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# IAS Corporate Partnership Programme HIV Vaccine Industry Partnership

## Biomarkers of efficacy and clinical trial design

**Workshop, 15 November 2022**

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## Background

HIV prevention is evolving rapidly with the roll out of prevention tools, such as pre-exposure prophylaxis (PrEP), and with treatment making a significant contribution towards controlling the epidemic.

As a result, the design and conduct of HIV prevention trials is becoming challenging and is further affected by the outcomes of ongoing efficacy trials, including injectable antiretrovirals and passively infused monoclonal antibodies.

The window of opportunity for conducting double-blind placebo-controlled randomized clinical trials, the gold standard of epidemiology studies, is closing. New counterfactual approaches are required to evaluate product efficacy.

Biomarkers, as surrogate endpoints of vaccine efficacy, are one approach under evaluation. If one or more biomarkers, probably of an immune nature, could reliably predict the efficacy of a vaccine in a clinical trial, replacing HIV acquisition as the primary clinical endpoint, such marker(s) could alleviate the need for a placebo group.

Biomarker(s), if measurable shortly after immunization, could also be useful to quickly screen vaccine candidates for further improvement, reducing the time and cost of efficacy trials, and accelerate iterative research.

The use of biomarkers as surrogate endpoints for clinical efficacy comes with challenges and limitations, including identifying and validating biomarkers. It is also important to understand regulatory and community perspectives on the use of biomarkers in clinical trials.

The workshop was conducted in partnership with the Global HIV Vaccine Enterprise at IAS – the International AIDS Society – and followed a series of events, titled "Design approaches for current and future HIV prevention efficacy trials". It brought together industry and non-industry representatives with a stake in HIV vaccine R&D to explore how biomarkers can be used as surrogate markers of clinical efficacy in counterfactual vaccine trials.

By debating the design of future efficacy trials, the workshop aimed to contribute to addressing the industry's concern that, in a changing prevention landscape, conducting efficacy trials can be an obstacle to investment in HIV vaccine R&D.

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# Agenda

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| 1600 – 1602 | Welcome – Tuuli Reissaar, Project Manager, IAS, Switzerland |
| 1602 – 1610 | Co-chairs opening – HIV vaccine efficacy trials today<br>*Linda-Gail Bekker, Desmond Tutu HIV Centre, South Africa*<br>*Carey Hwang, Vir Biotechnology, USA* |
| PART 1 | UNDERSTANDING THE ROLE AND POTENTIAL OF BIOMARKERS OF EFFICACY FOR HIV VACCINE TRIALS |
| 1610 – 1615 | A short introduction to biomarkers and surrogate endpoints in clinical trials<br>*Susan McCune, US Food and Drug Administration, USA* |
| 1615 – 1630 | Evaluating the surrogacy of multiple vaccine-induced immune response biomarkers in HIV vaccine trials<br>*Sayan Dasgupta, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, USA* |
| 1630 – 1640 | Q&A – Lead by co-chairs |
| 1640 – 1730 | What biomarkers for HIV vaccine efficacy trials?<br>Perspectives (3 minutes each)<br>1. *Larry Corey, Fred Hutchinson Cancer Research Center, USA*<br>2. *Tomas Hanke, University of Oxford, UK*<br>3. *Hanneke Schuitemaker, Janssen Vaccine Prevention, the Netherlands*<br>Group discussion |
| 1730 – 1740 | *Break* |
| PART 2 | USING BIOMARKERS AS SURROGATE ENDPOINTS IN HIV PREVENTION EFFICACY STUDIES - CHALLENGES AND OPPORTUNITIES |
| 1740 – 1755 | PT80: A neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition<br>*Yunda Huang, Fred Hutchinson Cancer Research Center, University of Washington, USA* |
| 1755 – 1805 | A regulator perspective on the use of biomarkers as surrogate endpoints<br>*Marco Cavaleri, European Medicines Agency, Netherlands* |
| 1805 – 1820 | Q&A – Lead by co-chairs |
| 1820 – 1855 | Can biomarkers of efficacy be included in the design of efficacy trials and how?<br>Perspectives (3 minutes each)<br>1. *Myron Cohen, The University of North Carolina at Chapel Hill, USA*<br>2. *Moupali Das, Gilead Sciences, USA*<br>3. *Daisy Ouya, AVAC, Kenya*<br>Discussion |
| 1855 – 1900 | Closing |

