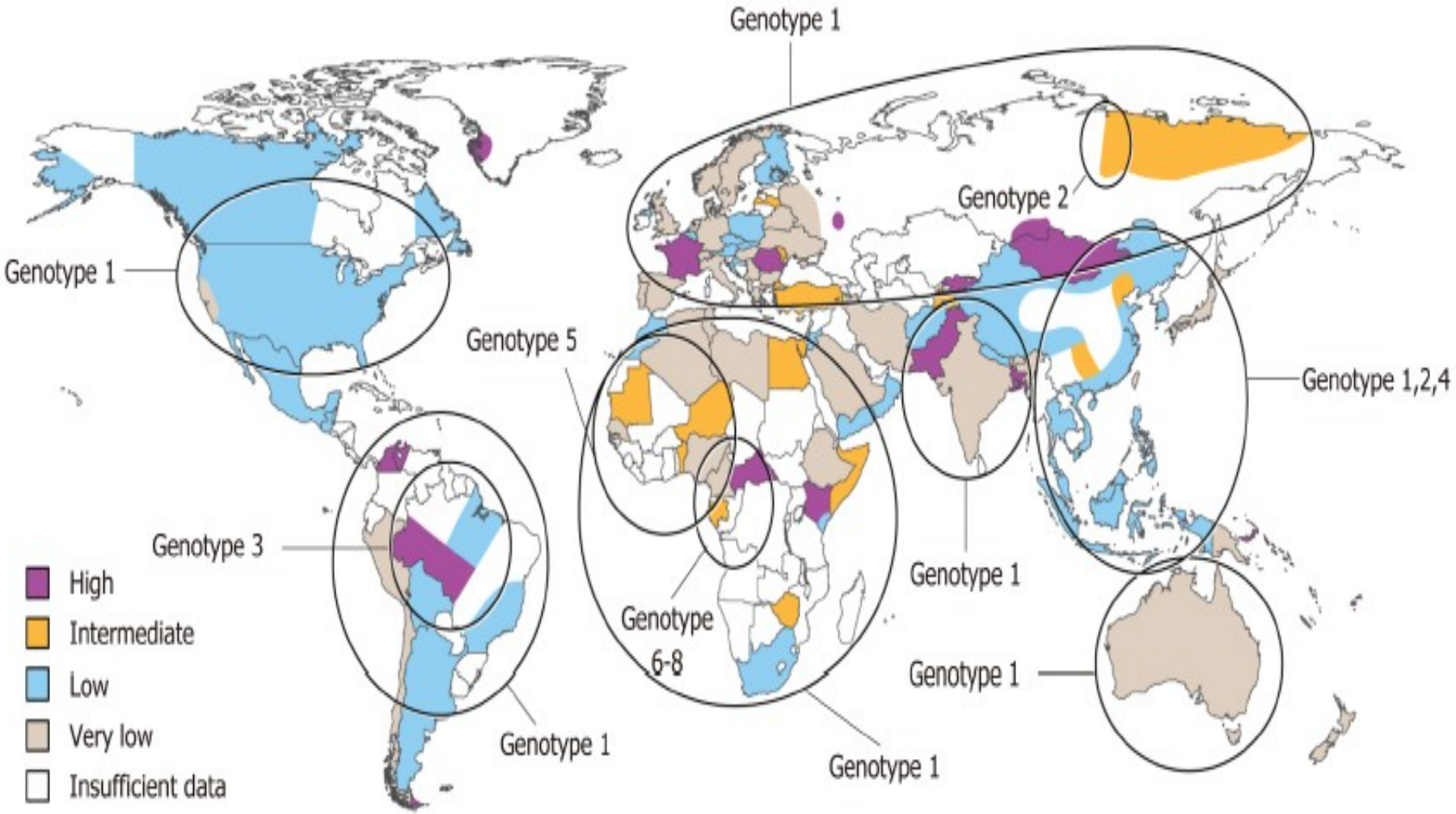
Hepatitis Delta

New epidemiology of hepatitis delta ?

How to optimize current therapy with PEG IFN ?

New drugs for HDV ?

Estimated prevalence of HDV infection with genotype distribution



Gilman C et al. World J Gastroenterol 2019; 25: 4580-97.

New epidemiology of hepatitis delta ?

- HDV infection: global health problem - increased liver related and overall mortality
- Global HDV prevalence: probably underestimated
- HDV: still endemic in many developing countries
- Illicit drug users, people with high-risk sexual behaviors and HIV co-infected: high-risk groups in the Western world
- Genuine decrease in HDV prevalence in developed countries in 1990's - no further decline and perhaps a slight increase in the last decade due to migration from endemic countries
- Need for universal HBV vaccination and universal HDV screening for HBV+ patients

How to optimize current therapy with PEG IFN ?

