



# WHO preferred product characteristics for monoclonal antibodies for HIV prevention



World Health  
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# Abbreviations

Ab	antibody	LNG	levonorgestrel
ADAs	antidrug antibodies	LSHTM	London School of Hygiene & Tropical Medicine
AHFG	aluminium hydroxide fluid gel adjuvant	mAbs	monoclonal Abs
ALFQ	Army Liposomal Formulation adjuvant	MPER	membrane-proximal external region
AMP	Antibody-Mediated Prevention	MPLA	monophosphoryl lipid A
ANRS	French Agency for Research on AIDS and Viral Hepatitis	MRC/UVRI	Medical Research Council/Uganda Virus Research Institute
ART	antiretroviral therapy	mRNA	messenger RNA
ARV	antiretroviral	MSM	men who have sex with men
bNAb	broadly neutralizing antibodies	MVA	modified vaccinia virus Ankara
CAB	cabotegravir	MVA-CMDR	multigenic, recombinant MVA
CAB-LA	long-acting cabotegravir	NIAID	National Institute of Allergy and Infectious Diseases
DPR-VR	dapivirine vaginal ring	PEPFAR	President's Emergency Plan for AIDS Relief
EHVA	European HIV Vaccine Alliance	PPCs	preferred product characteristics
EMA	European Medicines Agency	PrEP	pre-exposure prophylaxis
Env	envelope	PWID	people who inject drugs
FDA	United States Food and Drug Administration	RSV	respiratory syncytial virus
F/TAF	Emtricitabine + tenofovir alafenamide	SHIV	simian-human immunodeficiency virus
GLA-SE	glucopyranosyl lipid adjuvant-stable emulsion	SRH	sexual and reproductive health
HIV	human immunodeficiency virus	TDF/FTC	tenofovir disoproxil fumarate and emtricitabine
HPTN	HIV Prevention Trials Network	TLR	toll-like receptor
HPV	human papillomavirus	UNAIDS	Joint United Nations Programme on HIV and AIDS
HSV	herpes simplex virus	USAID	United States Agency for International Development
HVTN	HIV Vaccine Trials Network	WHA	World Health Assembly
IM	intramuscular	WHO	World Health Organization
IV	intravenous		
IVB	Immunization, Vaccines and Biologicals		
LMICs	low- and middle-income countries		



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# I. Introduction and background on

## WHO PPCs

It is a priority for WHO 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 (PPCs) technical documents are developed to articulate preferred attributes of products for licensure, policy and programmatic implementation in LMICs settings.

PPCs are developed based on criteria that include 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 the prevention and research and development landscape. 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 (mAbs) for HIV-1 prophylaxis (table 1). PPCs that address the preferred product attributes for HIV vaccines are also a key priority.

The HIV epidemic continues to cause extensive morbidity and mortality globally. Despite progress in reaching 73% [56 - 88%] of people living with HIV with antiretroviral therapy (ART), gaps in HIV prevention and treatment contributed to 1.5 million [1.0-2.0 million] new HIV infections and 680 000 [48 000 – 1.0 million] AIDS-related deaths globally in 2020 (1). *Young children (aged 0-14 years) accounted for 150 000 [100 000 - 240 000] new HIV infections globally, the vast majority during infancy (1).*

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“The HIV epidemic continues to cause extensive morbidity and mortality globally. Despite progress in reaching 73% of people living with HIV with antiretroviral therapy, gaps in HIV prevention and treatment contributed to 1.5 million new HIV infections and 680 000 AIDS-related deaths globally in 2020.”

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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 (PWID), 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 (2). Additionally, in the HIV Prevention Trials Network (HPTN) 083 and HPTN 084 trials, long-acting PrEP with cabotegravir (CAB-LA) administered as a bimonthly injection demonstrated high effectiveness in preventing HIV infection among cisgender men who have sex with men (MSM), transgender women who have sex with men and cisgender women in sub-Saharan Africa (3, 4).

