WHO Preferred Product Characteristics for broadly neutralizing monoclonal antibodies for HIV prevention

Note:

This draft Preferred Product Characteristics (PPC) has been prepared in collaboration with IAVI and in consultation with the WHO HIV vaccines and monoclonal antibodies Working Group and with WHO's Product Development for Vaccines Advisory Committee (PDVAC). This document is being posted for the purpose of inviting comments and suggestions on the content contained therein, which will then be considered by PDVAC for endorsement. Written comments proposing modifications to this text must be received by 23 July 2021 and entered in the Comment Form (available separately) and should be addressed to the Responsible Officer: Ms Erin Sparrow at sparrowe@who.int.

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Contents

Abbreviations and glossary

ADAs	Antidrug antibodies
AGYW	Adolescent girls and young women
AMP	Antibody Mediated Prevention
ART	Antiretroviral therapy
ARV	Antiretroviral
bNAb	Broadly neutralizing antibodies
CAB	Cabotegravir
COGS	Cost of goods sold
CTC	Controlled temperature chain
DPR-VR	Dapivirine vaginal ring
DSMB	Data and safety monitoring board
EMA	European Medicines Agency
F/TAF	Descovy
FSW	Female sex workers
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IV	Intravenous
IVB	Immunization, Vaccines and Biologicals
LA	Long-acting
LMICs	Low and middle income countries
mAbs	Monoclonal Antibodies
MOUD	medicines for opioid use disorder
MPER	Membrane-proximal external region
mRNA	Messenger RNA

MSM	Men who have sex with men
MSW	Male sex workers
NIAID	National Institute of Allergy and Infectious Diseases
PK	Pharmacokinetics
PMTCT	Prevention of Mother to Child Transmission
PPC	Preferred Product Characteristics
PQ	Prequalification
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
SC	Subcutaneous
SRH	Sexual and Reproductive Health
SSA	sub-Saharan Africa
TasP	Treatment as Prevention
TDF/FTC	tenofovir disoproxil fumarate and emtricitabine
TGW	Transgender women
UNAIDS	Joint United Nations Programme on HIV and AIDS
US FDA	US Food and Drug Administration
VMMC	Voluntary male medical circumcision
WHA	World Health Assembly
WHO	World Health Organization

I. Introduction and Background on WHO PPCs:

It is a priority for the World Health Organization to ensure that products are developed in a manner that supports optimal use globally, including in low- and middle-income countries (LMICs). To support this goal, Preferred Product Characteristics (PPC) technical documents are developed to articulate preferred attributes of products for licensure, policy, and programmatic implementation in LMIC settings.

PPCs are developed based on criteria including feasibility and unmet medical need for prevention interventions in WHO priority disease areas. The primary target audience for WHO PPCs is any entity intending to seek eventual WHO policy recommendation and prequalification for their products. WHO PPCs do not override existing WHO guidance and are meant to be updated regularly to account for changes in prevention and research and development landscapes. PPCs do not include minimally acceptable characteristics. Regardless of whether a product candidate meets PPC criteria, it can still be assessed by WHO for policy recommendation. The current PPC addresses the preferred product attributes for monoclonal antibodies for HIV prophylaxis. A PPC that addresses the preferred product attributes for HIV vaccines is also a key priority.

The HIV epidemic continues to cause extensive morbidity and mortality globally. Despite progress in reaching 73% of people living with HIV with antiretroviral therapy (ART), gaps in HIV prevention and

treatment contributed to 1.5 million new infections and 690,000 HIV-related deaths in 2020.[1] Young children accounted for 160,000 new HIV infections, the vast majority during infancy.[2]

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 challenges. New products that offer longer duration of protection are poised to have a significant impact on HIV prevention efforts. The dapivirine vaginal ring (DPR-VR) for women recently received a positive opinion from the European Medicines Agency (EMA) as a monthly prevention option.[3] Additionally, in the HPTN083 and HPTN084 trials, long-acting pre-exposure prophylaxis with cabotegravir (CAB-LA), administered as a bi-monthly injection, 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.[4] [5]

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.[6] Several HIV vaccine and monoclonal antibody (mAb) 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) Phase 2 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, and among women in Eastern and Southern Africa (NCT02716675 and NCT02568215).[7, 8] 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, but suggested the need to assess combinations of antibodies that provide broader, more potent protection than VRC01 alone.[9] A number of putatively more potent combinations and engineered antibodies are also undergoing early clinical evaluation.[10]

The HIV vaccine development community faced a setback in early 2020, when the National Institute of Allergy and Infectious Diseases (NIAID) stopped administration of an investigational prime-boost vaccine regimen, containing ALVAC and gp120, in the HVTN 702 clinical trial due to independent data and safety monitoring board (DSMB) interim findings that the regimen did not prevent HIV.[11] Nevertheless, several promising vaccine candidates continue to progress into late-stage development. The Phase 3 Mosaico study (NCT03964415) and the Phase 2b Imbokodo studies both evaluate an investigational adenovirus-26-based candidate vaccine combination with “mosaic” immunogens comprised of elements from multiple HIV subtypes, with the goal of inducing immune responses against a broad array of global HIV strains.[12] The PrEPVacc Phase 2b trial (NCT04066881), which is scheduled to begin enrollment later in 2020, evaluates two experimental HIV vaccine regimens-- one combining DNA with protein-based candidate vaccines and the other combining DNA, modified vaccine Ankara (MVA) and protein-based candidate vaccines.[13] More information on the pipeline of HIV vaccine and prevention candidates is included in Annex 1 and 2.

II. WHO vision and strategic goals for HIV immunoprophylaxis

WHO's *Global Health Sector Strategy on HIV, 2016–2021* sets out a vision of ending HIV/AIDS as a public health threat, including reaching zero new HIV infections, by 2030. [14] At the current pace, the global community will miss this target, having failed to reach interim Fast Track targets, under the *UN Political Declaration on HIV/AIDS,* of achieving less than 500,000 new HIV infections by 2020. [15]

Scale-up of current HIV prevention efforts—including antiretroviral therapy for people living with HIV, oral PrEP, voluntary medical male circumcision, treatment of sexually transmitted infections, and male and female condom usage—is critical, but insufficient, to meet 2030 targets. The COVID-19 pandemic has further set-back the scale-up of these services.

As a complement to existing measures, the *Global Health Sector Strategy on HIV* identifies HIV prevention and treatment innovation as one of five strategic priorities for sustainably ending the epidemic. [16] Ultimately, development of a safe, effective, and accessible vaccine will be critical to deliver the vision of ending AIDS as a public health threat. [17] As we work toward the long-term goal of an HIV vaccine, additional biomedical tools are needed to accelerate progress toward 2030 targets.

