2021 WHO Product Development for Vaccines Advisory Committee (PDVAC) Virtual Consultation 1: HIV monoclonal antibodies Preferred Product Characteristics 15-16 April 2021

Participants:

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Apologies: Klaus Cichutek

WHO: Rachel Baggaley, Martin Friede, Birgitte Giersing, Michelle Rodolph, Erin Sparrow

Observers and non-member participants (open session only): Susan Buchbinder, Mike Chirenje, Patricia Fast, Lucio Gama, Shelly Malhotra, Nelly Mugo, Velislava Petrova, Roger Tatoud, Mitchell Warren (see list of participants for affiliations)

Executive Summary

Rationale for the meeting:

The HIV epidemic continues to cause extensive morbidity and mortality globally. Despite progress in reaching 61% of people living with HIV with antiretroviral therapy (ART),[i] gaps in HIV prevention and treatment contributed to 1.7 million new infections and 690,000 HIV-related deaths in 2019. [ii] Young children accounted for 150,000 new HIV infections, the vast majority during infancy.[iii]

With the exception of voluntary medical male circumcision, the existing arsenal of prevention tools, including oral pre-exposure prophylaxis (PrEP), condoms, and medication-assisted treatment for people who inject drugs (PWIDs), require frequent usage contributing to implementation and adherence challenges. New and forthcoming products that offer longer duration of protection are poised to have a significant impact on HIV prevention efforts. The dapivirine (DVP) vaginal ring for women recently received a positive opinion from the EMA as a monthly prevention option and was found to reduce the risk of HIV infection by 31% overall in cisgender women aged 18 to 45 years.[ivv] Additionally, in the HPTN083 and HPTN084 trials, long-acting pre-exposure prophylaxis with cabotegravir (CAB-LA), administered as an injection given once every two months, demonstrated high effectiveness in preventing HIV infection among cisgender men who have sex with men (MSM), transgender women (TGW) who have sex with men, and cisgender women in sub Saharan Africa.[vi] [vii]

Alongside these promising developments, the continued need to identify interventions that can provide durable, or even life-long, protection against HIV infection has been identified by WHO and UNAIDS as a top public health priority.[viii] Several HIV vaccine and monoclonal antibody (mAbs) candidates are currently advancing through clinical development. Given their ability to directly target specific epitopes, antibodies represent a promising preventative modality against HIV. Two parallel antibody-mediated protection (AMP) efficacy proof-of-concept trials were recently completed, testing intravenous delivery of the single broadly neutralizing antibody, VRC01, among men who have sex with men (MSM) and transgender persons in the Americas (NCT02716675) and among women in Eastern and Southern Africa (NCT02568215).[ix,x] The studies demonstrated proof-of-concept that the VRC01 broadly neutralizing antibody (bnAb) was effective at preventing the acquisition of HIV strains that were sensitive to the bnAb (at 75.4% efficacy in pooled data across both trials), but suggested the need to assess

combinations of antibodies that provide broader, more potent protection than VRC01 alone, as the overall efficacy was only 8.8% (95% CI: -45.1 to 42.6, P=0.70) in cisgender women and 26.6% (95% CI: -11.7 to 51.8, P=0.15) MSM and transgender persons.[xixii] [xiii] A number of putatively more potent combinations and engineered antibodies are also undergoing early clinical evaluation.[xiv]

WHO and IAVI entered into a project collaboration agreement in November 2019 to co-develop preferred product characteristics (PPC) for HIV antibody products. A WHO Working Group on HIV Vaccines and Monoclonal Antibodies was established in 2020 and contributed to the development of this PPC. In November 2020, a virtual stakeholder consultation was held to review the draft monoclonal antibody PPC with a broad range of stakeholders. This was done prior to the results of the AMP trial of VRC01. Following the stakeholder consultation, the WHO Working Group on HIV Vaccines and mAbs met to discuss the implications of the AMP trials on the PPC and to refine it in the context of those data.

The intended outcomes of this PDVAC session were 1) to gather input from PDVAC in order to finalize the draft PPC for public comment, and 2) to highlight critical aspects that require further consideration to facilitate future research, policy and implementation discussions for development and use of HIV mAbs, to be reported separately in a scientific journal.