*Alongside these promising developments, the continued need to identify interventions that can provide durable, or even lifelong, protection against HIV infection has been identified by WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) as a top public health*



Photograph courtesy of WHO/Xenia Finnerty

priority (5). Several HIV vaccines and 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 proof-of-concept efficacy trials were recently completed, testing intravenous (IV) delivery of the single broadly neutralizing antibody (bNAb) VRC01 among women in eastern and southern Africa, and among MSM and transgender persons in the Americas (HVTN 703/HPTN081, NCT02568215 and HVTN 704/HPTN 085, NCT02716675) (6, 7). The studies demonstrated proof of concept that the VRC01 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 (8). A number of putatively more potent combinations and engineered antibodies are also undergoing early clinical evaluation (9).

The HIV vaccine development community has faced recent setbacks. Specifically, the National Institute of Allergy and Infectious Diseases (NIAID) decided to

stop the HIV Vaccine Trials Network (HVTN) 702 clinical trial due to interim findings from an independent data and safety monitoring board that the vaccine did not prevent HIV. Moreover, results from the Imbokodo study (HVTN 705/HPX2008; NCT03060629) found that the vaccine regimen did not provide sufficient protection against HIV infection in young women in sub-Saharan Africa at high risk of acquiring HIV (10). Nevertheless, several promising vaccine candidates continue to progress into late-stage development. The Phase 3 Mosaico study (HVTN 706, NCT03964415) evaluates an investigational adenovirus-26-based candidate vaccine and gp140 protein combination with “mosaic” immunogens comprising elements from multiple HIV subtypes, with the goal of inducing immune responses against a broad array of global HIV strains (11). The PrEPVacc Phase 2b trial (NCT04066881), which began enrolment in 2020, evaluates two experimental HIV vaccine regimens – one combining DNA with protein-based candidate vaccines and the other combining DNA, modified vaccinia virus Ankara and protein-based candidate vaccines (12). More information on the pipeline of HIV vaccine and prevention candidates is included in Annexes 1 and 2.



Photograph courtesy of IAVI/Sokomoto Photography

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## 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 (13). At the current pace, the global community will miss this target, having failed to reach interim fast-track targets under the UN's Political declaration on HIV/AIDS of achieving fewer than 500 000 new HIV infections by 2020 (14).

Scale-up of current HIV prevention efforts – including ART for people living with HIV, oral PrEP, voluntary medical male circumcision, treatment of sexually transmitted infections, and consistent and correct usage of male and female condoms – is critical, but insufficient, to meet 2030 targets. The COVID-19 pandemic has further set back the scale-up of these services (15).

As a complement to existing measures, the *Global health sector strategy on HIV: 2016–2021* identifies HIV prevention and treatment innovation as one of five strategic priorities for sustainably ending the epidemic (14). Ultimately, developing a safe, effective and accessible vaccine will be critical in delivering the vision of ending AIDS as a public health threat (16). As we work towards the long-term goal of an HIV vaccine, additional biomedical tools are needed to accelerate progress towards 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 PPCs for HIV vaccines and mAbs in the pipeline, as well as critical considerations to support programmatic suitability, emerged as key priorities from the consultation (17).

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## III. Public health need for mAbs 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 consistent and correct usage of male and female condoms, voluntary medical male circumcision, use of clean needles and syringes among people who inject drugs, medicines for opioid use disorder, treatment for people with HIV to prevent onward transmission (treatment as prevention) and, more recently, the use of antiretroviral (ARV) medicines as oral PrEP. In 2012, WHO issued guidance for the use of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for oral PrEP in serodiscordant couples, men and transgender women who have sex with men and are at high risk of HIV (18). 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 (19). As of March 2021, an estimated 1 115 000 individuals had initiated oral PrEP, towards achievement of the WHO/UNAIDS target of initiating at least 3 000 000 people by 2020 (20). However, of 69 countries implementing PrEP, 56 (81%) report at least one barrier to PrEP access (21).