- Off-label use of PegIFN (48 weeks) is currently the only recommended therapy by international guidelines
- Indications: chronic hepatits and compensated cirrhosis
- Virologic response: approx 20%-30% at week 24 post-treatment but high risk (50%?) of late relapse
- Strategies to improve effectiveness: combo with NUC, extension to 96 weeks, lambda IFN…….(no/limited evidence so far)
- Predictors of response: early on therapy decline of HBsAg and/or HDV-RNA (to be confirmed)
- Long-term outcome: improved in sustained responders
- New anti-HDV therapies are urgently needed (with pegIFN ?)

New drugs for HDV ?

- Drugs in development include entry inhibitors (Bulevirtide), prenylation inhibitors (Lonafarnib), and HBsAg release inhibitors (NAP: REP 2139).
- There is a need for long-term robust end-points (HCC, cirrhosis decompensation).
- HBV cure program will also lead to HDV cure, but only in a long-term.

Awards PHC 2020

The future of autoimmune liver disease

The future of Autoimmune liver disease

- New biomarkers are needed to predict non-response to UDCA in PBC
- Obeticholic acid (OCA) and bezafibrate are used for non-response to UDCA in PBC, the combination of both and novel drugs like Selective peroxisome proliferator-activated receptor (PPAR) and fibroblast growth factor 19 (FGF19) agonists are under development.
- There is no existing treatment that alters the natural course of PSC apart from transplantation
- Several medical therapies for PSC are under clinical development like Nor-UDCA, Fecal Microbiota Transplantation (FMT) and others.
- However, generally accepted treatment endpoints as well as biomarkers for the risk-stratification are still needed for the development of novel PSC therapies

The future of Autoimmune liver disease

- Therapies for non-responders to standard-of-care are an unmet need for AIH patients
- Promising AIH therapies under development are targeting B cells, cytokines like TNF and IL 2 and Tregs

Hepatitis C : the elimination

The last difficult to treat patients

Macro elimination

Micro elimination

The last difficult to treat patients

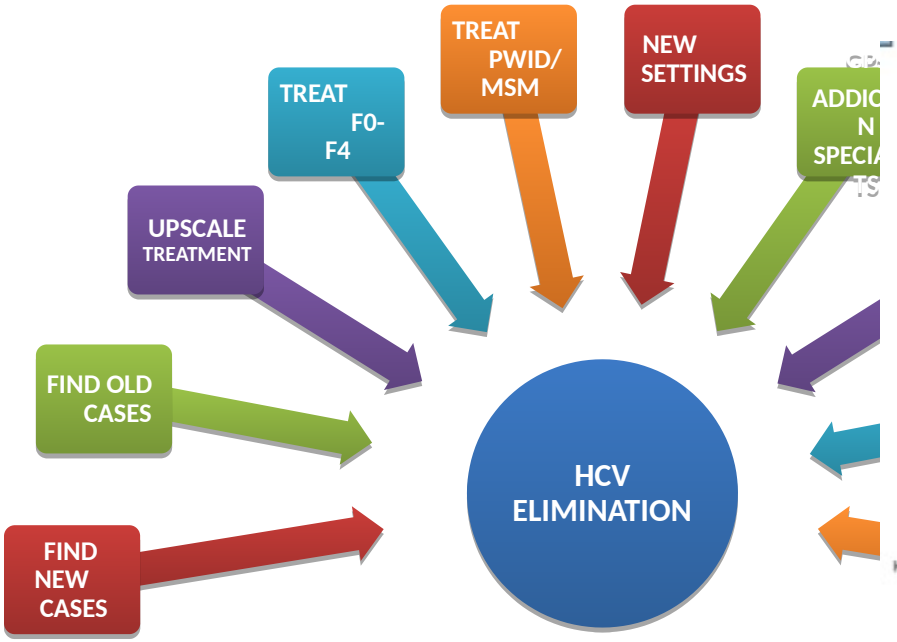
- Several challenge :
  - Homeless people / PWID
  - DDI
  - Treatment of patients with CKD 4/5 patients and decompensated cirrhosis
  - Treatment of decompensated cirrhosis with or without LT options
  - Non responders to SOF/VEL/VOX HCV
  - treatments with HCC BCLC stage B/C
  - Pregnant women
- Several challenges remain in small populations. Most likely that these populations disappear faster than the challenges are solved
  - e.g. patients with decompensated cirrhosis
- Key challenges to reduce the burden of disease in geographic regions and populations:
  - Diagnosis rates
  - Linkage to care
  - Access to DAAs