PDVAC Conclusions and Recommendations:

General:

- PDVAC agreed that the PPC would be useful to inform developers of LMIC preferences but acknowledged that the PPC is being developed in the context of a dynamic field of alternative interventions and relatively early in product development of HIV mAbs and Therefore, the PPC would need review and likely updating as new data become available. Currently, the public health value of HIV mAbs in the context of other potential interventions is not clear. Ongoing robust value assessments would better inform future iterations of this PPC.
- PDVAC recommended that SAGE consider an update in the near future on the fast-moving field of monoclonal antibodies (not just for HIV) developed for passive immunization and potential use in LMICs. A PDVAC session on this topic in advance of a SAGE presentation was also recommended.

Related to specific attributes within the draft HIV mAb PPC guidance:

- **Indication**:
  - PDVAC agreed with the consensus on prevention of HIV infection as the indication and agreed that treatment is out of scope for this PPC.
  - PDVAC recommended adding the following to the notes: While mAbs could be used in HIV negative women during pregnancy and the post-partum period, they should not be used in HIV infected pregnant women as it would not be desirable to select for and transfer resistant viruses to the infant.

- **Target population**:

- PDVAC agreed with the proposed target populations; however, PDAVC highlighted that the optimal delivery strategies and associated preferred product attributes may likely differ for different populations/settings especially young adults and adolescents vs. infants.
- As such, PDVAC recommended that the PPC stratify the proposed delivery strategies and product characteristics by the different target populations included in the PPC. A separate line item in the PPC or an appendix on "mAb delivery strategies" should be considered.
- PDVAC recommended that key populations be identified in the PPC consistent with current WHO terminology.

- **Access and Affordability:**
  - PDVAC recommended strengthening the statement in the notes "Manufacturers should plan for making products broadly available, particularly in a timely manner in those countries and populations in which the investigational product will be tested."
  - PDVAC also recommended that IVB draft a standardized statement on supply security and access, in addition to the one above, to be used in this PPC and other PPCs going forward.

- **Safety:**
  - PDVAC recommended moving the note on "Transplacental transfer should be factored into evaluations" into the efficacy section.

- **Efficacy**:
  - PDVAC recommended adding the following to the preferred characteristic column:
    - Demonstrated clinical benefit (e.g. comparable efficacy with improved delivery, adherence, duration of protection, and/or safety) in addition to benefits from standard of care.
  - PDVAC recommended adding the following to the notes:
    - While developers should aim to determine non-inferiority or superiority to current standard(s) of care, logistical challenges and cost barriers in conducting non-inferiority and superiority trials are acknowledged. Appropriate trial design should be discussed with key ethical and regulatory stakeholders, including national regulatory agencies.
    - Specimens should be collected during efficacy trials to support the identification of correlates of risk/protection and for breakthrough virus sequencing.
    - There may be a need to tailor mAb combinations for regional use by the prevalence of strains in different regions.

- **Formulation/ Presentation:**
  - PDVAC recommended adding the following to the notes:
    - Other approaches to increase the volume that can be injected subcutaneously are being evaluated and may become available in the future.

- **Dose regimen**:
  - PDVAC agreed to keep the preferred characteristic as 6 months or longer.
  - PDAVC recommended the following changes to the notes:
    - Change to "durations of at least 3 months would be considered"
    - Add: Antibody kinetics should be well characterized to ensure that subsequent doses are administered before the level of antibody drops below the threshold of protection.

- **Co-administration:**
  - PDVAC did not agree with the current language because it was unclear and inexplicit.
  - PDVAC proposed the following for the preferred characteristic column:
    - Demonstration of favourable safety upon coadministration with relevant vaccines or other products.
  - PDVAC recommended adding the following to the notes:
    - Concomitant administration of bnAbs for HIV prevention are not expected to interfere with immune responses to non-HIV vaccines; however, policy makers may request data to support co-administration of relevant vaccines or other products.