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 (Partners PrEP, NCT00557245), daily oral TDF/FTC reduced the risk of HIV infection by 75% (95% confidence interval [CI]: 55–87;  $P < 0.001$ ) (22); however, the same regimen demonstrated only

a 44% reduction (95% CI: 15–63;  $P = 0.005$ ) in HIV acquisition among MSM in a multicountry trial (iPrEx, NCT00458393) (23), and no evidence of effectiveness in two large Phase 3 trials in African women (FemPrEP, NCT00625404 and VOICE, NCT00705679) (24, 25). In more recent trials in England, Canada and France, both oral daily (PROUD, NCT02065986) and event-driven PrEP (IPERGAY, NCT01473472) in MSM reduced HIV acquisition by 86% (90% CI: 64–96;  $P = 0.0001$  and 95% CI: 40–98;  $P = 0.002$ , respectively) (26, 27). 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 (28, 29, 30, 31).

In October 2019, emtricitabine/tenofovir alafenamide (F/TAF) was approved by the United States Food and Drug Administration (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 real-world implementation challenges similar to those of TDF/FTC due to a comparable product profile and daily dosing requirements (32). Efficacy data on F/TAF as a PrEP agent for women or PWID are lacking.

Two Phase 3 trials examined the efficacy of the DPV-VR as a monthly prevention option. The Ring Study demonstrated an HIV reduction of 31% (hazard ratio, 0.69; 95% CI: 0.49–0.99;  $P = 0.04$ ) among women using the DPV-VR, and the ASPIRE study demonstrated a 27% (95% CI: 1–46;  $P = 0.046$ ) reduction in risk of HIV infection among African women (33, 34). Significant reductions in protection were observed, with no protection from HIV infection among women aged 18–21, which could have been driven mainly by lower levels of adherence among women under 25 years of age. An open-label extension study of the monthly DPR-VR (DREAM), showed increased product use compared to the previous Phase 3 RING study, with modelling data suggesting that women's HIV-1 risk was reduced by 63% (35). The DPR-VR received a positive scientific opinion from the EMA under the Article 58 procedure and was prequalified by WHO in November 2020 for use in women who are at higher HIV risk and aged 18 years and over (36). The EMA and prequalification opinions recommend the DPR-VR be used in combination with safer sex practices when oral 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 DPR-VR be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches (37).

### **Pipeline of HIV prevention products**

Results from the HIV Prevention Trials (HPTN) 083 Phase 3 study showed CAB-LA administered every 2 months to be 66% more effective in preventing HIV acquisition than daily oral PrEP with TDF/FTC among MSM and transgender women (40). In the HPTN 084 Phase 3 study (NCT03164564) of CAB-LA for HIV prevention in women at increased risk of HIV acquisition in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda and Zimbabwe, CAB-LA was 89% (hazard ratio, 0.11; 95% CI: 0.04–0.32) more effective at preventing HIV acquisition than TDF/FTC (41). There are no planned studies of CAB-LA among PWID. CAB-LA was authorized as a monthly treatment for use in combination with rilpivirine by the European Commission in December 2020 and by the FDA in January 2021 (42). Rolling regulatory submission with the FDA for the prevention indication for CAB-LA was initiated in May 2021.

Acceptability research suggests that delivering PrEP through a long-acting injectable product could address some challenges associated with daily oral regimens (43, 44). 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,

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For those at high risk of HIV infection, mAbs could constitute an important alternative biomedical prevention option, if key determinants of implementation feasibility can be addressed.

