



Addressing Regulatory Challenges of Novel HBV Therapeutic Interventions

The HBV Forum

HBV Forum 1: Summary of Proceedings

**Thursday, November 15th, 2016
The Hyatt Regency Hotel
Boston, Massachusetts**

Table of Contents

Table of Contents.....	2
Background	3
Agenda.....	4
Summary of Proceedings.....	5
<u>Session # 1: Welcoming Remarks and HBV Forum Overview</u>	5
Welcoming Remarks and Introductions	5
The Forum for Collaborative Research	5
The HBV Forum.....	5
Update on Tenofovir Alafenamide (TAF), Anuj Gaggar, Gilead Sciences	6
<u>Seeking FDA Approval of Assays that Quantify HBsAg from Patient Blood</u>	7
Discussion	7
<u>Working Group Updates: Diagnostics & Biomarkers</u>	8
Discussion	9
<u>Working Group Updates: Treatment Combinations</u>	10
Discussion	11
<u>Working Group Updates: Surrogate Endpoints</u>	12
Discussion	13
Panel Discussion: Natural Disease Progression Definitions...need for a working group?.....	14
Opportunities for Collaboration	16
<u>International Coalition to Eliminate HBV (ICE-HBV)</u>	16
Discussion	18
<u>Eradication of HBV: Singapore Translational Clinical Research Grant</u>	18

Background

The “HBV Forum: Addressing Regulatory Challenges of Novel HBV Therapeutics Intervention” project was launched in January of 2016 after a series of consultations with stakeholders in the field of HBV. The HBV Forum is aimed at advancing the regulatory science for HBV novel therapeutic interventions and its associated morbidities in real-time by providing an independent and neutral environment for ongoing multi-stakeholder dialogue.

The HBV Forum is currently comprised of 134 members representing different stakeholder groups, including members of academia, researchers, representatives of pharmaceutical and diagnostic companies, regulators from the US and Europe, and patient advocates/representatives.

The HBV Forum has a Steering Committee (SC) consisting of 18 members that provide overall scientific leadership, suggest topics for consideration, and prioritize the research questions to be addressed in the project. The SC had its first in-person meeting in June of 2016 where members prioritized the different topics of interest for the project, and three working groups were organized:

- 1. Diagnostics/Biomarkers Working Group**
Co-chairs: Ed Marins, MD and Gavin Cloherty, MD.
Aim: Develop clarity on what is needed for biomarker acceptance and validation for HBV drug/diagnostic development
- 2. Surrogate Endpoints Working Group**
Co-chairs: Marion Peters, MD and Oliver Lenz, PhD.
Aim: Strengthen the link of surrogate markers (endpoint in clinical studies) with long term clinical outcomes (e.g., liver disease progression/HCC)
- 3. Treatment Combination Working Group**
Co-chairs: Prof. Lim Seng Gee, MD and Bruce Given, MD.
Aims: I.) Provide clarity on the requirements of novel agents in clinical development, and II.) Identify mechanisms to speed up the development of combinations of different promising agents across companies

On November 15th, 2016, the HBV Forum held its first face-to-face meeting (HBV Forum 1) at the Hyatt Regency Hotel Boston, in Boston, Massachusetts following the AASLD Liver Meeting. This is the summary of proceedings of the HBV Forum 1.

Agenda

1:00	Light Lunch Reception	
1:30	Welcoming Remarks	Veronica Miller & Bill Symonds
1:35	HBV Forum Overview	Pedro Goicochea
1:55	Update on Efforts to Get Quantitative HBsAg Assays	Timothy Block & Robert Gish
2:15	WG Update: Diagnostics & Biomarkers	Gavin Cloherty & Ed Marins
2:35	WG Update: Treatment Combinations	Bruce Given & Seng Gee Lim
2:55	WG Update: Surrogate Endpoints	Oliver Lenz & Marion Peters
3:15	Natural Disease Progression Definitions	Panel Discussion
3:45	Break	
4:05	Opportunities for Collaboration: ICE-HBV	Peter Revill
4:20	HBV Cure Project U of Singapore	Seng Gee Lim
4:35	Wrap-up + Next Steps	Veronica Miller & Bill Symonds
4:50	Networking Reception	
7:00	Adjourn	

Summary of Proceedings

Session # 1: Welcoming Remarks and HBV Forum Overview

Moderators: Veronica Miller, The Forum for Collaborative Research; Bill Symonds, Arbutus Biopharma