In February 2018, a WHO-UNAIDS joint consultation was convened to consider the future state of readiness for HIV vaccines and prophylactic mAbs. The need to determine the preferred product characteristics for HIV vaccines and mAbs in the pipeline, as well as critical considerations to support programmatic suitability, emerged as key priorities from the consultation. [18]

III. Public health need for monoclonal antibodies for HIV prophylaxis in the context of existing interventions

Overview of existing interventions:

Several interventions have proven effective in reducing the risk of HIV infection, including male and female condom usage, voluntary male medical circumcision (VMMC), use of clean needles and syringes, medicines for opioid use disorder (MOUD), treatment for people with HIV to prevent onward transmission (Treatment as Prevention [TasP]), and more recently, the use of antiretroviral medicines as pre-exposure prophylaxis (PrEP). In 2012, WHO issued guidance for the use of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for oral pre-exposure prophylaxis (PrEP) in serodiscordant couples, men, and transgender women who have sex with men at high risk of HIV. [19] In 2015, WHO broadened its guidance to include all people at substantial risk of HIV infection (defined as a population group with an incidence >3 per 100 person years) as part of combination prevention approaches. [20] As pf March 2021, an estimated 1,115,000 individuals had initiated oral PrEP in an effort to achieve the WHO/UNAIDS target of initiating at least 3,000,000 people by 2020. [21] However, of 69 countries implementing PrEP, 56 (81%) report at least one barrier to PrEP access. [22]

The efficacy of oral PrEP with TDF/FTC has varied widely across a range of clinical trials and enrolled populations. Among HIV serodiscordant heterosexual couples in Kenya and Uganda (NCT00557245), daily oral TDF/FTC PrEP reduced the risk of HIV infection by 75% (95% confidence interval [CI], 55 to 87; P<0.001);[23] however, the same regimen demonstrated only a 44% reduction (95% CI, 15 to 63; P=0.005) in HIV acquisition among MSM in a multi-country trial (iPrEx, NCT00458393),[24] and no evidence of effectiveness in two large Phase 3 trials in African women (FemPrEP, NCT00625404 and VOICE, NCT00705679).[25, 26] In more recent trials, both oral daily (PROUD, NCT02065986) and event-driven PrEP (IPERGAY, NCT01473472) in MSM reduced HIV acquisition by 86% (90% CI, 64 to 96; p=0·0001; and 95% CI, 40 to 98; P=0.002, respectively).[27] [28] For those initiating oral PrEP, challenges adhering to a daily-- or for MSM an event-driven-- regimen, side effects, and stigma associated with use of the same product for both treatment and prevention have contributed to non-adherence or discontinuation, with a significant impact on PrEP's effectiveness.[29, 30, 31, 32]

In October 2019, emtricitabine/tenofovir alafenamide (F/TAF] (Descovy) was approved by the US FDA for daily oral PrEP to reduce the risk of HIV infection through sex, excluding those who have receptive vaginal sex. Despite strong adherence in the clinical trial setting, F/TAF could face similar real-world implementation challenges as TDF/FTC due to its comparable product profile and daily dosing requirements.[33] Efficacy data on F/TAF as a PrEP agent in women or people who inject drugs is lacking.

Two Phase 3 trials examined the efficacy of the dapivirine vaginal ring as a monthly prevention option. The Ring Study demonstrated an HIV reduction of 31% (hazard ratio, 0.69; 95% CI, 0.49 to 0.99; P=0.04) among women using DPV-VR, and the ASPIRE study demonstrated a 27% (95% CI, 1 to 46; P=0.046) reduction in risk of HIV infection among African women.[34, 35] Significant differences in protection were observed, driven by lower levels of adherence among women under 25 years of age. An open-label extension study of the monthly dapivirine ring, known as DREAM, showed increased product use compared to the previous Phase III RING study with modeling data suggesting that women's HIV-1 risk was reduced by 63%.[36] The dapivirine ring received a positive scientific opinion from the European Medicines Agency (EMA) under the Article 58 procedure and was WHO prequalified in November of 2020 for use in women who are at higher HIV risk, aged 18 years and over, in combination with safer sex practices when oral pre-exposure prophylaxis (PrEP) is not used or cannot be used.[37] [38] A systematic review of the literature on DPV-VR acceptability suggests that most women users in LMIC settings have a positive view of the ring that increases with usage; and, that many would consider the ring an acceptable delivery device for HIV prevention or other indications.[39] In January 2021, WHO recommended that the dapivirine vaginal ring be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches.[40]

Pipeline of HIV prevention products:

Results from the HPTN 083 Phase 3 study showed long-acting injectable cabotegravir (CAB LA) administered every two months to be 66% more effective in preventing HIV acquisition than daily oral prep with TDF/FTC among MSM and transgender women.[41] In the HPTN 084 Phase 3 study (NCT03164564) of CAB LA for HIV prevention in women at increased risk of HIV acquisition in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda and Zimbabwe, long-acting cabotegravir was 89% (hazard

ratio, 0.11 95% CI, 0.04 to 0.32) more effective at preventing HIV acquisition, than TDF/FTC.[42] There are no planned studies of CAB LA among PWID. In January 2021, Cabotegravir was licensed by the US FDA as a monthly treatment for use in combination with Rilpivirine.[43] Regulatory submission for the prevention indication for CAB-LA is expected in 2021.

Acceptability research suggests that delivering PrEP through a long-acting (LA) injectable product could address some challenges associated with daily oral regimens.[44, 45] Women report a general preference for prevention technologies delivered by injection over those delivered either through a monthly vaginal ring or daily pill, particularly among young women in sub-Saharan Africa, where injectable contraceptive use is widespread.[46, 47, 48] However, some studies of CAB-LA cited concerns regarding the frequency of clinic visits and users' preference for fewer injections[49]; and, the injectable contraception literature documents a high rate of non-adherence among analogous injectable hormonal contraceptives,[50] which suggests that an LA injectable PrEP formulation would not completely solve adherence challenges for all patients in regions where HIV is endemic.[51] Additional implementation challenges relate to requirements for a daily oral lead-in period of four weeks prior to the administration of CAB-LA. For those discontinuing use, there are also concerns regarding the products' prolonged presence for more than a year in some people— which could theoretically lead to increased risk of drug resistance and selection of escape mutants that endanger the class of drugs for treatment indications if individuals contract HIV.

Alongside CAB-LA, there are additional promising long-acting ARVs in the pipeline. Merck is launching in Sub-Saharan Africa and the United States the IMPOWER 22 Phase 3 study in early 2021, which will evaluate the efficacy and safety of islatravir, a nucleoside reverse transcriptase translocation inhibitor, administered orally once-monthly as PrEP in cisgender women who are at high risk for HIV-1 infection, and IMPOWER 24 in additional key populations, including men who have sex with men (MSM) and transgender women.[52] Additionally, Gilead is planning to evaluate the use of lenacapavir, a long-acting HIV-1 capsid inhibitor, as an injectable PrEP option administered every six months in cisgender adolescent girls and young women and in a separate trial, in cisgender men, persons of trans experience and gender non-binary individuals who have sex with men.[53] See Annex 2 for additional information on these and other HIV prevention products in the pipeline.