- **Route of administration:**
  - PDVAC recommended adding the following to the notes:
    - The focus of this PPC is populations in LMICs for which intravenous administration is not considered programmatically appropriate. However, intravenous administration might be suitable in some highly specific settings but would significantly reduce the ability to deliver these products in most LMIC contexts and should be discussed with WHO in advance.
  - PDVAC recommended that if the intravenous route of administration is included as suitable in some settings, then a note may need to be added to the PPC under **Formulation/Presentation.**

Meeting summary

1. Welcome, Objectives and expected outcomes of the meeting (*Birgitte Giersing, WHO, Martin Friede, WHO, David Kaslow, PATH*)

The draft PPC has been developed in consultation with IAVI and an expert working group and was presented to a broad range of stakeholders at a consultation in November 2020. This is the first time that PDVAC is reviewing the draft and presents an opportunity to review the PPC to ensure that it is ready for public consultation. The objectives of the session are to:

- Present the rationale and context for developing WHO PPC guidance for HIV monoclonal antibodies, with a focus on meeting the needs of LMICs, including in the context of other prevention products on the market or on the horizon.
- Evaluate the draft PPC document tables and discuss key characteristics & related issues.
- Gather input on key issues/research priorities to include in an article in a peer reviewed journal, to complement and contextualise the PPC guidance.

The expected outcomes of the session are to:

- Obtain PDVAC recommendations for finalization of the HIV mAb PPC document as a draft for public consultation.
- To identify critical product attributes/characteristics that require further consideration for research and/or evidence to support policy and implementation discussions.

1. The context for development of PPCs for HIV monoclonal antibodies (*Michelle Rodolph, WHO*)

While new HIV infections in children have continued to decrease, in adults the decline has levelled off in recent years. At least 44% of new infections are occurring in key populations including sex workers, people who inject drugs, men who have sex with men, transgender people and clients and other sex partners. HIV prevention is complex as there are multiple options for prevention as well as several specific populations at higher risk for HIV infection, many within different delivery settings. Collectively, these factors determine the optimal product characteristics and these may be nuanced depending on the use case.

WHO recommendations on oral PrEP were first made in 2012 and have evolved over time. WHO makes recommendations for HIV prevention based on the results of RCTs and observational studies, the values and preferences of users and providers, as well as considerations on costs, feasibility and benefits vs. harms. There have been key lessons with PrEP implementation and while PrEP is highly effective, adherence is critical and uptake and continuation can be variable in different populations/settings. Further, people are not always at risk of HIV infection so this needs to be considered in the delivery of different products. It is important to implement strategically, starting in the highest incidence areas with the highest incidence risk groups and ensuring there is integration and linkages to existing services. In 2021, WHO gave a conditional recommendation to include the dapivirine vaginal ring as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches. During the roll out of this product, several implementation considerations and research questions will need to be addressed.

In 2021 WHO and UNAIDS published updated Ethical considerations in HIV prevention trials. In the era of PrEP, the concept of placebo-controlled trials in HIV prevention is no longer an ethical option and standard of care must be offered. Researchers and trial sponsors should, at a minimum, ensure access to the package of HIV prevention methods recommended by WHO for every participant throughout the trial and follow-up, along with the need for post-trial access by participants to products that are shown to be effective. Inclusion of standard of care may reduce the incidence of HIV in the trial population and will

need to be factored into statistical power calculations for efficacy. Alternative clinical trials designs and ways of estimating a counterfactual HIV incidence for comparison are also being explored.

2. Update on development of HIV prevention products ***(Sinead Delany-Moretlwe, Wits RHI; Barney Graham, NIH; Jerome Kim, IVI)***

Long-acting antiviral PrEP landscape

Since first recommendations for PrEP in 2012 there has be wide expansion globally and by the end of 2020 oral PrEP was included in >70 country programmes with PrEP being initiated by almost 1 million people. However, this falls short of the goal set by UNAIDS to have 3 million people on PrEP by 2020. Furthermore, initiation of PrEP does not translate to continued use, and an estimated 1/3 of people discontinue PrEP after one month. There are several reasons why people discontinue PrEP including: changes in risk profile; concerns about side effects; the burden of taking a pill every day; costs; access; the burden of repeat visits to get refills; and issues around stigma, discrimination, and fear of intimate partner violence. Long-acting products could overcome some of these barriers and many people seek discreet prevention products that require minimal daily effort.