Welcoming Remarks and Introductions

The Forum for Collaborative Research

- The Forum of Collaborative HIV Research is now The Forum for Collaborative Research (The Forum). Though based in Washington D.C., the Forum is affiliated with the University of California Berkeley, School of Public Health.
- The Forum's overall principle for all disease areas is: once new drugs and therapeutic strategies are identified, their efficient, safe development is in the best interest of all stakeholders, most of all, the patients.
- The Forum seeks to increase clarity, efficiency, collaboration and innovation, and decrease uncertainty, redundancy, development time, and risk.
- All stakeholders are involved in the process. There is a co-ownership and everybody has an equal voice.
- Participation in the Forum is by invitation only, and is not a venue for marketing or investors. These meetings are meant to be a safe space for participants to be as open as they choose. What is said at the Forum stays at the Forum.
- The Forum gratefully acknowledges the AASLD/EASL HBV Treatment Endpoints Workshop in September 2016 for the great effort to set the stage for the discussions that will occur in this meeting.

The HBV Forum

- The HBV Forum was organized after a series of informal stakeholder consultations conducted in 2015 - 2016 by Jonathan Liu, a Forum intern from the University of California Berkeley, School of Public Health. There are currently 134 members that represent academia, industry, regulatory agencies, and patient and community groups.
- A steering committee (SC) for the HBV Forum sets the agenda, prioritizes topics, and identifies the major questions that should be addressed. William (Bill) Symonds is the HBV Forum industry co-chair, and the academic co-chair is to be determined.
- Jonathan Liu wrote his thesis based on the interviews he conducted, for which he was awarded the Sandy Elberg Award for the best Master's comprehensive paper at the School of Public Health. This thesis then became a paper co-authored by members of the HBV Forum SC and was published by the Journal of Virus Eradication in January 2017.
- The Forum supports the HBV Forum operations by providing a project manager and graduate student assistants.

Update on Tenofovir Alafenamide (TAF), Anuj Gaggar, Gilead Sciences

Presenter: Anuj Gaggar, Gilead

- TAF was approved in the U.S. on November 10th, 2016 for the treatment of HBV. Two Phase 3 studies of 1,300 patients were conducted in e positive and e negative patients in 220 sites and 19 countries using a 48-week endpoint to compare TAF versus TDF.
- With every drug, the populations studied need to be expanded to others you'd like to have involved. It was difficult getting African Americans enrolled, which is something to focus on moving forward, especially as we think about HBV in Africa.
- Other challenges included finding decompensated liver disease for hepatitis B, and getting enough experienced patients in that patient group during a Phase 3 trial.
- Gilead struggled with different agencies on what the exact definition of treatment experience should be, especially with nucleos(t)ides and analogues, and these became sticking points for some agencies. It would be good to have a uniform definition of how to approach a treatment-experienced population.
- Another important point is the fluctuation of ALT DNA levels, and e antigen status changes.
- Enrollment in studies is based on the screening criteria of ALT and DNA; however, many things can happen in the intervening 28 days.
- Getting a better understanding of how to deal with those fluctuations in patient populations from the time of screening to enrollment, and how to define patient population based on the single ALT level at baseline versus the screening plus the baseline levels is relevant.
- In HCV, the negative predictive factors for treatment worked out well. While there are things that go into trials expecting to be negative predictors, we learned additional negative predictors for antiviral treatment (many of them published in the posters in the AASLD meeting). When thinking about designing a trial, we need to think about treatment experience, viral load, and baseline cirrhosis data, and also HBV genotype.
- Gilead has learned a lot about genotype D patients and how different they can be from genotype A patients, and then genotype B and C which are traditionally grouped together.
- When designing trials it is important think about those distributions because as you get into smaller subgroups, the differences in those distributions make a big difference.
- Prioritizing these negative predictors depending on the agent and patients could be a topic for the HBV Forum.
- How should we continue doing in-depth evaluation to determine resistance by more advanced sequencing methods?
- Moving from population sequencing to deep sequencing, and moving away from just *pol* RT sequencing to whole genome deep sequencing.
- Continue building infrastructure for phenotype testing is a very labor-intensive, complicated process but a very important one.