Need for monoclonal antibodies for HIV prophylaxis:

Varying implementation requirements and product preferences in the context of persistently high rates of new HIV infections highlight the ongoing need to diversify biomedical options for prevention of HIV. For key populations, there remains a need for novel prevention products that are not only safe and effective, but support adherence and are suitable for implementation in a range of LMIC contexts. Evaluation of new prevention options must take place within the context of other existing and pipeline interventions, and consider potential trade-offs for use across geographies, demographics, and key population groups.

The use of mAbs to treat and prevent disease is one of the most rapidly growing areas of biomedical research. More than 100 mAbs for different indications have been licensed or submitted for regulatory

review in the US or EU alone,[54] and mAbs are now the single-largest class of molecules undergoing clinical investigation.[55] In 2018, Ibalizumab (Trogarzo®) became the first mAb to receive FDA approval as salvage therapy in HIV positive patients whose viruses are resistant to multiple existing antiretroviral drugs.[56]

Broadly neutralizing monoclonal antibodies (bNAbs) derive from naturally occurring antibodies with potent neutralizing activity against a broad array of HIV strains *in vitro*. Research suggests structural modifications to bNAbs can increase their breadth, potency, and half-life, potentially extending their duration of protection and enabling dosing on a bi-monthly, quarterly, or semi-annual basis.[57, 58] Given their favorable safety and pharmacokinetic profiles, bNAbs offer potential advantages over use of antiretroviral drugs (ARVs) for the prevention of HIV.[59] Since bNAbs have a different mechanism of protection than antiretroviral drugs, they could mitigate risk of resistance to ARVs and minimize stigma associated with the use of ARV-based products for prevention. It is also possible that bNAbs might have fewer adverse effects than certain antiretroviral drugs, particularly during pregnancy. For those at high risk of HIV infection, bNAbs could constitute an important alternative biomedical prevention option, if key determinants of implementation feasibility can be addressed.

IV. State of the Art:

Preclinical studies suggest that even relatively low concentrations of potent anti-HIV-1 neutralizing antibodies can block infection.[60] Several bNAbs with significant breadth and potency that target different HIV envelope epitopes have entered clinical trials and are being evaluated for their potential as long-acting alternatives to antiretrovirals for HIV prevention and therapy.

The first bNAb to be tested for efficacy in HIV prevention was VRC01. Phase 1 studies of VRC01 administered as a monthly or bimonthly IV infusion (10-40 mg/kg) or as a bi-weekly subcutaneous (SC) injection (5 mg/kg) found it to be safe, well-tolerated, and to maintain drug concentrations consistent with neutralization of the majority of tested HIV strains.[61, 62] VRC01 has also demonstrated promising safety, tolerability, and pharmacokinetics in HIV-exposed infants.[63]

Based on these promising results, the NIAID HIV Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN)-sponsored Antibody Mediated Prevention (AMP) efficacy trials evaluated whether providing VRC01 as an intravenous infusion of either 30 mg/kg or 10 mg/kg every 8 weeks is safe, tolerable and effective at preventing HIV infection. Overall, the primary endpoint of prevention of HIV infection did not achieve a significant difference between the intervention and the control. Additional analysis showed that VRC01 was 75.4% effective (95% CI, 45.5 to 88.9%) at preventing acquisition of HIV strains that were susceptible to the bNAb (in vitro sensitivity to the antibody of IC80 of <1 µg/ml) in women vulnerable to HIV acquisition in sub-Saharan Africa and men and transgender persons vulnerable to HIV acquisition in South America, Switzerland and the United States. However, investigators found that only 30% of the HIV strains circulating in the regions where the trials were conducted were sensitive to VRC01. Additional findings were that in the AMP trial, Ab neutralization appeared to correlate with efficacy. In addition, the trials offered insight into the concentration of antibodies required to afford protection against HIV in humans.[64] [65]

Antibodies and engineered antibody-like molecules that are more potent, broader or long-lasting than VRC01 are currently in early clinical testing.[66, 67, 68, 69, 70, 71, 72, 73, 74] (*See Annex 2 for overview of ongoing* trials). Given that neutralization escape from single antibodies can readily occur, and global viruses exhibit a wide range of sensitivities to individual bNAbs, the AMP trial results confirm the need to advance a combination of protective antibodies.[65] Recent studies of *in vitro* neutralization have established that combinations of bNAbs targeting distinct epitopes can act in a complementary and additive manner, exhibiting improved neutralization breadth and potency compared to single bNAbs.[75, 76] For both the prevention and treatment of HIV infection, combinations with higher numbers of complementary bNAbs appear advantageous.[77] *In vitro* neutralization assessments on a panel of 125 HIV-1 Env-pseudotyped strains representing the major circulating HIV-1 clades showed that while two mAb combinations provided coverage against more than 89% of the viruses tested, the coverage of triple and quadruple combinations exceeded 98%.[75] Given within-host diversity and the need to have two or more bNAbs simultaneously active for adequate coverage, some have posited that at least three bNAbs may be needed for protection against HIV-1 acquisition in diverse populations to prevent breakthroughs of resistant viral variants.[78]

Co-formulation of multiple bNAbs can streamline supply chain management and administration of antibody combinations. However, combining multiple bNAbs together could substantially raise costs and increase dose requirements. Engineered bi- and tri-specific neutralizing antibodies (bNAbs) that combine the breadth and potency of multiple antibodies into one molecule could potentially allow for dose reductions, more streamlined clinical development and regulatory pathways, and reduced costs, while minimizing the likelihood of breakthrough infection and erecting a higher genetic barrier for viral resistance. Engineered bispecific antibodies that target epitopes on HIV Env and host-cell CD4 (10E8-iMAb) have been found to outperform respective individual antibodies and combinations of two conventional antibodies.[79] The 10E8.2/iMab bispecific antibody, targeting the human CD4 receptor and the HIV-1 Env MPER neutralized 100% of circulating HIV-1 strains in a 118 multi-clade panel.[80] Likewise, engineered tri-specific antibodies targeting the CD4 binding site, V1V2 glycan site, and MPER region (VRC01/PGDM1400/10E8v4) were found to exhibit higher potency and breadth than any previously described single bNAb, conferring complete immunity against a mixture of simian-human immunodeficiency viruses (SHIVs) in nonhuman primates, with pharmacokinetics similar to those of human bNAbs.[79]

The high affinity for specific targets and selectivity of antibodies means they are less likely to have side effects or unexpected safety problems. Single and repeat bNAb administrations of anti-HIV-1 antibody combinations have generally been well tolerated with infrequent adverse events reported.[76] One concern with long-term infusion of human monoclonal antibodies is triggering the production of antidrug antibodies (ADAs) that may reduce activity or lead to adverse responses. Greater complexity in the structure of multi-specific antibodies may increase the risk of unwanted immunogenicity.[80] Further clinical testing is needed to confirm whether engineered bi- and tri-specific molecules will maintain the favorable safety profiles of the naturally occurring bNAbs tested to date without inducing clinically significant ADAs.[81]