The most advanced long-acting product is the monthly dapivrine ring which is self-inserted each month and releases dapirivine over 30 days. The advantage is that there is low systemic absorption leading to less side effects. Two Phase 3 trials showed the ring to be well-tolerated and reduced HIV risk (compared to placebo) in women by ~30%. Reduced efficacy was found to be associated with low adherence, particularly in young women. In open-label extension studies, greater use showed an estimated ~50% risk reduction. On this basis, EMA issued a favourable opinion in July 2020 to recommend it be used as an alternative for women who could not use oral PrEP. WHO has now prequalified the ring and included it in clinical guidance in early 2021. This has paved the way for in-country approvals and many countries are now considering to include the ring in their PrEP programmes. The ring is a promising technology and an alternative prevention option for women. This technology is being further developed into a 90-day ring and with co-delivery of contraceptives. Other ARVs could also be delivered using this platform. However, additional data is needed including in adolescents, on ARV resistance in seroconverters and safety data in pregnant and breastfeeding women. Another concern is cost and cost effectiveness (CE), with each ring costing US$ 6-9.

Countries are currently considering CE relative to other long-acting prevention options which will soon become available, such as long-acting injectable cabotegravir (CAB-LA). In 2020, the results of two phase 3 trials of CAB-LA found the product to be highly effective: One trial was conducted in MSM and TGW in the Americas and south east Asia with an estimated 68% reduction in HIV infection in the CAB-LA arm compared to Tenofovir/emtricitabine (TDF/FTC). The other trial was conducted in cisgender women in Sub-Saharan Africa and found CAB-LA to have an 89% lower risk of infection compared to TDF/FTC alone. In both trials the products were found to be safe and well tolerated with no evidence of weight gain. These results demonstrate the promise of long-acting products including the potential to be cost-effective even at higher price given the prevention benefit. Long acting injectables also have the potential to be developed as a multi-purpose prevention product with contraceptives. However, there are concerns about resistance and breakthrough infections and, with only 20 HIV infections across the CAB-LA clinical

trials, more data are needed through demonstration projects. There are also no data yet in pregnant or breastfeeding women but these data will be gathered in open-label extension studies. In addition, there are other long-acting injectable products in the pipeline, including some that may be able to be given every 6 months. Monthly oral pills and annual implants are so being explored. However, the acceptability of a monthly pill will need to be determined and there are issues around acceptability and health system capacity of health care workers to insert and remove implants.

There are an increasing number of PrEP options on the horizon, and these have the potential to increase HIV prevention coverage and have a public health impact. However, new HIV prevention options will need to have similar or better effectiveness and safety profile compared to current PrEP. They would also need to be acceptable and usable for adolescents, pregnant and breastfeeding women. It would also be ideal if they could be combined with other indications such as contraceptives. They should also show no interference with current HIV diagnostic algorithms and have minimal resistance concerns. They will also need be acceptable to users and providers with reasonable cost and cost-effectiveness. They will need to be delivered within constrained health systems so reduced requirements for specialist skills or infrastructure is needed. Time and more data will address many of the current unknowns.

Monoclonal antibodies landscape

Recent results from the Antibody Mediated Prevention (AMP) trials tested a single mAb, VRC01 in countries in Southern Africa and the Americas. VRC01, was given as either a 10mg/kg or 30mg/kg dose via intravenous infusion compared with placebo, every two months over 1.5 years. The results did not show a significant efficacy signal with this product, however there is evidence from sub analyses that efficacy was higher against viruses that were sensitive to the mAb. Modelling studies have estimated that with broadly neutralizing, highly potent mAbs with adequate levels of neutralizing activity it may be feasible to achieve very high efficacy. There are several highly potent mAbs with broader neutralizing activity being explored, including some with extended half-lives. With double and triple mAb combinations and potency of 1ug/ml, up to >90% neutralization of viruses can be achieved. In order to achieve effectiveness, mAb potency of <1 µg/ml IC_{80} is needed. Achieving ~1:250 IC_{50} neutralization activity in serum is needed for ~75% point efficacy. However, there may be cost implications with combinations of several mAbs and increase product volume.