Seeking FDA Approval of Assays that Quantify HBsAg from Patient Blood

Presenters: Timothy (Tim) Block and Robert Gish, Hepatitis B Foundation

- Almost every therapeutic that involves new approaches addresses quantitative levels of the circulating viral envelope protein sAg, and it seems that it is going to be an essential laboratory value that we will have to follow.
- The quantitative sAg “quantifies” the circulating sAg, which is important to establish correlates of health, relative levels of health, staging, and is important in terms of monitoring therapy.
- In Europe and Asia, quantitative sAg is available for guiding patients through approved tests.
- After the AASLD/EASL Endpoints Workshop meeting in September 2016, there was an action call to facilitate the adaptation of quantitative sAg.
- Resulted in bringing together scientists, academics, experts, and US FDA members, with the aim of having quantitative HBsAg approved by the US FDA.
- There is a body of data where a quantitative sAg has been measured in patient samples and we are seeking to use that information and specimens with guidance from FDA representatives to avoid having to do expensive prospective studies. The first task was to call together a working group of representatives.
- This is not a diagnostic test since patients are already coming with HBV, but it could be useful to make a diagnosis of how severe their liver disease is, what their risk of progression is, if they should go on a therapy, or stay on a therapy.
- Quantitative sAg can help find what stage of disease a patient is. It is very hard with ALT to decide how sick somebody is because ALT is only done twice a year or four times a year. There is also liver biopsy, transient elastography, APRI score, and FIB-4, blood tests for staging patients, but quantitative sAg is part of that process.
- Hepatitis delta RNA testing has been available for 4 – 5 years through the CDC, and should be requested to be available in U.S.
- What the task force is aiming at is to get an approval or clearance for quantitative sAg assays, using the existing data, information, and specimens that are available. It will probably be more narrow and within the class III designation, but it will be an airtight assay that correlates very well. If we get clearance for stopping rules or for sAg levels on NUC therapy, it will then be available for use with patients.

Discussion

- As a task group we just understand what information is available and what the appropriate approaches are to move forward with the FDA. **This** will involve looking at the data and consulting with them around what intended uses the data might support and whether or not they would require additional testing, prospective testing of retrospective samples. Hopefully, we can pick the path of least resistance so that this can be done in an expedited and cost-effective manner.

- There are positions that have the notion that having a quantitative sAg test available to use as stopping rule for interferon therapy is essentially irrelevant in the U.S., however, there are many other potential applications for quantitative HBsAg testing.
- The challenge here is to use information that is out there and is unambiguous for which approval can be obtained by using prospectively collected samples that are now retrospective in access.
- Those already exist, and apparently the data is sound and good enough that an approval or clearance can be obtained with this information.
- Whether or not quantitative HBsAg is used strictly for interferon stopping rules will depend on clinical judgment.
- *There ought to be a good guidance document, whether under the auspices of AASLD or the task force so anybody who is interested knows the potential utilities of this assay.*
- Outside of the U.S., the quantitative sAg is extensively used not only related to interferon but to diagnose patients with inactive disease or that are e negative where there is a gray area on what their prognosis will be for stopping NUCs. There is an abundance of literature supporting this. A couple of questions would be:
 - What is the definition of sound data for the FDA?
 - What do you need to get to them?

Working Group Updates: Diagnostics & Biomarkers

Presenters: Ed Marins, Roche Diagnostics and Gavin Cloherty, Abbott Diagnostics

- The mandate of the working group is to map out markers that might be needed for drug development and approval, and to review and discuss the potential regulatory paths for these markers.
- There are several potential biomarkers available that are used in clinical practice, others that are still in research, but what is available commercially is limited mostly to HBV DNA and serologic markers for surface and envelope antigens.
- The working group is also working on quantitative sAg to have a picture of its status worldwide, identify the need in the U.S., and how we can tackle some of the challenges. Also working on identifying the new markers that are in the pipeline, and how we can use the experience from the previous markers that are already registered to expedite the process.
- The activities the working group are focusing on include identifying what is the regulatory status of the following markers:
 - Anti-HBc, Anti-HBs, qHBsAg, qHBeAg, HBcrAg, HBsAb/Ag complex, HBsAg Epitope Mapping, HBV DNA, HBV cccDNA, HBV RNA, HBV Genotype, HBV Resistance, HBV CP/BCP,
 - Markers of inflammation
 - HCC

- Not all could be used in clinical practice, but based on the input from the different stakeholders and the other working groups, the working group will prioritize them to define what would be necessary to get them available to market.
- A second activity is to perform a systematic review of the literature supporting the performance and utility of these potential tests. The working group is organizing the first article review on sAg quantification, which will include recommendations for the registration paths for the key identified markers that are pending registration.
- A third activity is to identify if there have been similar markers in other disease areas like HIV or CMV, and research what was the regulatory pathway these went through to get their registration and assess/evaluate if some of this experience can be applied for the approval of new HBV markers.
- In terms of outcomes and products, the working group aims to produce a markers assessment tool (spreadsheet) where all different markers are listed to then assess what is their availability, use, limitations and what is expected of them. This tool will be aligned with the work the Surrogate Endpoints working group is doing to decide and prioritize what are the most important markers the group should be focusing on.