V. Target Populations

Despite the heterogeneity of HIV epidemics within and across regions, addressing the prevention needs of certain key populations and vulnerable groups must be a strategic priority given the disproportionate impact of the epidemic on these groups, and their central role in HIV transmission:

Developing safe, effective and accessible HIV bNAbs for key populations

Marginalized or hard to engage key populations – which may include men who have sex with men (MSM), male and female sex workers (MSW and FSW) and their clients, people who use drugs (PWID), transgender individuals, and incarcerated populations-- are disproportionately affected by the HIV epidemic in all regions.[82] Despite comprising a small proportion of the general population, key populations and their sexual partners account for more than 60% of new infections globally and in some regionas these groups account for more than 95% of new HIV infections.[83] In 2018, HIV acquisition among key population groups was 12-22 times higher than for the general population.[84] Additionally, transmission from current and former key populations to their intimate partners remains a critical driver of infection in the general population, reinforcing their centrality to HIV prevention strategies.[85] [86]

Addressing the needs of at-risk adolescents

A third of new infections globally are among youth aged 15 to 24 years old.[87] In sub-Saharan Africa (SSA), given emerging demographic trends contributing to a so-called "youth bulge," projections indicate that the number of incident infections in this at-risk population will increase in coming years, unless addressed.[88] Modeling efforts suggest that age-based prevention strategies targeting this key demographic can be highly efficient and cost-effective in reducing HIV incidence in SSA.[89, 90]

Among adolescents in SSA, females are more than twice as likely as their male counterparts to acquire HIV.[91] Partner age pairings across high-risk female age groups and older males play a critical role in perpetuating the cycle of HIV transmission.[92] Understanding and addressing the product needs of adolescent girls and young women (AGYW) and other adolescents at high risk of HIV acquisition, including MSM and PWID, is therefore a critical priority for prevention efforts.

Prevention of transmission among pregnant and breastfeeding women, neonates and infants

Together, ART for pregnant and breastfeeding women with HIV-infection and ARV prophylaxis for their infants have resulted in dramatic decreases in HIV transmission from mothers to their infants. Still, an estimated 160,000 infections in infants and young children occurred in 2020.[93] Perinatal infections persist due to late diagnosis of maternal infection, non-adherence to ART, ARV resistance, and breast-milk transmission. Although ART significantly reduces vertical transmission in high HIV incidence settings, a significant proportion of women acquire HIV during the antenatal and breastfeeding periods. Breakthrough infections in breastfeeding infants now occur at rates as high as 2–5% by six months of age and 6% by 12 months of age, contributing to the majority of infant infections in settings with

Prevention of Mother to Child Transmission (PMTCT) programmes.[94, 95] For HIV negative women, and pregnant and breastfeeding women, efforts are needed to prevent HIV acquisition and vertical transmission.

Passive immunization with bNAbs holds promise as a safe and durable intervention to prevent maternal HIV acquisition and reduce mother-to-child transmission.[63, 96] Given bNAbs' long half-life, they may be effective in supporting PMTCT implementation through less frequent administration, potentially compensating for gaps in adherence when used as an adjunct to, or in the place of, ARVs.[97] Given their potentially promising role in preventing perinatal HIV transmission, development of bNAbs for use in pregnant and breastfeeding women, neonates, and infants should also be a strategic priority.

VI. Clinical research and development considerations

Demonstrating the effectiveness of prevention options in diverse geographies is important given the genetic variability across clades prevalent in different regions. Different modes of transmission may also have implications in terms of the types of immune mechanisms playing a role in protection, with an impact on efficacy.[101] These factors highlight the need for inclusion of diverse geographies and populations, including pregnant and breastfeeding women, key populations, and adolescent girls and young women in clinical trials; however, many LMIC countries currently lack frameworks for the testing, licensure, and use of mAbs.[98]

Advances in HIV prevention, such as the availability of oral PrEP and likely availability of other long-acting products such as the DPV-VR ring and CAB-LA, introduce complex issues in the design of HIV prevention trials, such as balancing the need to protect research participants by providing them with the current optimal standard of HIV prevention and the ability to implement trials capable of meaningfully evaluating potentially life-saving interventions.[99, 100] The rate of events in a population with alternative standards of prevention may be lower, which requires that a larger number of individuals be enrolled in trials to observe the same number of events. Adjusting sample size calculations to account for incidence rates that are reduced by effective prevention modalities can have a significant impact on study size, and by extension, on the cost and feasibility of implementing efficacy trials.[101] The use of novel trial designs may overcome some of these issues.

Preclinical studies have suggested a correlation between in-vitro potency of neutralization and the dose required to afford protection against viral infection in non-human primates.[102] Results from the AMP trials further validate the predictive value of the non-human primate model and the use of in vitro serum neutralization as a biomarker for HIV protection, which could potentially streamline clinical development and accelerate future progress in HIV vaccine and antibody development.[103]

VII. Production and Manufacturing

In addition to meeting safety and efficacy criteria, antibody products must also meet a set of criteria regarding feasibility of manufacture and production scale up, related to quality attributes, pharmacokinetics (PK), and stability.[104] The need for high-concentration formulations for parenteral delivery of monoclonal antibodies can present manufacturability challenges related to viscosity levels

and the propensity for aggregation.[105] Product optimization strategies being investigated to drive cost reductions and enhance breadth, such as multi-specific antibody formats, can also introduce manufacturing challenges related to the potential for aggregation, immunogenicity, and low GMP cell line titers.[59, 74] Other downstream chemistry, manufacturing, and controls obstacles—such as antibody purification and stability concerns— may contribute to lower final product yields and quality issues for engineered multi-specific molecules than with typical mAbs.[74] Scientifically rigorous approaches to enhance developability of promising bi-specific or tri-specific antibodies, particularly their physico-chemical stability and formulation, are needed to overcome these hurdles.

Antibody production advances enabling process improvements – including integrated continuous biomanufacturing platforms, single-use automated operations, and modular and transportable facility units – hold the potential to increase efficiency and lower mAb production costs.[106, 107, 108] Innovative DNA and mRNA delivery platforms for mAbs in proof-of-concept trials could likewise enable faster and cheaper production.[109, 110] Taken together, improvements in antibody-expression yields and innovative manufacturing processes could contribute to significant reductions in the cost of goods sold (CoGs) for mAbs.[111, 112]

VIII. Value proposition

Ensuring the affordability of bNAbs will be critical. Biologics, particularly mAbs, are currently among the highest priced pharmaceutical products, a factor which currently limits global access. Robust health economic assessments that evaluate the cost-effectiveness of mAbs for HIV prophylaxis in the context of broader health systems delivery costs and anticipated epidemiological impact are needed to strengthen understanding of their potential value proposition.