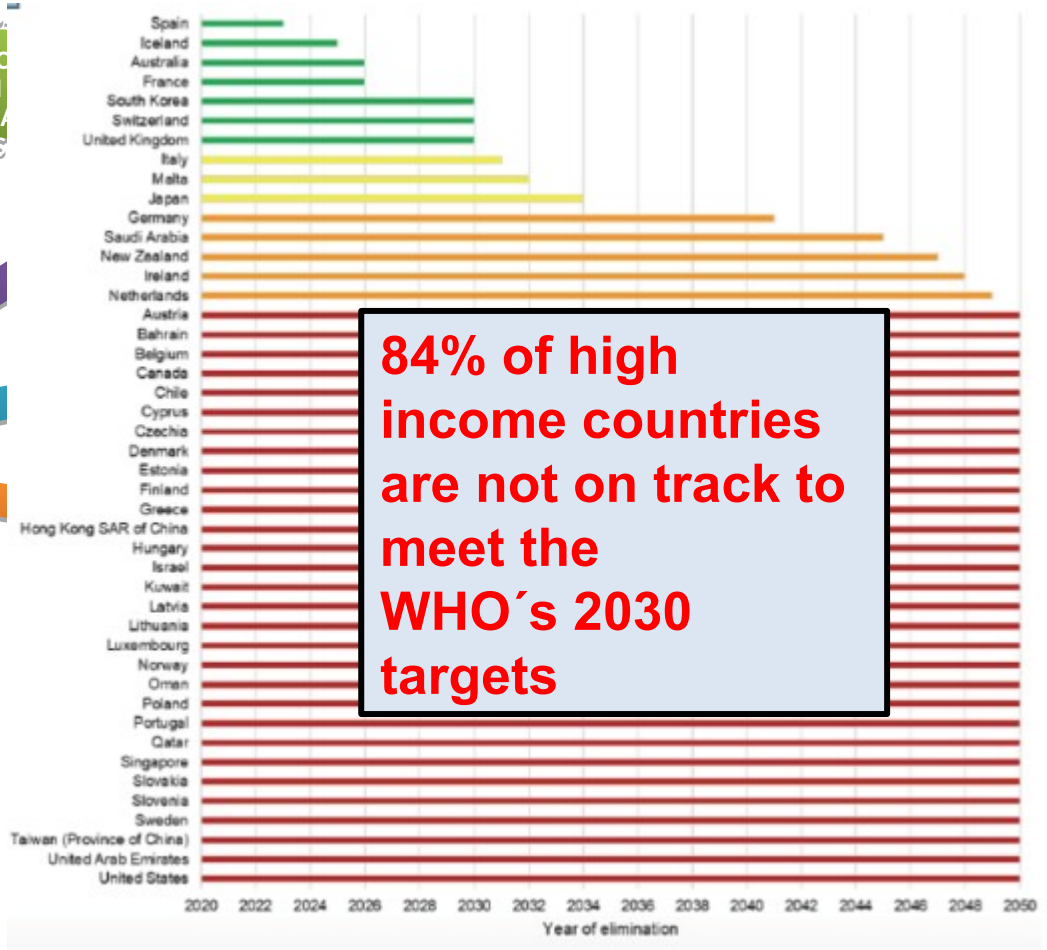
HCV Macro-elimination

- **WHO elimination goals to be reached 2030**
- **HCV diagnosis 90%, treatment coverage 80%, reduction of deaths 65%**
- **By 2017 only 12 countries on track to reach these goals**
- **Barriers for elimination still remain, awareness of the infection, economy for testing and treatment, linkage to care**
- **Reducing global burden depends on success of prevention, outreached screening and treatment and progress in key high-burden countries**