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where injectable contraceptive use is widespread (45, 46, 47). However, some studies of CAB-LA cited concerns regarding the frequency of clinic visits and users' preference for fewer injections (48). Moreover, the injectable contraception literature documents a high rate of nonadherence among women using analogous injectable hormonal contraceptives (49). This suggests that a long-acting injectable PrEP formulation would not completely solve adherence challenges for all patients in regions where HIV is endemic (50). Additional implementation challenges relate to requirements for a daily oral lead-in period of 4 weeks prior to administration of CAB-LA. For those discontinuing use, there are also concerns regarding the product's potentially prolonged declining serum concentrations, which has been demonstrated to last more than a year in some people. Although it has not been demonstrated, there is a risk this could lead to an increase in 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. In early 2021, Merck launched the IMPOWER 22 Phase 3 study in sub-Saharan Africa and the USA. This study evaluates the efficacy and safety of islatravir (MK-8591), a nucleoside reverse transcriptase translocation inhibitor. Islatravir will be administered orally once monthly as PrEP in cisgender women who are at high risk for HIV-1 infection. In addition, the IMPOWER 24 study will evaluate other key populations, including MSM and transgender women (51). However, in December 2021, US FDA put on hold all studies for treatment and prevention of HIV infection with islatravir. The decision was taken based on observations of unexpected decreases in total lymphocyte and CD4+ T-cell counts in some study participants on use of islatravir (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 6 months in cisgender adolescent girls and young women. In a separate trial, the use of lenacapavir will also be studied in cisgender men, persons of trans experience and gender nonbinary 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 mAbs 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 that also 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. Such evaluation must also 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 USA and European Union alone (54), and mAbs are now the single-largest class of molecules undergoing clinical investigation (55). In 2018, ibalizumab (TNX-355) became the first mAb to receive FDA approval as salvage therapy in HIV-positive patients whose viruses are resistant to multiple existing ARV drugs (56). In 2019, it was also approved by the EMA for use in combination with other ARVs for the treatment of adults infected with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

bNAbs derive from naturally occurring antibodies with potent neutralizing activity against a broad array of HIV strains in vitro. Research suggests structural modifications to mAbs can increase the breadth, potency and half-life of mAbs, potentially extending their duration of protection and enabling dosing on a bimonthly, quarterly or semi-annual basis (57, 58).

Given their favourable safety and pharmacokinetic profiles, mAbs offer potential advantages over the use of ARVs for the prevention of HIV (59). Since mAbs have a different mechanism of protection than ARV 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 mAbs might have fewer adverse effects than certain ARV drugs, particularly during pregnancy and breastfeeding. For those at high risk of HIV infection, mAbs could constitute an important alternative biomedical prevention option, if key determinants of implementation feasibility can be addressed.



Photograph courtesy of WHO/Blink Media–Uma Bista

## 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 mAbs 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 ARVs 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 biweekly subcutaneous injection (5 mg/kg) found it to be safe, well tolerated and to maintain serum 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 HPTN-sponsored AMP efficacy trials evaluated whether providing VRC01 as an IV 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 in the trial. Additional analysis showed that VRC01 was 75.4% effective (95% CI: 45.5–88.9) at preventing acquisition of HIV strains that were susceptible to the bNAb (in vitro sensitivity to the antibody of IC80 <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 USA. 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, virus sensitivity (IC80 neutralization <1 µg/ml) to VRC01 neutralization appeared to correlate with protective 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 an overview of ongoing trials). Given that neutralization escape from single antibodies occurs readily, 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 (64). 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 individual bNAbs (75, 76). For both the prevention and treatment of HIV infection, combinations with larger 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% (73). 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 breakthrough of resistant viral variants (78).