## Introduction to the workshop

**Linda-Gail Bekker**, Director of the Desmond Tutu HIV Centre (University of Cape Town, South Africa) and former President of the IAS, opened the workshop, saying that the onset of very effective HIV prevention technologies brings complexity and conundrums as to how to conduct HIV vaccine efficacy trials. New ways to conduct counterfactual studies to evaluate a product's efficacy are needed and biomarkers can be potential surrogates of efficacy. If one or more biomarkers can reliably predict the efficacy of a vaccine in a clinical trial, thereby replacing the need for HIV acquisition as primary clinical endpoint, such markers can then facilitate, accelerate and make research affordable from an early stage. The use of biomarkers as surrogate endpoints for clinical efficacy, in their own right, comes with several challenges and limitations, including their identification and validation. Regulatory, scientific and community perspectives also matter.

**Carrie Hwang**, Senior Vice President, Clinical Research and Head of Chronic Infections at Vir Biotechnology, said that many in the industry perceive the conducting of vaccine efficacy trials as a major hurdle. There are now several vaccine candidates being developed and there is a need to evaluate them quickly in a cost-effective fashion to determine if they elicit protective immune responses against HIV acquisition. Identifying correlates of protection could also play an important role in cure research, where vaccines may play a role. There remains a great unmet need in preventing new HIV acquisitions. Around one and a half million people acquired HIV in 2021, with women and girls accounting for about 49% of these new acquisitions. Although new acquisitions have declined by about 32% since 2010, we need an HIV vaccine to control the epidemic in the long term. A simple-to-use vaccine is an essential tool in reaching populations most affected by HIV. A vaccine with even 50% efficacy will have a major impact on the epidemic. Hwang described this meeting as a great opportunity for industry to engage with academic researchers and for the community of stakeholders to ask questions and make suggestions on how to develop relevant and acceptable biomarkers, especially with regulatory approval in mind.

# PART 1 - Understanding the role and potential of biomarkers of efficacy for HIV vaccine trials

## Presentations

0:08:10 - **How Biomarkers Can Improve the Drug Development Process**. McCune S. US Food and Drug Administration, USA. Available online

0:14:00 - **Evaluating the surrogacy of multiple vaccine-induced immune response biomarkers in HIV vaccine trials**. Sayan Dasgupta, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, USA

## Materials

- **Dasgupta S,** Huang Y. Evaluating the surrogacy of multiple vaccine-induced immune response biomarkers in HIV vaccine trials. Biostatistics. 2021 Apr 10;22(2):421-436. Available online

## Q&A

**Ying Huang** (Fred Hutchinson Cancer Research Center, University of Washington, USA) clarified that the work presented by **Sayan Dasgupta** for combining multiple biomarkers in deriving a surrogate endpoint is important to the field since a single biomarker might not have adequate performance in predicting vaccine efficacy. **Huang** also noted that several biomarkers are being measured in different laboratories and that a means to combine these to produce a stratification score that can predict efficacy is needed. There are different statistical frameworks for surrogate marker development. The methods presented by **Dasgupta** are based on the principal stratification framework that utilizes an augmentation of study design to deal with missing potential outcomes. In response to a question from **Thomas Hanke**, **Huang** said that the approach had been applied to RV144 for exploratory analyses, which require further validation. The methods provide a foundation for more work on how to combine biomarkers.