Discussion

- A question for the regulators is if HBsAg needs to be validated as a biomarker or an endpoint in the U.S., *since* sAg loss is a surrogate, not a clinical event.
- To consider HBsAg as a surrogate marker requires clinical data to support that as a biomarker *it* is sufficient as a surrogate marker so that it becomes validated. We would not be calling it a surrogate marker at that point. For hepatitis B we would need to know what does it exactly mean when you have a decline in quantitative sAg. What does that translate to? What benefit are patients receiving when their surface antigen drops?
- Depending on the different mechanisms of action of the drugs, no matter how you reduce the antigen, the effect on clinical progression should be the same. By analogy, the sAg loss would be the surrogate for actually accelerated approval, not for full approval.
- *Full* approval comes when you show the clinical benefit of surface antigen loss and you validate surface antigen loss as the appropriate validate surrogate for clinical benefit.
- *The* validation that needs to go with the traditional approval, if we're talking about using that biomarker for accelerated approval, given hepatitis B is a serious and life-threatening disease, should be confirmed with clinical data within a reasonable amount of time.
- If the endpoint is sAg loss versus cancer survival, this could be a problem because there is no need *for* surface antigen quantification. Quantitatively, the approach would not be sAg loss but sAg decline (half log, one log, two logs), if this is the way, then really there is very few data.
- There are two issues: What is the clinical value of qualitative sAg with a reasonably sensitive assay?
- We believe that sAg loss with an approved diagnostic assay with reasonable sensitivity could be an approvable endpoint in phase 3 trials, using historical data.

- For quantitative sAg, the problem is the positive predictive value for various changes in quantitative sAg is a little fuzzy right now, though the negative predictive value at least for interferon is very good. Can we use historical data to get approval of quantitative sAg as an efficacy endpoint?
- Currently, the HBV DNA is an approved marker. With loss of sAg the inference is that there is no detectable HBV DNA. It is not only just surface antigen quantification, but also absence of detectable virus at the same time. Whatever the quantification is, this must be viewed *ed* in light of the absence of HBV DNA. That also needs to be acceptable as an endpoint for long-term outcome because that has been looked at on therapy.
- HBV DNA is incredibly important as is HBsAg, but if the discussion is on HBV cure, we need to realize that there are different types of cure, and that the viral kinetics in HBV DNA, the viral kinetics of decline in sAg, and the viral kinetics of decline or lack thereof in cccDNA, all together, gives us a much better insight into who is going to have a cure in those different categories and then how sustained that might be.
- There is work done on samples from the adefovir phase 3 trials comparing the decline in HBV DNA and HBsAg, and then the assays that were done from liver biopsies on cccDNA, and then the work that Alan Perelson did looking at those different kinetics and how long would it take to clear, and how long would you need to treat as we bring in these new combinations that are going after different targets. It could be very valuable to do those kind of kinetic evaluations to do the mathematical modeling with those regimens so that we understand if we can really clear cccDNA.
- There is need to standardize all assays internationally and it is the most important thing going forward.
- The FDA has a biomarker qualification program. It is worth looking to see what types of data and information are needed to apply through this biomarker qualification program. The working group will look into it and get back to the full group on that:
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm>).

Working Group Updates: Treatment Combinations

Presenter: Dr. Seng Gee Lim, National University of Singapore and Bruce Given

- The treatment combinations working group is a topic of interest. There is a wonderful class of drugs (NUCs) which do a great job, but still a lifelong therapy for most, and interferon that we would like to replace with a less toxic approach.
- The aim of the working group is to facilitate the advancement of the regulatory science specific to HBV and combination therapy development in HBV through an open, adaptive and iterative design concept for testing these combinations, focusing on phase 2 trials to work with combinations early in development.
- The working group aims to find one or more “recipes” that make a big difference relative to our rate of HBsAg clearance than what we have with currently available drugs.