Previously mentioned technological advances in monoclonal antibody identification, optimization, and manufacturing have increased the possibility for producing lower-cost monoclonal antibodies. By allowing for lower doses, longer duration of protection, and in the case of multi-specifics — by streamlining manufacturing, storage, transport, and administration costs — optimization and process improvements could potentially reduce both delivery expenses and CoGs.[113]

IX. Access and supply security

Developers and manufacturers should plan to make products broadly available, particularly to countries and populations with the highest disease burden, and that participate in the clinical development of the intervention. Intellectual property filings, out-licensing, and pricing should not be barriers to global access. Voluntary licensing of novel mAb technologies to low-cost manufacturers through platforms such as the Medicines Patent Pool or Product Development Partnerships, and long-term investments in regional manufacturing capacity, including technology transfer, could also support affordable mAbs production and delivery. Alternative business models that expand lower-cost manufacturing of innovative mAbs can further help support affordability.

X. Programmatic suitability

Efforts are needed to ensure that, where applicable to mAbs, WHO-defined criteria for programmatic suitability related to presentation, packaging, thermostability, storage volume, and disposal are met. [114]

The structure and stability of mAbs precludes oral delivery due to degradation in the gastrointestinal tract. [115] While mAbs are often delivered intravenously, the IV route requires facility-based administration by a health care professional, which increases the cost and limits the feasibility of implementation in resource-limited settings. A prospective randomized study of the mAb, trastuzumab, showed that an overwhelming majority of patients prefer subcutaneous over intravenous administration. [116] Subcutaneous (SC) delivery can increase programmatic suitability, reduce health systems costs, and enable self-administration. To be delivered subcutaneously at infrequent intervals, antibodies will require a long half-life and high concentration formulation. Efforts will be required to balance the desire for fewer, less frequent injections with injection volume to ensure dosing schemes are well tolerated and conducive to adherence. While some manufacturers are exploring user-friendly devices to support mAb delivery, such as slow-release implant devices, further efforts will be needed to ensure these innovations are cost-effective and amenable to global use. [117, 118]

Another key consideration with respect to programmatic suitability for antibody products is potential requirements for cold-chain storage. Cold-chain systems are expensive to maintain and as a result, there is often limited capacity in LMIC settings to absorb new products requiring cold-chain beyond existing Expanded Programme on Immunization (EPI) vaccines. Thermostable formulations of antibodies would greatly facilitate storage in a range of settings; however, for mAbs requiring cold-chain storage, presentation and packaging should be space-saving to minimize cold-chain footprint.

XI. WHO Prequalification

For procurement by United Nation agencies and financing by agencies such as Gavi, the Vaccine Alliance, products should meet criteria for programmatic suitability and be WHO Prequalified. [119] The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low- and middle-income country programmes. WHO encourages developers and manufacturers to be aware of the prequalification process and to discuss products and regulatory requirements with the WHO PQ team early in development processes.

In May 2014, the World Health Assembly (WHA) adopted Resolution WHA67.21 on *Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy*, which urged member states to strengthen national regulatory assessment capacity and to facilitate pathways to meet the public health need for biotherapeutic products. [120] Recognizing that regulatory assessment of mAbs can be challenging for many countries, WHO has published guidance on the regulatory requirements for biotherapeutics and similar biotherapeutics. [121] WHO also launched a pilot project to prequalify select biosimilars, which resulted in WHO prequalification of the first mAb in late 2019, a trastuzumab biosimilar for the treatment of breast cancer. [122] Additional efforts are needed to support development of the scientific expertise and regulatory frameworks to promote access to high quality, affordable, safe, and efficacious mAbs in LMIC settings.

XII. Preferred product characteristics for bNAbs for HIV prophylaxis

Table 1. Preferred product characteristics

Parameter	Preferred Characteristic	Notes
Indication for use	Prevention of HIV-1 infection in confirmed HIV-negative individuals. Prevention of HIV-1 infection in neonates and infants with HIV exposure.	Treatment or curative indications are out of scope of this PPC. 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 populations	People at substantial risk of HIV infection and their sexual partners including:	
	Men who have sex with men, male and female sex workers, people who use drugs, transgender people, and people in prisons and closed settings.	Key populations and their sexual partners account for more than 60% of new infections globally and therefore are critical to HIV prevention efforts.
	Adolescents and cisgender men and women in high prevalence settings.	Adolescent girls and young women (AGYW) account for 3 out of every 4 new infections in sub-Saharan Africa—the epicenter of the HIV epidemic—and therefore are priority in prevention efforts.
	Pregnant and breastfeeding women in settings with high HIV prevalence.	Identifying prevention products that are appropriate for use during conception, pregnancy, and while breastfeeding is important.
	Neonates and infants with HIV exposure.	Given bNAbs' potentially long half-life, they may be effective in supporting Prevention of Mother to Child Transmission (PMTCT) implementation. [123]
	Serodiscordant couples.	PrEP can protect the HIV-negative partner in a serodiscordant relationship when the HIV-positive partner is either not on antiretroviral therapy (ART) or has not yet achieved viral suppression. [124]

	Other target populations at high risk may be considered based on local epidemiology.	Additional research is needed to determine the potential role of bnAbs in post-exposure prophylaxis for those facing sexual exposure or occupational risk (e.g. from needle-stick or other nosocomial exposure).
Access and Affordability	Product and health systems delivery costs should be affordable and cost-effective in LMIC settings.	Cost should be considered relative to efficacy and impact vis-a-vis comparable products. Further evidence on the cost-effectiveness, acceptability, and full value proposition of bnAbs, including from a LMIC perspective, is needed. Manufacturers should plan to make products broadly available, particularly to countries and in populations with the highest disease burden, and that participate in the clinical development of the intervention. Intellectual property filings, out-licensing and pricing should not be barriers to global access.
mAb delivery strategies	Newborn infants: alignment with existing PMTCT programmes. Neonates and infants: alignment with existing vaccine delivery infrastructure. Populations at substantial risk: integration with HIV prevention programmes and other SRH services. People who use drugs: integration with harm reduction services.	The most appropriate delivery strategies in different settings will be determined by target populations, mAb characteristics, and related health systems and programmatic factors. In settings where HIV infection incidence is low in the general population but concentrated within specific populations at substantial risk, a more focused delivery programme might more efficiently decrease transmission, depending on acceptability and accessibility among the target populations at substantial risk. Demand creation and provider education are key strategies in informing the community and healthcare providers about the product. Such strategies are effective in delivering HIV Prevention products as has been demonstrated through the delivery of oral PrEP. When possible, integrating delivery when possible with other health services, e.g., HIV prevention, SRH services can increase uptake and acceptability. Communication, community outreach, and marketing strategies regarding HIV mAbs should be considered in advance.