**Deborah Donnell** (Fred Hutchinson Cancer Research Center, University of Washington, USA) asked if this approach is only useful to develop biomarkers in the context of a placebo-controlled trial that has been conducted with a successful vaccine. In a situation where breakthrough acquisitions do not occur in the placebo arm because participants are receiving another protective intervention (for example, cabotegravir), is there a path forward to compare breakthrough acquisitions in the vaccine arm for developing surrogate endpoints or biomarkers that can predict whether a person given a vaccine is protected? **Bekker** said that having breakthrough acquisitions in the non-vaccinated arm may be needed to identify what the vaccine did to protect people. Breakthrough acquisitions may still occur for several reasons in the vaccine arm. Collecting data on how individual participants use products will therefore be very important to identify a correlate of protection. **Hanneke**

**Schuitemaker** suggested that comparing high and low responders for relative risk of acquisition will remove the need for a placebo arm.

## Perspectives

### Larry Corey

**Corey** said that historically, clinical trials used standards of care as the comparative arm in an efficacy trial. COVID-19 vaccine research has shown that a reasonable surrogate marker can be used to predict efficacy. Yet, no vaccine has been licensed for primary vaccinations using only a surrogate marker. Some form of approval was given for booster immunizations using a surrogate marker. There seems to be a difference between a mechanistic surrogate marker (for example, an antibody titre such as those identified in the passive immunisation studies) and a marker that will be a correlate of protection (such as neutralization, which in COVID-19 studies, is at best 60% predictive for mRNA vaccines). The immunology for an HIV vaccine has not yet been solved, and although there may be monoclonal antibodies, the titre required for protection has not yet been reached. A higher bar is needed to prevent acquisition, and multifactorial adaptive immune responses may also play an important role in protection. Corey concluded that, at this point, other than really using high titres of broadly neutralizing antibodies to multiple viral components, it is not possible to develop a biomarker of efficacy.

### Tomas Hanke

**Hanke** agreed that it is difficult to develop markers of protection with a vaccine that has not been seen yet. There are multiple modalities to induce protection (such as T/B-cells, preventive and curative) and the protection will result from complex combinations of factors, including magnitude, breadth, functionality, tissue localization for T-cell response, functionality of the Fc, activation of the complement, and binding to different receptors for neutralizing antibodies. The presence of these factors will be required. Guidance for the development of a biomarker of efficacy is currently lacking.

### Hanneke Schuitemaker

Janssen Vaccine Prevention has been working with partners to develop an HIV vaccine. Biomarkers have been used to support go/no-go decisions along the way. Some were used to set go/no-go criteria for human immunogenicity in the earlier trials to proceed with efficacy studies (for example, levels of cellular and humoral immunity that, in combination, correlated with protection in non-human primates against repeated intrarectal SHIV challenges). The protection in non-human primates (NHPs) correlated well with the magnitude of a combination of biomarkers, but this did not translate into overall vaccine efficacy in a human Ph2b study

(HVTN 705/Imbokodo). This could result either from the biomarkers selected for NHP not being appropriate for human protection or from NHP not being a relevant model, at least not for the human population in the Imbokodo study. However, Imbokodo allowed comparing the immune response of vaccinated women who had breakthrough acquisitions during the study with the immune responses of women who did not acquire HIV.

Much can be learned from efficacy studies, even those with overall negative outcomes. For example, the breadth of V1/V2 responses was inversely correlated with risk. This is a stand-alone biomarker, but the observation does not stand on its own as it confirms observations in HVTN702 and RV144 that non-neutralizing antibodies to V1/V2 are associated with protection. It will be challenging to use a biomarker to license an HIV vaccine. However, it is interesting to further explore the relevance of this biomarker and determine if higher levels of this biomarker can be achieved in more people and translate into significant overall vaccine efficacy.

## Group discussion: What biomarkers for HIV vaccine efficacy trials? (00:50:45)

- Collection of samples and selection of biomarkers in the absence of a clinical outcome

Collecting samples will allow researchers to do retrospective analysis and potentially identify a correlate of risk or correlate of protection. **Schuitemaker** commented that although it was costly and time consuming, collecting samples was worth the investment and effort.