- Want to develop a conceptual framework taking care of adequate safeguards for trial participants. The goal here is to get enough of an idea if we have found a “recipe” in phase 2 studies to try to move into phase 3 and change the paradigm of HBV treatment from a chronic treatment to a shorter term, curative approach.
- We will identify the complete landscape of the existing regulatory policies, identify what HBV guidelines are missing and what other guidelines are not specific to HBV but could be under consideration, assess them by relevance to the specifics of HBV, and work with representatives of the regulatory agencies to facilitate the process.
- A second task is to produce an inventory (pipeline) of all existing products that are in development, their mechanisms of action, new agents in phase 1, safety considerations, and review toxicology studies.
- A spreadsheet has already been produced and will be circulated to all working group members to get feedback and contributions. We are trying to look at this instrument in a tridimensional way in terms of combination.
- Flares have been an important topic of discussion, especially as they relate to patients who go on to seroclearance. There is the perspective that flares may be a very important part of the process in a positive way, leading to viral clearance. But historically, flares have been thought of as a sign of toxicity by regulatory agencies. How we deal with flares in the context of the always present concern for drug-induced liver injury (DILI) is challenging.
- Many companies are putting in place/ have flare protocols or recommendations of how to look at ALT elevations, how to evaluate those, when stopping seems to be the right thing to do versus not, etc. A good place to start is to get access to those protocols and reach the regulatory colleagues about how all of this works in the context of drug-induced liver injury and start to try to see if we can find some common ground or a sort of common flare protocol that everybody agrees with that we put into these trials.
- The working group is planning on ultimately producing a white paper or a manuscript regarding the regulatory guidelines and guidance documents and a map of current drugs that are coming along and what we think about combinations.
- In terms of timelines, the collection of regulatory guidance documents and inventory of drugs approved or in the pipeline are underway and will be completed on the first quarter of 2017.
- The collection of “flare protocols” will start by requesting industry colleagues if they have flare protocols as part of their clinical studies and asking them if they can share those. Once the task is complete the group might organize a sub team to work on this area and on a publication in 2017.

Discussion

- Collection of flare protocols is not suitable for the objectives of the treatment combination working group. A suggestion would be to have a separate working group that would work with new drugs and safety.
- The word “flares” is confusing and connotes a danger signal of some type, which may not be. Maybe have this new working group/committee to work on new terminology

- Independently of the name we want to call the increase of the ALT, for clinicians, the extent of liver fibrosis is crucial when speaking about flares. Though it is not easy to make a diagnosis of cirrhosis before therapy, many of these new combinations will be tried, tested in the model of the long-term orally suppressed patients.
- The problem today is how we define cirrhosis in someone treated for 5-10 years on oral therapy. This is a major challenge in general terms, but more specifically, if you think an ALT flare will be necessary at least for some combinations and some patients to achieve HBsAg loss. So it is related to the treatment endpoints or the treatment combination, but it is strongly related to the safety issue.
- It would be good to invite Will Tream from the IQ Consortium to build a bridge with that working group working on DILI. It would be wise to keep safety in this working group for now and see how it evolves; there is the issue of dose escalation rules, stopping rules, etc.
- One of the issues on combination therapy is to get the companies to agree to work with each other.

Working Group Updates: Surrogate Endpoints

Presenters: Marion Peters, UCSF and Oliver Lenz, Janssen Pharmaceuticals ID&V

- The Surrogate Endpoints working group consists of 19 members with representatives from biotech, diagnostics and pharmaceutical companies, academic researchers, FDA representatives, however other regulatory agencies are missing.
- The WG objectives are to:
 - Assess the relationship of specific surrogate endpoints with long-term clinical outcomes, identify gaps, and recommend research to fill these gaps to advance the regulatory process for HBV therapeutic interventions
 - Review, discuss and formulate evolving consensus on HBV cure definition and appropriate surrogate endpoints for HBV phase 2b and Phase 3 clinical studies. The purpose is not to focus on the early proof of mechanism studies or concept studies but endpoints that can then allow approval of these drugs.
- Surrogate markers are biomarkers that can be assessed within the time of an interventional clinical study; usually finite in duration. The long-term clinical outcome can take a long time to see, 5 - 10 years, and are related to liver disease progression, liver disease related death, or HCC.
- Activities for objective 1 include:
 - Performing a systematic literature review and meta-analysis of all published data trying to find other data sources describing the link between surrogate endpoints and long term clinical outcomes. This would include references from all type of treatments as well as natural disease progression.