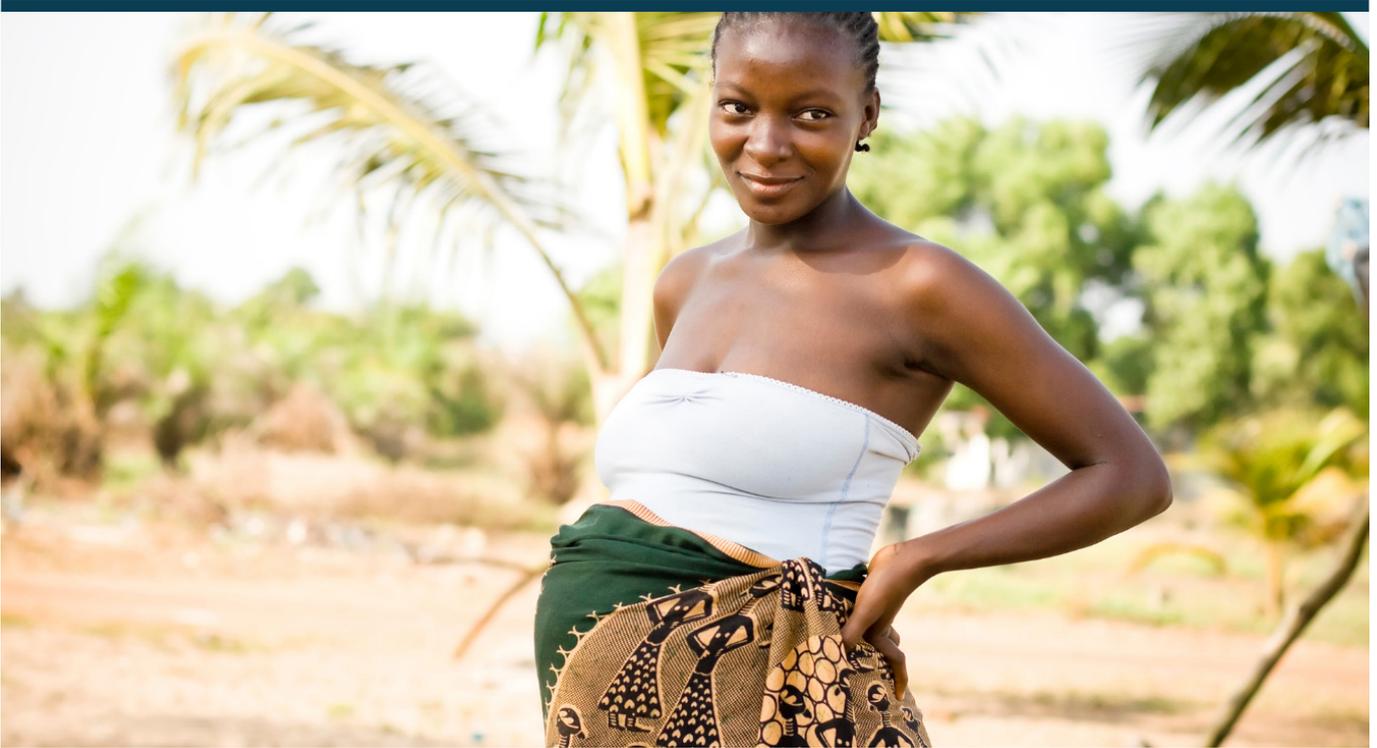
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The high affinity for specific targets and selectivity of antibodies means they are less likely to have side effects or unexpected safety problems.

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Coformulation of multiple mAbs can streamline supply chain management and administration of antibody combinations. However, combining multiple mAbs together could substantially raise costs and increase dose requirements. Engineered bi- and tri-specific neutralizing antibodies 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 bi-specific 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 bi-specific antibody targeting the human CD4 receptor and the HIV-1 Env membrane-proximal external region (MPER) neutralized 100% of circulating HIV-1 strains in a multiclade panel of 118 viruses (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 individual bNAb, conferring complete immunity against a mixture of simian-human immunodeficiency viruses (SHIVs) in nonhuman primates, with pharmacokinetics similar to those of human bNAbs (77).

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 administration of anti-HIV-1 antibody combinations has generally been well tolerated with infrequent adverse events reported (74). One concern with long-term infusion of human mAbs is triggering the production of antidrug antibodies (ADAs) that may reduce activity or lead to adverse responses. Greater complexity in the structure of multispecific antibodies may increase the risk of unwanted immunogenicity (78). Further clinical testing is needed to confirm whether engineered bi- and tri-specific molecules will maintain the favourable safety profiles of the naturally occurring bNAbs tested to date without inducing clinically significant ADAs (81).