- Antibodies as potential markers of efficacy

**Myron Cohen** said that antibodies can be tools to identify attributable risks or benefits of non-antibody effects of vaccines. There are added benefits to giving a vaccine over giving mAbs alone. Vaccines do more than injected mAbs. Vaccines trigger multifactorial adaptive and innate immune responses that are not fully understood. What levels of monoclonal antibodies are required in addition to the effect of the vaccine to provide protection? This is an unanswered question. A combination of how much antibody is produced and of required titres needed for protection may provide an appropriate surrogate marker to support licensure.

- NHP model

Animal models have been disappointing. One of the problems is that the virus challenges are not real because these are not clade C viruses. MOSAICO may provide important information on their continued use. **Corey** said that it will be very hard to find biomarkers without solving the immunology.

- Trial design

**Corey** added that a way forward will require proof of efficacy and that this will not be possible without a study group that doesn't have the vaccine. He commented that it is possible to construct a trial with the control group receiving the standard of care. However, he pointed out that a definition of "standard of care" continues to be discussed and that there is tension in the field to acknowledge and distinguish what is ethical and what is exclusionary when enrolling study participants.

**Richard Hayes** (London School of Hygiene & Tropical Medicine, UK) agreed about the importance of giving potential trial participants a choice. One can make a sound ethical argument that if a trial participant has been given the choice of accepting a preventive measure that has been proven to work and refuses that choice, knowing what they are doing, then enrolment may be judged as ethical. Hayes said that long-acting PrEP (cabotegravir LA-PrEP) has made it more difficult to conduct HIV prevention trials. LA-PrEP intervention can be monitored. It is safe, highly effective and highly acceptable and has much fewer problems with adherence. It may be difficult to find many trial participants who would decide not to use LA-PrEP.

- Biomarker specificity

The question was asked: is the use of any surrogate of efficacy appropriate for different vaccine products? Is there an HIV vaccine that has shown clear evidence of protection in a clinical trial? Based on the data from that trial, a surrogate measure or a combination of measures has led to the development of a highly predictive marker of protection, would it be possible to move forward with another product, which may well work through different immune mechanisms?

**Hanke** gave an example from cure research with ATI, where two individuals were controlling their viral load through different mechanisms, suggesting that there will be different pathways to protection with different vaccines in different individuals. **Hwang** said trying to correlate

different technologies and strategies that elicit different types of immune responses across populations and trials will be challenging.

- Biomarkers as correlates/surrogates of protection

**Elizabeth Wonderlich** (ViiV Healthcare, USA) said that COVID-19 triggered T-cell and bnAb responses, but people are still contracting COVID-19; therefore, there is no correlate of protection with COVID-19 vaccines. The vaccines protect against severe diseases, hospitalization and death, but are not considered protective against acquisition. Likewise for HIV, people still acquire HIV despite an immune response. Looking at the 5% top cases in trial participants, especially in RV144, with a high level of antibodies may provide important information to drive the biomarker discussion.

**Jim Rooney** (Gilead Sciences, USA) said that identifying surrogates of protection will be ideal and that with other vaccines like influenzas, these are used as a standard method for regulatory approval. If it is too challenging to conduct trials, the efficacy of an intervention can be measured with an alternative estimate of acquisition. In the field of PrEP, sexually transmitted infections and recency assays are emerging as a potential alternative strategy in specific populations and settings. This would require more studies in the vaccine field as there are significant limitations to the success of these strategies.

**Wonderlich** said that correlates of protection have been elusive for several respiratory viruses, including influenza, COVID-19 and RSV. Finding a strong mechanistic marker may lead to the identification of a correlate of protection.

- Biomarkers to evaluate platforms

**Hwang** said that from an industry perspective, biomarkers can be used to evaluate a platform and determine whether the expected immune response is elicited before taking a product to the clinic. If taken to the clinic, a biomarker can be used as a surrogate for protection to support regulatory approval. There will still be a need for a clear correlation between the clinical prevention of HIV acquisition and a high correlation with the biomarker itself.