- Focus on the identified/prioritized endpoints: HBsAg loss with or without anti-HBs gain which is commonly referred to as “functional cure,” although this could be challenging for quantifiable HBsAg levels as long-term clinical outcome.
- Defining criteria for selection and ranking of the references of the data sources depending on how these were obtained and which type of studies have been performed.
- Followed by a sub-analysis looking at age, genotype, liver disease status, etc. including all type of treatments and natural disease progression. The aim is to focus first on HBV mono infection to later extend it to co-infections.
- Assess the evidence of the link between the surrogate marker and the long-term clinical outcome and also the strengths of the effect observed.
- Would be great to also assess how the strength of the effect observed compares to what is currently described with the current standard of care, mainly the long-term NUC treatment.
- Determine the regulatory perspective and requirements in terms of level of evidence needed to accept these surrogate endpoints and what is required before registration of a drug before approval and what could be provided post-approval.
- Once the evidence is available and we know what the requirements are, we will assess the gaps that need to be filled and facilitate opportunities to create additional evidence coming from different sources like collaboration with HBV cohorts, cross pharma initiatives, initiatives of medical societies, etc.
- Activities for objective 2 include:
 - Defining cure (including surrogate endpoints) to be endorsed by the HBV Forum and develop/prioritize a list of (surrogate) endpoints for phase 2b and phase 3 studies.
 - This will encompass reviewing the literature, conference proceedings, etc. from different stakeholders (AASLD-EASL workshops, regulatory documents, clinical evidence, etc.) and having discussions within the HBV Forum and achieve consensus.
- Once the group has identified and agreed on which endpoints would be a good definition of cure, assess the available level of evidence of these surrogate markers with respect to long-term clinical outcome.
- The outcomes of this working group will include a white paper or peer-reviewed manuscripts and a collection of data and references that will be made accessible to HBV Forum members.
- Data are being collected and organized and will be finalized by the first quarter of 2017. Regarding Objective 2, the first consensus proposal will be presented at the HBV Forum 2 for comments and suggestions.

Discussion

- Some overlap between the diagnostics and biomarker working group and the surrogate endpoints working group relates to the difference between hepatitis B drug development and HIV or HCV. Since many of the patients in clinical development are going to be NUC suppressed, there is no HBV DNA as a marker of efficacy, and particularly for

immunomodulators. That means we may have to go forward in combinations without really having a good marker of efficacy.

- A second overlap relates to whether we should be taking on immunological biomarkers, which lie in the diagnostic group. But it also lies in the endpoint group because if you're looking at immunomodulators, in the absence of HBV DNA as a marker of efficacy, there is only quantitative sAg, and that may be rather insensitive marker of efficacy. So the question is if we take on immunological biomarkers with all the challenges that that brings on.
- Going back to the qualitative assays, most clinicians and drug developers would appreciate to have s loss, but during our discussion it came up that the sensitivity of the current available qualitative assays varies and we do not have an international standard. When proposing a phase 3 endpoint of s loss, it would be s loss alone; it would be with non-detectable DNA. There is need to get standardization of qualitative assays for loss and it should be part of a composite efficacy endpoint and never by itself.
- We are talking about surrogate endpoints, but it is also important to make sure that we define what is the primary endpoint. Is the ultimate endpoint that you can stop treatment and viral load stays zero and sAg stays zero and the patients have no further disease? Or would we be satisfied as a field if viral load and sAg go to what we currently are calling inactive HBV? The patients now have low level of s and low level HBV but no active disease, which are patients that actually do not have a lot of problems if you follow them over an extended period of time.
- An important question is: what is our overall goal when we say HBV cure in the immediate term and the long term. Both have to be defined before we can define what is the surrogate of each of those.
- The immunology working group at ICE-HBV is aimed at reviewing the immunological biomarkers associated with the different stages of HBV.

Panel Discussion: Natural Disease Progression Definitions...need for a working group?

Panelists: Jordan Feld (Toronto Western Hospital), Harry Janssen (University of Toronto), Pietro Lampertico (University of Milan), Norah Shire (AstraZeneca), William (Bill) Symonds (Arbutus Biopharma), Veronica Miller (The Forum for Collaborative Research)

- There are different studies being planned, designed and conducted, but more clarification is needed on the patient population since the definition of immunotolerant population differ slightly in different parts of the world. We have the opportunity to discuss and agree on a framework for the natural history and to have definitions that can be used.
- *When* talking about patient populations in clinical trials you need to be able to compare those populations without the need to figure out what exactly was the intake criterion or who exactly were those patients. The idea of the panel is to discuss if there is a need to have a standardized definition and what the ideas are about that.
- *There* are the guidelines (EASL, AASLD, etc.) that have definitions, but they do have gaps, and there are patients who may fall in between the definitions. There are “re-definitions” and modifications that might be needed particularly for trials that need very strict and distinct definitions.