Safety	Should have a favorable and acceptable safety and reactogenicity profile. Safe to use in pregnancy & breastfeeding. Safe in older adolescents (15-19 years). Safe in infants.	In clinical trials, single and repeat bNAb administrations of anti-HIV-1 antibody combinations have generally been well tolerated with infrequent adverse events reported.[76] Monitoring for clinically relevant anti-drug antibodies in clinical trials is important.[i] [125]
Efficacy	Efficacy trial with standard of prevention incorporated.[ii] 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. Evidence of broad coverage of genetic diversity of HIV-1 across geographies, populations, and modes of transmission. Antibody combinations and/or multi-specific formats, with antibodies targeting different epitopes in a complementary manner	Efficacy trial design should conform to relevant regulatory standards and be conducted with reference to the UNAIDS/WHO *Ethical Considerations in HIV Prevention Trials*.[100] As outlined in this guidance document, researchers and trial sponsors should ensure access to a package of recommended prevention methods. 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. Alternative trial designs may be needed to establish the value of specific agents for HIV prevention in the context of evolving standards of prevention. Further regulatory guidance on alternative trial designs is needed. Trials should also conform to WHO *Guidelines on the quality, safety and efficacy of biotherapeutic*

[i] Per ICH S6(R1): For monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term safety study (see ICH S6 Guideline) in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate. Alternatively, when animal models of disease are used to evaluate proof of principle, a safety assessment can be included to provide information on potential target-associated safety aspects. Where this is not feasible, appropriate risk mitigation strategies should be adopted for clinical trials.

[ii] If a correlate of neutralization titer is determined and accepted by regulators this can potentially support alternative study design for next generation products.

	to achieve broad protection and to prevent viral escape. [iii] Efficacy maintained with repeated use.	*protein products prepared by recombinant DNA technology.* [126] Programmatic benefits -- such as less frequent administration, increased acceptability, improved safety or improved cost-effectiveness-- may be considered alongside efficacy. Evaluation of sustained protection with repeated use based on long-term follow-up studies and post-introduction surveillance. High breadth of protection will be key to support sustained use across diverse geographies. Specimens should be collected during efficacy trials to support the identification of correlates of risk/protection and for breakthrough virus sequencing. Population level data will be important in determining whether there is selection for resistance to specific antibodies over time. Transplacental transfer should be factored into efficacy evaluations. There may be a need to tailor mAb combinations for regional use by the prevalence of strains in different regions.
Formulation/ Presentation	WHO defined recommendations on presentation, packaging, storage volume and disposal should be met, where applicable to mAbs. [127] A single vial product preferred. For infants, 0.5 ml per dose preferred.	For volumes >2 mL, multiple injections are typically used. [128] However, in clinical studies, target injection volumes of as high as 3 ml have been well tolerated and may be preferred over multiple injections.[115] [129] Further evaluation of preferences with respect to injection frequency, volume, and site is needed. Other approaches to increase the volume that can be injected subcutaneously are being evaluated and may become available in the future.

[iii] In preclinical studies, Xu, Pegu et al. found that a trispecific targeting the V1V2, MPER, and CD4bs sites was highly potent and broadly neutralized 99% of HIV viruses when tested against >200 different HIV strains.[47] The 10E8.2/iMab bispecific antibody, targeting the human CD4 receptor and the HIV-1 Env MPER neutralized 100% of circulating HIV-1 strains in a 118 multi-clade panel.[72]

	For children aged 5 years or younger 1 ml per dose or less preferred.[114]	While intravenous infusion is not preferred (see route of administration), if used, best practices for IV administration should be followed. [130]
Dose regimen	Administration every 6 months or longer preferred. Fixed, non-weight-based dosing is preferred, with appropriate fixed dosing presentations for: - Adolescents/adults - Infants - Neonates Co-formulation of mAb combination products is preferred. Single site, single injection preferred but not required.	Durations of at least 3 months would be considered, in the context of other favorable attributes (e.g. superior safety or effectiveness, tolerability, acceptability, ease of access, affordable cost, and supply chain benefits, compared to other available options). Pharmacokinetic studies demonstrating half-life sufficient to support schedule of administration needed. 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	Demonstration of favourable safety upon co-administration with relevant vaccines or other products. [iv]	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	Subcutaneous or intramuscular injection is highly preferred for use in LMICs.	Per defined criteria for prequalification, WHO specifies that an intravenous route of administration is not broadly suitable for programmatic implementation in LMIC settings.[115] The focus of this PPC is populations in LMICs for which intravenous administration is not considered programmatically appropriate. While intravenous administration might be suitable in

[iv] MAb-vaccine interaction studies are generally not required by regulatory authorities to support licensure. To date, conduct of mAb-vaccine interaction studies has been limited to mAbs that bind a human target associated with immune function. The recent guidance issued by EMA and FDA covering the clinical development of RSV mAbs for prophylaxis neither require or suggest conducting coadministration studies with other vaccines, although the EMA guidance does include such recommendations for development of RSV vaccines (FDA draft 2017, EMA 2018).

		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.
Product stability and storage	At a minimum mAbs should be stable at refrigerated condition (2° to 8°C); a controlled temperature chain (CTC) product is preferred. [131] Storage footprint should be minimized.	A room temperature, lyophilized product may be preferable. However, technical and implementation considerations, including preferences for ready-to-use formats, must be factored into formulation decisions.
Registration, prequalification and programmatic suitability	WHO prequalification preferred.	WHO prequalification is often used as a reliance mechanism to support licensure in LMIC settings and can enable procurement through UN agencies and other global mechanisms. Additionally, WHO prequalification can facilitate broad registration through the *Collaborative Procedure for Accelerated Registration of Prequalified FPPs procedure.* [132] Close cooperation and coordination with WHO and with national and international regulatory authorities is of high importance. Product attributes that support programmatic implementation and adherence— such as extended duration of protection and tolerability— hold the potential to lower delivery costs and improve the real-world effectiveness of HIV prevention products. There may be benefits in aligning dosing schedule with other care-seeking timepoints, such as injectable contraceptives. Engagement to understand the product preferences and needs of local decision makers and end users is important.

Annex 1: Table of ongoing HIV vaccine trials

Trial	Product	Sponsor	Description	Phase	Estimated Completion	Identifier
HVTN 702	ALVAC-HIV-C (vCP2438); Bivalent Subtype C gp120/MF59	NIAID	To evaluate the preventive vaccine efficacy, safety, and tolerability of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 in HIV-seronegative South African adults.	III	Sep-21	NCT02968849
HVTN 706	Ad26.Mos4.HIV; Clade C and Mosaic gp140 HIV bivalent vaccine	Janssen Vaccines & Prevention B.V.	To evaluate the vaccine efficacy (VE) of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection.	III	Jan-23	NCT03964415
PV1	DNA-HIV-PT123; AIDSVAX B/E with PrEP	MRC/UVRI and LSHTM Uganda Research Unit	To compare experimental combination vaccine regimens i.e. DNA/AIDSVAX (weeks 0,4,24,48) and DNA/CN54gp140 (weeks 0,4) + MVA/CN54gp140 (weeks 24,48) with placebo control.	IIb	Mar-23	NCT04066881
HVTN 118 IPCAVD-012	Ad26.Mos4.HIVBiological; Clade C gp140 plus adjuvant; Clade C gp140/Mosaic gp140 plus adjuvant; gp140 HIV Bivalent Vaccine	Janssen Vaccines & Prevention B.V.	To assess the safety and tolerability of the different vaccine regimens and of a late boost vaccination, and to assess envelope (Env)-binding antibody (Ab) responses.	II	May-23	NCT02935686
RV 305(A)	ALVAC-HIV AIDSVAX B/E	U.S. Military HIV Research Program	To assess the safety and tolerability of late boost regimens of AIDSVAX B/E alone, ALVAC-HIV alone, or ALVAC-HIV and AIDSVAX B/E in combination in HIV-uninfected participants from RV 144.	II	Jul-21	NCT01435135
ChAdOx1.HTI and MVA.HTI	ChAdOx1.HTI and MVA.HTI	University of Oxford	To assess safety and immunogenicity of candidate T-cell vaccines ChAdOx1.HTI and MVA.HTI given sequentially to healthy HIV-1/2 negative adult volunteers.	I/II	Oct-21	NCT04563377