## PART 2 – Using biomarkers as surrogate endpoints in HIV prevention efficacy studies – Challenges and opportunities (01:19:44)

## Presentations

01:21:45 - **PT80: A neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition.** Yunda Huang – Fred Hutchinson Cancer Research Center, University of Washington, USA

01:41:10 - **A regulator perspective on the use of biomarkers as surrogate endpoints.** Marco Cavaleri – European Medicines Agency, Netherlands

## Materials

Gilbert PB, **Huang Y**, deCamp AC, *et al*. Neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition. Nat Med 28, 1924–1932 (2022). Available online

## Q&A (01:58:28)

**Wonderlich** asked **Huang** whether there is a vaccinal effect following the injection of bnAbs, especially in people with high titers, such as an increase in anti-CD8 T-cell responses or changes in immune markers (pro-inflammatory cytokines), possibly in response to an increased antigen presentation. **Huang** said that anti-antibody responses (ADA) are being investigated and a very low percentage, less than 8% of 400 participants in the AMP trials, had developed ADA after 10 infusions. T-cell responses had not been looked at.

**Bekker** asked if the results can be generalizable and if it is possible to use PT80 for regulatory purposes. **Marco Cavaleri** said that EMA is open to discussing the use of composite surrogate markers; this has been evaluated for Ebola and influenza, but nothing meaningful emerged. For example, with Ebola, T-cell responses are very important, but they are not changing the ability of antibodies to be predictive of protection.

**Cavaleri** was more concerned about the use of different platforms, which can lead to huge differences in immune responses. Remarkably, with COVID-19, different platforms indicate that neutralizing antibodies, no matter how they are elicited, are correlates of protection. This is not the case with many other pathogens, which emphasizes the need for comparing platform technologies.

**Donnell** asked **Huang** how much data support the predicted 90% efficacy of the triple monoclonal antibodies' combination. **Huang** said that placebo data had been used in the modelling, with some of the participants acquiring HIV during the study; the viruses were isolated in these participants and the IC 80 measured. Extensive animal data also

supported the model. **Huang** said that there is still a need for caution and it is not yet known if the same relationship applies to other bnAbs. However, more potent bnAbs with a longer half-life (five to six times longer) are now available. Only one-tenth of antibody is needed to obtain the same level of PT80 and longer intervals between infusion are also possible. Altogether, adding complementary in virus neutralization and predictable pharmacokinetics, **Huang** was optimistic about the estimated 90% efficacy for bnAbs combination.

## Perspectives (02:15:05)

### Myron Cohen

**Cohen** said that the work of Peter Gilbert and colleagues is both inspiring and daunting. The concentrations of antibodies necessary for HIV prevention are probably beyond what can be achieved with any vaccine currently, but the approach is shining a light on the idea of using mAbs for HIV prevention. mAbs can become PrEP agents if they are cheap and effective enough, but currently there is a limited number of antibodies available for HIV; they have been more popular in such fields as rheumatology, cancer and dermatology for many years. Infectious disease specialists have focused on small molecules, but COVID-19 brought about a rethink.

There is an urgent need to create an environment where monoclonal antibodies can be used with people who cannot respond to COVID-19 and to approve these vaccines based on their *in vitro* activity and/or neutralizing titre activity. When giving passive infusions of monoclonal antibodies, it is possible to determine what concentrations of mAbs might let regulators move forward without further clinical trials. This is the highest priority right now in that space. There may be less urgency for HIV than there is for COVID-19, but several other diseases for which there are no small molecules may benefit from passive immunity for either prevention or treatment.

### Moupali Das

**Das** said there are many parallels and challenges between mAbs and small molecules when designing prevention trials. Lessons from these trials with small molecules can be applied to HIV prevention trials with mAbs. Using exposure range, threshold for efficacy, safety range and other factors, it may be possible to conduct a fully powered trial to evaluate efficacy in different populations without having to recruit large numbers of participants. An earlier step showing efficacy in NHP or *in vitro* may lead to the next stage of study design and trials.