- Part of the problem is that population definitions are intimately tied to treatment guidelines, and it may be that the current treatment guidelines are not necessarily the people who we want to start treating.
- *In* the space of immune checkpoint inhibitors or agonists, you might want to go to an earlier place where the relevant T cells against the relevant epitopes are still there.
- The four phases definition using three very simple variables: ALT, serology e antigen status, and DNA are over 20 years. Overall, we can classify probably 70% of all patients today. This is a very good specification method using very simple tools. The four phases have been designed to highlight the natural history of the disease and then because phase 2 and phase 4 are so much linked to prognosis, cancer, decompensation, survival, and need of transplantation we are treating these patients.
- If we have another drug targeting viremia or viral load and being able to provide functional cure in everybody, then there is no need of this classification.
- If you are looking at a therapy to break tolerance, you want to make sure you have an immune tolerant group, and that is probably the least well-defined group. *There* are a lot of studies that talk about the immune tolerant patients, and everybody has used slightly different populations, so it really depends on what you are doing.
- When you are trying to figure out whether your therapy works, making sure you have a very well-defined groups is not that difficult and much more helpful. There is utility in defining these groups more tightly than they have been defined. You may have a perfect definition and then a slightly expanded definition that you allow when you go to bigger populations where not everyone's going to fit the cubbyhole.
- Semantically, "healthy carriers" are now "inactive carriers". Immunologists do not want to use the word "immune tolerant" and it is a very defined and distinct clinical definition and they could be called "high replicative carriers," "low inflammatory," "high replicative state."
- There is a need for a subset of hepatitis B patients to be treated with current guidelines and this has been validated with long-term follow up that these patients have complications down the line.
- We cannot use sAg level as a single value to define active carriers, unless the sAg level is very low, (*e.g.*, below 1000). There are many inactive carriers with sAg levels above 1000; sAg level decline is a function of time. If you make a diagnosis of an inactive carrier, which just became inactive carrier today, sAg levels are probably high. But in this same person, after 20 years, the sAg will go down.
- *The* HBV Forum should focus on the discussion of disease staging in the absence of liver biopsy as a priority for trial design.
- We have discussed about disease progression in individuals who have mono infection, but it is also important to discuss disease progression in people who have co-infections or tri-infections or significant co-morbidities: HIV, HDV or/and HCV
- One of the things that has happened since the early work on HBV therapy, either with interferon, Peg, and then with the NUCs is the epidemic of NASH and fatty liver disease and

NASH, and not just in the United States. On top of that, with the aging of the population, the impact that immunosenescence has on natural disease progression.

- *With* the explosion of immunotherapies for other diseases, (psoriatic disease, dermatologic disease, arthritic diseases), there is not HBV alone anymore. This is going to be important for the HBV Forum to look at.
- Is the natural history different in those different subpopulations? How do agents work in the face of the other therapies that they may be on for those important co-morbidities?
- Although natural history of disease is without treatment, patients that studies will be facing as a reference group will be on stable NUCs and then can come off stable NUCs, so what will be the reference group the studies will be paired against? Patients who would have continued their NUCs treatment and we do not stop them or patients who never received treatment?
- There are two distinct populations that need treatment: patients who are suppressed but are not yet cured, and patients who are on treatment.

In conclusion: there is a need of a working group.

Opportunities for Collaboration

International Coalition to Eliminate HBV (ICE-HBV)

Presenter: Peter Revill, ICE-HBV/University of Melbourne

- The International Coalition to Eliminate Hepatitis B or ICE-HBV is a recent initiative. The incredible success of the curative regimens of hepatitis C has raised expectations of the possibility to cure hepatitis B.
- ICE-HBV is the management committee that will coordinate the multi-disciplinary working groups. If there are gaps with what the HBV Forum is working on, potentially ICE-HBV can fill those. Initially, ICE-HBV is focusing on virology, immunology, and innovative tools. We believe these pillars of HBV research will drive and coordinate an approach to HBV research worldwide.
- ICE-HBV has a governing board formulated from members from the ANRS, the Doherty Institute, and the International HBV Meeting. The genesis for this initiative came out of the scientists from the International HBV Meeting, but the management is from the Doherty Institute. Capucine Penicaud is the project manager and there are also project officers from the ANRS.
- There will be a stakeholder consulting group (advisory group) that will include representation of the community, the HBV Forum and the HBV Foundation. The Stakeholder Consulting Group will be co-chaired by Veronica Miller and Tim Block.