HVTN 117 (TRAVERSE)	Ad26.Mos.HIVBiological, Ad26.Mos4.HIVBiological, Clade C gp140	Janssen Vaccines & Prevention B.V.	To assess the safety and tolerability of the 2 different vaccine regimens: 1. priming with trivalent Ad26.Mos.HIV and boosting with trivalent Ad26.Mos.HIV and Clade C gp140 plus adjuvant; or, 2. priming with tetravalent Ad26.Mos4.HIV and boosting with Ad26.Mos4.HIV and Clade C glycoprotein (gp)140 plus adjuvant.	I/II	Apr-23	NCT02788045
HVTN 121	AIDSVAX B/E	NIAID	To evaluate the breadth and potency of HIV-1 neutralizing antibody (nAb) responses and examine the safety and tolerability of an HIV gp120 protein vaccine (AIDSVAX® B/E) in HIV-uninfected adults diagnosed with Systemic Lupus Erythematosus (SLE).	Ib completed	Sep-20	NCT03618056
G001	eOD-GT8 60mer Vaccine;#859	IAVI	To assess the safety, tolerability, and immunogenicity of eOD-GT8 60mer vaccine, adjuvanted.	I	Jan-20	NCT03547245
VRC 018	VRC-HIVRGP096-00-VP (Trimer 4571)	NIAID	To assess if the vaccine Trimer 4571 is safe and well-tolerated, and to study immune responses to it.	I completed	Feb-20	NCT03783130
HVTN 124	Env (A,B,C,A/E)/gag (C) DNA Vaccine;#841;#gp120 (A,B,C,A/E) Protein Vaccine;#842	NIAID	To evaluate the safety, tolerability, and immunogenicity of env (A,B,C,A/E)/gag (C) DNA and gp120 (A,B,C,A/E) protein/GLA-SE HIV-1 vaccines (PDPHV-201401) as a prime-boost regimen or co-administered in repeated doses.	I completed	May-20	NCT03409276
W001	BG505 SOSIP.664 gp140;#853 (Duplication)	IAVI	To evaluate the safety and immunogenicity of recombinant HIV envelope protein BG505 SOSIP.664 gp140 vaccine, adjuvanted.	I	May-20	NCT03699241
HVTN 106	MVA-CMDR;#725;#DNA Mosaic Env;#655;#DNA CON-S env;#659;#DNA Nat-B env;#658	NIAID	To evaluate the safety and immune response to three DNA vaccines and a MVA-CMDR vaccine that may boost the immune response to the DNA vaccines in healthy, HIV-uninfected adults.	I completed	Jul-20	NCT02296541

HVTN 133	MPER-656 Liposome Vaccine	NIAID	To evaluate the safety and immunogenicity of an HIV-1 gp41 MPER-656 liposome vaccine in healthy, HIV-uninfected adults.	I	Nov-20	NCT03934541
HVTN 123	CH505 sequenced Envs	NIAID	To compare the safety, tolerability, and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells in healthy, HIV-1-uninfected adult participants.	I	Sep-20	NCT03856996
IAVI C101	BG505 SOSIP.GT1.1 gp140	IAVI	To evaluate the safety, tolerability, and immunogenicity of HIV-1 envelope protein BG505 SOSIP.GT1.1 gp140 trimer vaccine, adjuvanted.	I	May-21	NCT04224701
HVTN 137	BG505 SOSIP.664 gp140	NIAID	To evaluate the safety and immunogenicity of HIV-1 BG505 SOSIP.664 gp140 with TLR agonist and/or alum adjuvants in healthy, HIV-uninfected adults.	I	May-22	NCT04177355
EHVA P01	Drep-HIV-PT1 and CN54gp140/MPLA; DNA-HIV-PT123 and CN54gp140/MPLA-L	ANRS, Emerging Infectious Diseases	To evaluate the safety and immunogenicity of HIV Clade C DREP alone and in combination with a Clade C ENV Protein in healthy HIV-uninfected adults	I	Jun-22	NCT04844775
HIV-CORE 006	ChAdOx1.tHIVconsv1, MVA.tHIVconsv3 and MVA.tHIVconsv4	University of Oxford	To test three experimental HIV vaccines in healthy adults.	I	Jun-22	NCT04553016; NCT04586673
HVTN 135	CH505TF gp120, adjuvanted with GLA-SE.	HIV Vaccine Trials Network	To evaluate the safety and immune response to the HIV-1 CH505 transmitted/founder gp120 adjuvanted with GLA-SE in healthy, HIV-exposed uninfected Infants.	I	Oct-22	NCT04607408
IHV01 and A244/AHFG	IHV01 and A244/AHFG with and without ALFQ	U.S. Army Medical Research and Development Command	To evaluate IHV01 and A244/AHFG with and without ALFQ at a full dose and at a fractional dose (one-fifth of a full dose) in a late boost setting.	I	Oct-22	NCT04658667

HVTN 115	CH505 sequenced Envs ;#837;#DNA Mosaic-Tre Env;#838	NIAID	To evaluate the safety, tolerability, and immunogenicity of EnvSeq-1 and CH505 M5 gp120 Envs adjuvanted with GLA-SE.	I	Oct-22	NCT03220724
ACTHIVE-001	ConM SOSIP.v7 gp140	Academisch Medisch Centrum - Universiteit van Amsterdam	To determine the safety profile of the native-like HIV-1 envelope vaccine, ConM SOSIP.v7, adjuvanted with monophosphoryl lipid A (MPLA) liposomes.	I	Nov-22	NCT03961438
CD40.HIVRI.Env	CD40.HIVRI.Env (adjuvanted with Hiltonol) alone and co-administered with DNA-HIV-PT123.	ANRS, Emerging Infectious Diseases	Dose escalation trial of an adjuvanted anti-CD40 mAb fused to Env GP140 HIV Clade C ZM-96 (CD40.HIVRI.Env) vaccine combined or not with a DNA-HIV-PT123 HIV-1 vaccine in healthy participants.	I	Dec-22	NCT04842682
Env-C Plasmid DNA; HIV Env gp145 C.6980 protein	Env-C Plasmid DNA; HIV Env gp145 C.6980 protein	NIAID	To evaluate the safety and immunogenicity of priming with Env-C plasmid DNA vaccine alone, with different adjuvants, or with an adjuvanted HIV Env gp145 C.6980 protein vaccine and boosting with the adjuvanted HIV Env gp145 C.6980 protein vaccine with or without the Env-C plasmid DNA vaccine.	I	Feb-23	NCT04826094
Ad4-HIV Envelope Vaccine Vectors	Ad4-Env145NFL; Ad4-Env150KN; VRC-HIVRGP096-00-VP (Trimer 4571)	NIAID	To test the safety and effects of three new HIV vaccines- Ad4-Env150KN, Ad4-Env145NFL, VRC-HIVRGP096-00-VP (Trimer 4571)	I	Apr-24	NCT03878121