Daisy Ouya

Speaking as a prevention advocate, **Ouya** said that she is very excited by the work with biomarkers. Although there are many challenges ahead, the biomarkers agenda was re-energized with the discovery of the PT80 biomarker. Ouya wondered whether the virus subtype matters since the AMP study was primarily conducted in populations where subtypes B and C are circulating. There is a need to include more diverse populations in the biomarker discovery work so that findings are more acceptable and applicable. Collecting more samples will be necessary and it will be important to revise informed consent language on data banking and biobanking, in line with international and national ethical guidance.

She referenced UNAIDS Ethical Guidance Point 9 on informed consent. Sample collection may be hindered by some cultural barriers and regulators and ethicists should be sensitized about this. Also to investigate is whether biomarkers can be discovered in easier-to-collect samples, such as saliva, urine and hair. Ouya stressed the importance of building research literacy for advocates and engaging early with advocates and community stakeholders. The important work on biomarker discovery should not overshadow existing efficacy trials. Existing prevention strategies should be supported and rolled out (for example, condoms, oral PrEP, ring injectable PrEP, treatment as prevention and post-exposure prophylaxis) with an increasing sense of urgency because people need HIV prevention right now.

> *On the importance of viral clades,* ***Cohen*** *later said that there are differences between viruses and the potential for bnAbs to neutralize different viruses. Therefore, there is a need to combine bnAbs.*

## Group discussion: Can biomarkers of efficacy be included in the design of efficacy trials and how? (02:30:47)

- Community research literacy

**Bekker** asked **Ouya** how much community stakeholders understand biomarker research and what needs to be done as research is progressing. Ouya said that the term, biomarker, is already jargon for community stakeholders and researchers should find wording that community stakeholders can relate to. With COVID-19, community

stakeholders did not know about biomarkers being used as surrogates of efficacy. Most lay persons consider efficacy to be against a placebo.

**Das** reported on ongoing work with the Forum for Collaborative Research towards educating stakeholders, including regulators, on new counterfactuals approaches. Gilead Sciences went through a two-year engagement process co-sponsored with AVAC. Meetings were organized with a wide variety of stakeholders, including regulators, investigators, scientists, healthcare providers, physicians, site staff and advocates, to ensure that they understood the trial design and felt comfortable about explaining it to participants and others in the community.

- Trial design

**Das** described a process building on the work done for testing new pregnancy prevention options that can form the basis for an HIV study. In the HIV study, a recency assay is used to establish the counterfactual or background HIV incidence in the screened population. It is then used to measure efficacy in the active arm of the study. This approach allows for testing two products at the same time. There are challenges with the recency assays and it is therefore associated with surveillance data and data from other trials recently conducted in the same area, which provide incidence data in similar settings and populations.

**Bekker** asked how HVTN plans to conduct the next AMP trial. **Cohen** said that this is a consensus-building exercise and the ethics surrounding these trials are complicated. There are various ways to design a trial, including that described by **Das**; there is also a futility design where arms are stopped when there are too many cases versus a comparator. However, this may lead to a negative situation for further product development.

**Peter Gilbert** (Fred Hutchinson Cancer Research Center, University of Washington, USA) said that vaccine efficacy trials perform the same kind of virus-based neutralization sieve analysis that was done in AMP. This is a powerful way to learn about the correlates and it is perhaps underutilized in vaccine efficacy trials. This may lead to the identification of breakthrough viruses for which the vaccine is less effective.

## Concluding remarks

**Bekker** concluded that there is work to be done with filling gaps around T-cell immunity, NHP models, community literacy and trial designs and how to bring different areas of research together.

**Hwang** said there are important conversations to be had around biomarkers and trial design. These are critical issues for people living with HIV and people at high risk of HIV acquisition. The meeting was a great first step and he looked forward to hearing about this conversation in the future with this group and others.

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