Photograph courtesy of IAVI

## 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 mAbs for key populations***

Marginalized key populations – which may include MSM, male and female sex workers and their clients, PWID, transgender individuals and incarcerated populations – are disproportionately affected by the HIV epidemic in all regions (15). Despite comprising a small proportion of the general population, key populations and their sexual partners account for 65% of new infections globally in 2020 and 93% of infections outside of sub-Saharan Africa (15, 82). Additionally, transmission from current or former members of key populations to their intimate partners remains a critical driver of infection in the general population, reinforcing the centrality of key populations to HIV prevention strategies (83, 84).

### ***Addressing the needs of at-risk adolescents***

In 2020, 410 000 new infections globally were among young people aged 10–24 years (85). In sub-Saharan Africa, 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 (86). Modelling efforts suggest that age-based prevention strategies targeting this key demographic can be highly efficient and cost-effective in reducing HIV incidence in sub-Saharan Africa (87, 88).

Among adolescents in sub-Saharan Africa, females are more than twice as likely as their male counterparts to acquire HIV (89). Partner age pairings of younger women with older men play a critical role in perpetuating the cycle of HIV transmission (90). Understanding and addressing the product needs of adolescent girls and young women 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 vertical HIV transmission. Still, an estimated 150 000 [100 000 – 240 000] new infections in children (ages 0–14 years) occurred globally in 2020 (1). Perinatal and postnatal

infections persist due to late diagnosis of maternal infection, nonadherence to ART, ARV resistance and transmission through breast milk. Although ART significantly reduces vertical transmission in high HIV incidence settings, more than 35 000 additional vertical transmissions occurred among women who acquired HIV during pregnancy and breastfeeding (15). For all HIV-negative women – especially those of reproductive age, including pregnant and breastfeeding women at risk of HIV – 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 vertical HIV transmission (63, 91). Pharmacokinetic studies for several bNAbs (VRC01, VRC01-LS and VRC07-523LS) given

subcutaneously have demonstrated safety in HIV-exposed neonates (92, 93, 94). In a neonatal macaque model, administration of PGT121 and VRC07-523 in combination provided effective post-exposure prophylaxis in infants within 30–48 hours of oral SHIV exposure (95). Given the long half-life of bNAbs, they may be effective in supporting implementation through less frequent administration, potentially compensating for gaps in adherence when used as an adjunct to, or in the place of, ARVs (96). Given the potentially promising role of bNAbs in preventing perinatal and postnatal HIV vertical transmission, their development for use in pregnant and breastfeeding women, neonates and infants should also be a strategic priority. Early inclusion of pregnant and breastfeeding women and infants in clinical trials will be needed to establish dose requirements and safety in these populations.

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## 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 (97). These factors highlight the need for inclusion of diverse geographies and populations in clinical trials, including pregnant and breastfeeding women, HIV-exposed neonates and infants, key populations, and adolescent girls and young women. However, many LMICs currently lack the infrastructure necessary for conducting clinical trials, the regulatory review and approval of mAb products, and/or the resources to administer mAbs to key populations (98).

Advances in HIV prevention, such as oral PrEP, the DPV-VR and CAB-LA, introduce complex issues in the design of HIV prevention trials. It is important to properly balance in an ethical manner the protection of research participants through the provision of current standard of care for HIV prevention with the need to implement

clinical trials capable of evaluating the efficacy of new prophylactic therapeutics (98, 99). 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 (100). The use of novel trial designs may overcome some of these issues.

Preclinical studies have suggested a correlation between the in vitro potency of neutralization and the dose required to afford protection against viral infection in nonhuman primates (101). Results from the AMP trials further validate the predictive value of the nonhuman 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 (102).