Annex 2: Table of ongoing non-vaccine HIV prevention trials

Method	Product	Sponsor	Description	Route	Phase	Estimated Completion	Identifier
Long acting ARVs	Oral Islatravir	Merck	Once-monthly oral dose; being studied also as an annual implant	Oral	III	Mar-22	NCT04003103; NCT04644029; NCT04652700
	Cabotegravir	NIAID (ViiV Healthcare, Gilead)	Administered daily for 1 month as an oral tablet, then as a 3 mL IM injection at two time points 4 weeks apart, and every 8 weeks thereafter	Injection (Intramuscular)	III	May-22	NCT03164564; NCT02720094
	Lenacapavir	Gilead	Subcutaneous, twice yearly injection	Injection (Subcutaneous)	III	Apr-27	NCT04925752
mAbs	PGDM1400, VRC07-523LS, PGT121	IAVI	PGDM1400 mAb alone or combination of PGDM1400 mAb + PGT121	Intravenous infusion	I	Apr-20	NCT03205917
	VRC07-523LS	NIAID	IV infustion of VRC07-523LS	Intravenous infusion	I	Dec-20	NCT03735849 NCT03387150
	3BNC117-LS	Rockefeller University	3BNC117-LS administered as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or Intravenous infusion	I	Dec-20	NCT03254277
	PGT121, PGDM1400, 10-1074, VRC07-523LS	NIAID	IV administration of antibody combinations at a 4 month interval. Combinations include PGT121 + VRC07-523LS, PGDM1400 + VRC07-523LS, and 10-1074 + VRC07-523LS	Intravenous infusion	I	Jan-21	NCT03928821

	10-1074-LS, 3BNC117-LS	Rockefeller	10-1074-LS with 3BNC117-LS given every 3 months as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or Intravenous infusion	I	Jun-21	NCT03554408
	3BNC117-LS-J and 10-1074-LS-J	IAVI	3BNC117-LS-J and 10-1074-LS-J alone and in combination as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or Intravenous infusion	I/IIa	Dec-21	NCT04173819
	VRC-HIVMAB091-00-AB (N6LS)	NIAID	VRC-HIVMAB091-00-AB (N6LS) with or without recombinant human hyaluronidase PH20 given on a 4 month interval	Injection (subcutaneous) or Intravenous infusion	I	Dec-21	NCT03538626
	VRC01, VRC01LS, VRC07-523LS	NIAID	Monthly injections of VRC01, VRC01LS, or VRC07-523LS in HIV-1-exposed Infants	Injection (Subcutaneous)	I	Jan-22	NCT02256631
	PGT121.414.LS VRC07-523LS	NIAID	PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions	Injection (subcutaneous) or Intravenous infusion	I	Feb-22	NCT04212091
	SAR441236 (VRC01–10E8v4-PDGM-1400-LS)	NIAID	Tri-specific broadly neutralizing antibody, SAR441236, given as an IV infusion	Intravenous infusion	I	Feb-22	NCT03705169
	iMab/10e8v2.0	Aaron Diamond AIDS Research Center	Bispecific antibody 10E8.4/iMab given as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or Intravenous infusion	I	Apr-22	NCT03875209

	PGT121, VRC07-523LS, PGDM1400	IAVI	Ab combinations, including PGT121 + VRC07-523LS, and PGT121 + VRC07-523LS + PGDM1400	Intravenous infusion	I/Iia	Oct-22	NCT03721510
	CAP256V2LS, VRC07-523LS and PGT121	CAPRISA	CAP256V2LS alone and in combination with VRC07-523LS and PGT121	Injection (subcutaneous) or Intravenous infusion	I		PACTR202003767867253 CAPRISA 012B
	PGT121 and VRC07-523LS	CAPRISA	VRC07-523LS and/or PGT121 administered subcutaneously	Subcutaneous injection	I		PACTR201808919297244
Microbicides	Dapivirine	NIAID	Dapivirine gel administered rectally	Gel (rectal)	I (completed)	Dec-18	NCT03393468
	Dapivirine	International Partnership for Microbicides	Fast-dissolving dapivirine vaginal film	Film (vaginal)	I	Dec-18	NCT03537092; NCT01548560
	Tenofovir alafenamide and elvitegravir	CONRAD	Combination vaginal insert containing tenofovir alafenamide (TAF) and elvitegravir (EVG)	Insert (vaginal)	I	Mar-19	NCT03762772
	Tenofovir	Johns Hopkins University	Tenofovir (TFV) enema	Enema (rectal)	I (completed)	May-19	NCT02750540
	DuoGel	Johns Hopkins University	IQP-0528 1% gel administered rectally	Gel (rectal)	I (completed)	Jun-19	NCT03082690
	OB-002H	Orion Biotechnology	Vaginal and rectal gel containing OB-002H	Gel (vaginal and rectal)	I (completed)	Aug-20	NCT04791007
	Griffithsin	University of Pittsburgh	Q-Griffithsin (Q-GRFT) enema	Enema (rectal)	I	Feb-21	NCT04032717
	Tenofovir	University of Pennsylvania	Tenofovir rectal douche	Douche (Rectal)	I	Apr-22	NCT04686279

Multipurpose Prevention Products	MB66	Mapp Biopharmaceutical, Inc.	Monoclonal antibody-based vaginal film for HSV and HIV prevention	Film (vaginal)	I (completed)	Jul-18	NCT02579083
	Griffithsin and Carrageenan	Population Council	Griffithsin and Carrageenan, non-ARV based microbicide gel	Gel (vaginal)	I (completed)	Nov-18	NCT02875119
	PC-1005	NIAID	Topical gel for use both vaginally and rectally, active against HIV, HPV, and HSV-2	Gel (vaginal and rectal)	I (completed)	Apr-19	NCT03408899
	Dapivirine and levonorgestrel	International Partnership for Microbicides	Silicone matrix vaginal ring with 3 month duration containing DPV + LNG	Intravaginal ring	I (completed)	Oct-19	NCT03467347
	Tenofovir and levonorgestrel	CONRAD	Tenofovir/levonorgestrel polyurethane, 90-day intravaginal ring	Intravaginal ring	I	Apr-20	NCT03762382
	TDF/FTC and levonorgestrel and ethinyl estradiol	Population Council	Over-encapsulated dual prevention pill containing TDF/FTC combined with levonorgestrel and ethinyl estradiol	Oral		Jan-23	NCT04778514

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