HCV Macro-elimination

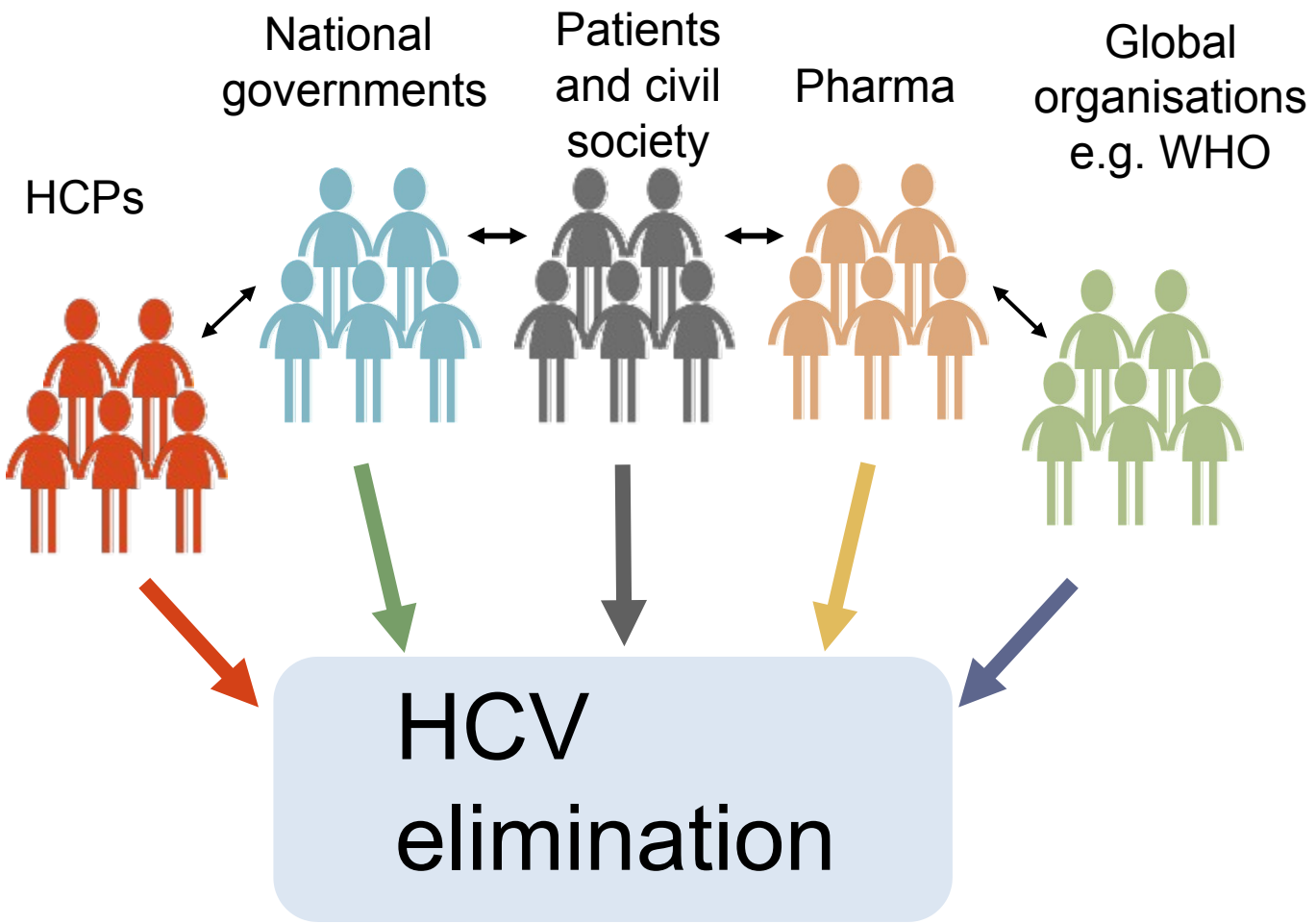
What is needed for HCV elimination and where are the patients?





84% of high income countries are not on track to meet the WHO´s 2030 targets

Collaboration between stakeholders is essential to achieve HCV elimination



HCP: healthcare provider

Micro-elimination

- At least three populations with increase complexity to reach:
  - Easy to screen patients
  - High risk of transmission patients
  - Difficult to reach patients
- Access to care even in easy to treat patients may be hard
- So be pragmatic and adopt policy at each situation

State of the art lecture

Vascular liver disease: new advance

Advance in vascular liver disease

- Diagnosis of congenital extrahepatic portosystemic shunt, and its closure, should be liberally considered.
- Slowing of portal blood flow parallels progression of cirrhosis and development of PVT. Still, no threshold of velocity triggering anticoagulation therapy has yet been established.
- Nonspecific beta-blockers may contribute to PVT. Direct evidence and exact mechanism still to be provided. No changes in current practice are yet warranted.
- Transient PVT is most common in cirrhosis. Its role as an indicator for subsequent extrahepatic extension or a factor for aggravating liver disease requires further studies.

Thank you for your attention

A great thanks to all speakers who provide me their presentation