The Virology Working Group

- The virology working group will address research questions such as:
 - What are the other possible receptors/co-receptors required for viral entry?
 - What are the host and virological factors that regulate HBV replication?

- Does cccDNA need to be eliminated, or will rendering it transcriptionally inactive be sufficient for effective cure?
- Would the elimination of virus be sufficient to result in the resolution/ reversal of established liver disease?
- Standardization of assays for analysis of cccDNA is urgently required.
- The first task of the virology working group is to perform standardization of assays of cccDNA. This is building on an existing French-German cooperation.
- The convener of our working group is Maura Dandri from the Hamburg University in Germany and the co-convener is Haitao Guo from Indiana University in the U.S.
- The members of the core working group are from different laboratories all over the world, and they will focus on producing a standardized approach and producing a position paper.
- The importance of having standards that can be shared across the world be they for sAg analysis, would be critical for cccDNA analysis. That is the major focus of this group at the moment.

The Immunology Working Group

- The immunology working group will address questions like:
 - Is HBV a stealth virus that sneaks under the immune response or is it actively suppressing immune responses to establish infection and maintain persistence?
 - What are the mechanisms for virus-induced T-cell exhaustion in persons with CHB?
 - Can this T-cell exhaustion be reversed, or are T-cell responses “hard wired” in most individuals?
 - Are there better immunological biomarkers of HBV natural history than ALT?
- One of the first tasks of this working group will be to review immunological biomarkers of HBV natural history, treatment response and disease progression, if there is a better biomarker than ALT, and identify what other things we should be looking at. This will then be put together into a position paper.
- The convener of the working group is Adam Gehring from Toronto University in Canada. There are huge opportunities for collaboration with the HBV Forum, the stakeholder consulting group and the scientific working groups.

The Innovative Tools Working Group

- The terms of reference for this working group are still in development. The convener is Jianming Hu, from the University of Pennsylvania in the U.S., and the co-convener is Fengmin Lu, from Wuhan University in China.
- The next steps for ICE-HBV are:
 - To develop proposals for each working group, secure resources, perform research and present and publish results.
 - To gather stakeholders to provide input on priorities (April 2017, EASL).
 - To support dedicated ICE-HBV Cure Symposia at existing conferences: Singapore Hepatology Conference (Singapore), AASLD (Washington), ANRS (Paris)
 - To create an HBV Cure research prize & foster travel scholarship programs
 - To publish ICE-HBV progress report in September 2018.

Discussion

- With the standardization of cccDNA the working group will coordinate the laboratory work in different laboratories across the world. There will be a core group that will do the sharing and the analysis, and then there will be an extended validation group.
- At present ICE-HBV is not working with companies but will be eventually involved in the stakeholders and advisory group.
- Presently ICE-HBV has received seed money from the Australian Centre for HIV and Hepatitis Virology and will be approaching donors and philanthropic bodies to ask for supplemental funds and eventually approach industry.
- Some of the questions that have come up frequently in extensive discussions with the FDA and the patient community is the issue of risk/benefit and benefit/risk and what patients understand and do not understand when they are asked to enroll in cure trials.
- The mention of the word cure in a protocol or in an informed consent is in a way coercive because of its therapeutic misconception. Even if you explain to them that they are not going to be cured.
- This could be part of what the stakeholder group could start addressing, the whole ethics of how these studies are done, where they are being done, and what are some of the appropriate informed consent processes and the patient education component.
- Need to be very careful not to create false expectations. A simple suggestion would be to use the term “increase the durable response rate” or “sustained response therapy.”
- From the patients’ perspective, they just want to know if they have to take the drug for a limited time, so it is worth considering asking what does “durable response” mean to a patient?
- There is a recent published paper on the ethics of HBV Cure Research¹.

Eradication of HBV: Singapore Translational Clinical Research Grant

Presenter: Prof. Seng Gee Lim, University of Singapore

- This is a grant awarded in 2015 founded on Professor Liaw’s work and is a long-term follow up of asymptomatic HBV carriers.
- There are 2,000 patients and almost 45% of them cleared sAg.
- This grant is a nationwide collaboration of four hospitals: Tan Tock Seng Hospital, Singapore General Hospital, National University Hospital and National University of Singapore; the Duke-NUS research and the Agency for Science, Technology and Research (ASTAR) that includes the Institute of Molecular and Cell Biology, the Genome Institute of Singapore, the Singapore Immunology Network and the Singapore Clinical Research Institute.

¹ Sugarman, J., et al., *Ethics and hepatitis B cure research*. Gut, 2016: p. gutjnl-2016-313009-5.