Photograph courtesy of WHO/Colin Cosier

## VII. Production and manufacturing

In addition to meeting safety and efficacy criteria, mAbs face development hurdles in the characterization and control of their critical quality attributes, their stability during storage and transport, and when manufacturing is scaled to levels required for market production (103). The need for high-concentration formulations for parenteral delivery of mAbs can present manufacturability challenges related to viscosity levels and the propensity for aggregation (104). Product optimization strategies being investigated to drive cost reductions and enhance breadth, such as multispecific antibody formats, can also introduce manufacturing challenges related to the potential for aggregation, immunogenicity and low GMP (good manufacturing practice) cell line titres (57, 72). Other downstream chemistry, manufacturing and control obstacles – such as antibody purification and stability concerns – may contribute to lower final product yields and quality issues with engineered

multispecific molecules compared with typical mAbs (72). Scientifically rigorous approaches to enhancing the developability of promising bi-specific or tri-specific antibodies, particularly their physico-chemical stability and formulation, are needed to overcome these hurdles.

Antibody production 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 (105, 106, 107). Innovative DNA and mRNA delivery platforms for mAbs in proof-of-concept trials could likewise enable faster and cheaper production (108, 109). Taken together, improvements in antibody-expression yields and innovative manufacturing processes could contribute to significant reductions in the cost of goods sold for mAbs (110, 111).

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## VIII. Value proposition

Ensuring the affordability of mAbs will be critical. Biologics, particularly mAbs, are currently among the highest-priced pharmaceutical products, a factor which 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 mAb identification, dose optimization and manufacturing have increased the possibility for producing lower-cost products. Lower doses, longer duration of protection, and investment in optimization and manufacturing process improvements could potentially reduce both delivery expenses and the cost of goods sold (112).

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## IX. Access and supply security

It is important to make products broadly available, particularly in countries and populations with the highest disease burden and that participate in clinical development of interventions. 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 support affordable, quality-assured mAb production and delivery.

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## X. Programmatic suitability

Efforts are needed to ensure that, where applicable to mAbs, WHO-defined criteria for programmatic suitability related to presentation, packaging, stability, storage volume and disposal are met (113).

The structure and stability of mAbs precludes oral delivery due to degradation in the gastrointestinal tract (114). While mAbs are often delivered intravenously, the IV route requires facility-based administration and monitoring by a health-care professional, which increases the cost and limits the feasibility of implementation in resource-limited settings. The IV route would limit not only the feasibility but also the demand for products – a critical factor for uptake of interventions. A prospective randomized study of the mAb trastuzumab showed that an overwhelming majority of patients prefer subcutaneous over IV administration (115). Subcutaneous delivery can increase programmatic suitability, reduce health system costs and enable self-administration. To be delivered subcutaneously at infrequent intervals, antibodies will require a long half-life and small volume

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, useful across populations and amenable to global use (116, 117).

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. As a result, there is often limited capacity in LMIC settings to absorb new products requiring a cold chain beyond existing Expanded Programme on Immunization 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 the cold-chain footprint.



Photograph courtesy of WHO/Olivier Asselin

## XI. WHO prequalification

For procurement by UN agencies and financing by agencies such as Gavi, the Vaccine Alliance, products should meet criteria for programmatic suitability and be WHO prequalified (118). The WHO prequalification process acts as an international assurance of quality, safety, efficacy and suitability for LMIC programmes. WHO encourages developers and manufacturers to be aware of the prequalification process and to discuss products and regulatory requirements with the WHO prequalification team early in the development process.

In May 2014, the World Health Assembly (WHA) adopted Resolution WHA67.21 – 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 (119). Recognizing that regulatory assessment of mAbs can be challenging for many countries, WHO has published guidance documents on the regulatory considerations for biotherapeutics, and on mAbs as similar biotherapeutic products (120). 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 and stomach cancer (121). Additional efforts are needed to support development of the scientific expertise and regulatory capacity required to promote access to high-quality, affordable, safe and efficacious mAbs in LMIC settings.