It is important to keep in mind than multiple modalities are likely to be required to drive down the incidence of HIV infections.

HIV vaccines landscape

There are multiple HIV vaccines in preclinical development and several in clinical development using different platforms. Two candidates are in advanced clinical development, Ad26 mosaic/gp140 (trial expected to end in 2022) and DNA, MVA gp120/gp140 (trial expected to end in 2023). However, both candidates are heterologous prime-boost regimens with multiple shots that may be programmatically challenging to deliver. There have been multiple failures in HIV vaccine development over the years and multiple challenges remain including sequence diversity, cryptic epitopes and glycosylation, high mutation rates and integration and multiple approaches are being explored to overcome these.

Open discussion:

A question was raised about the decrease in efficacy in the PrEP comparator arm seen in the CAB-LA trials. The simplest explanation is reduced adherence to the daily pill versus CAB-LA as the CAB-LA injections are essentially directly observed therapy and people were coming back for their visits at >90% visit return. However, this is in a trial setting, so the retention rates in the real-world setting would need to be assessed.

HIV mAb combinations tested so far do not have 100% coverage but high efficacy could be achieved. With regards to escape mutants, viruses that escape these mAbs are expected to have a lower fitness, furthermore these viruses may still be susceptible to ARVs. There is some concern about using these mAbs for therapeutic indications as this might lead to resistance. MAbs should not be used in HIV infected pregnant women as it would not be desirable to select for and transfer resistant viruses to the infant. MAb prevention would likely have value in populations like pregnant or breastfeeding HIV negative women or administered directly to infants in the delivery room. There may be a need to tailor mAb combinations by the prevalence of some strains in different regions. A series of new trials will be starting soon to test a combination of three mAbs with extended half-lives and this will provide information on whether there is a functional neutralization response in sera against a panel of viruses.

Offering the standard of care in trials as recommended in the updated UNAIDS/WHO guidance on prevention trials may impact the incidence of infection in studies. In the AMP trials, the mAb was tested against placebo, however education in HIV prevention and PrEP were offered to all participants. The DVP ring was also tested against placebo. However, now HIV trials may need to have an active comparator, as was done in the CAB-LA trials. This makes it difficult to conduct trials with an incidence endpoint. Alternative trial designs, such as using counterfactual levels of incidence to measure vaccine efficacy are being considered, and clinical study design will become more complex as additional long-acting products become available as standards of prevention.

Value proposition for monoclonal antibodies *(Susan Buchbinder)*

There are several reasons why mAbs could be an important component of the HIV prevention toolkit:

- There is a need to diversify the portfolio of prevention products in development to mitigate against failure, for examples the safety, efficacy and resistance with the current long-acting ARVs in development is not known. We also don't know what the uptake of or adherence to the new agents will be.
- Choice matters and people have different preferences; the availability of options may lead to increased uptake and adherence of products and HIV prevention.
- It is really important to keep all treatment options open as the ARVs being developed for PrEP are also being developed for treatment. As people develop resistance over time, having more options for alternative regimens is important.
- Avoiding toxicity or undesirable side effects associated with some ARVs.

- Providing privacy and avoiding stigma for some individuals is important. As keeping pills or going to the clinic every 2 months, or having an implant may not be discrete enough for some potential PrEP users who want utmost privacy. Therefore, injections every 6 month may be a better regimen to keep use of PrEP discrete.
- Development of mAbs also has the added benefit of helping the HIV vaccine field learning what/how much is needed in mAbs may help provide targets for active immunization program.
- Finally, there may be additional benefits by solving access issue for HIV mAbs may help increase access for mAbs against other diseases.

2. Facilitated discussion on selected PPCs for HIV mAbs (*Erin Sparrow, WHO*)

The aim of this presentation was to review specific attributes proposed for the HIV mAb PPC, based on input and comments from the drafting group, and the stakeholder consultation, and to seek guidance from PDVAC prior to issuing the PPC for public consultation. Comments from the open and closed discussion are summarized under the earlier section on *PDVAC Conclusions and Recommendations.* Note that the text summarises the most pertinent points from the PPC draft document; minor suggestions will be directly incorporated into the draft PPC.

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