# XII. PPCs for mAbs for HIV prophylaxis

**Table 1. Preferred Product Characteristics for mAbs for HIV prophylaxis**

Parameter	Preferred characteristic	Notes
Indication for use	<p>Prevention of HIV-1 infection in confirmed HIV-negative individuals.</p> <p>Prevention of HIV-1 infection in neonates and infants with HIV exposure.</p>	<p>Treatment or curative indications are beyond the scope of this PPC.</p> <p>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 to avoid selection for and transfer of resistant viruses to the infant.</p>
Target populations	<p>People at substantial risk of HIV infection and their sexual partners, including:</p> <ul style="list-style-type: none"> <li>MSM, male and female sex workers, PWID, transgender people, and people in prisons and closed settings</li> <li>Adolescents and cisgender men and women in high-prevalence settings</li> <li>Pregnant and breastfeeding women in settings with high HIV prevalence</li> <li>Neonates and infants with HIV exposure</li> <li>Serodiscordant couples</li> </ul> <p>Other target populations at high risk may be considered based on local epidemiology.</p>	<p>Key populations and their sexual partners account for more than 65% of new HIV infections globally in 2020 and therefore are critical to HIV prevention efforts.</p> <p>Adolescent girls and young women account for the majority of new infections among adolescents in sub-Saharan Africa – the epicentre of the HIV epidemic – and therefore are a priority in prevention efforts.</p> <p>Identifying prevention products that are appropriate for use during conception, pregnancy and while breastfeeding is important.</p> <p>Given the potentially long half-life of mAbs, they may be effective in preventing vertical transmission (97).</p> <p>PrEP can protect the HIV-negative partner in a serodiscordant relationship when the HIV-positive partner is either not on ART or has not yet achieved viral suppression (122).</p> <p>Additional research is needed to determine the potential role of mAbs in post-exposure prophylaxis for those facing sexual exposure or occupational risk (e.g. from needlestick or other nosocomial exposure).</p>
Access and affordability	<p>Product and health system delivery costs should be affordable and cost-effective in LMIC settings.</p>	<p>Cost should be considered relative to efficacy and impact vis-à-vis comparable products. Further evidence on the cost-effectiveness, acceptability and full value proposition of mAbs, including from an LMIC perspective, is needed.</p> <p>Manufacturers should plan to make products broadly available, particularly in countries and in populations with the highest disease burden and that participate in the clinical development of interventions. Intellectual property filings, out-licensing and pricing should not be barriers to global access.</p>



Photograph courtesy of WHO/Quinn Mattingly

Parameter	Preferred characteristic	Notes
mAb delivery strategies	<p>Newborn infants: alignment with existing programmes for preventing vertical transmission.</p> <p>Neonates and infants: alignment with existing vaccine delivery infrastructure.</p> <p>Populations at substantial risk: integration with HIV prevention programmes and other SRH services.</p> <p>PWID: integration with harm reduction services.</p>	<p>The most appropriate delivery strategies in different settings will be determined based on target populations, mAb characteristics and related health system and programmatic factors.</p> <p>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 health-care providers about products. Such strategies are effective in delivering HIV prevention products, as has been demonstrated through the delivery of oral PrEP.</p> <p>When possible, integrating delivery with other health services, e.g. SRH services, can increase uptake and acceptability.</p> <p>Communication, community outreach and marketing strategies regarding HIV mAbs should be considered in advance.</p>
Safety	<p>Should have a favourable and acceptable safety and reactogenicity profile.</p> <p>Safe to use in pregnancy and breastfeeding.</p> <p>Safe in older adolescents (15–19 years).</p> <p>Safe in infants.</p>	<p>In clinical trials, single and repeat mAb administrations of anti-HIV-1 antibody combinations have generally been well tolerated with infrequent adverse events reported, including in studies in neonates (61, 74, 94, 95, 123).</p> <p>Monitoring for clinically relevant ADAs in clinical trials is important (124).<sup>2</sup></p>

<sup>2</sup> Per WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology and ICH S6(R1)*: For mAbs 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 required. 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.

Parameter	Preferred characteristic	Notes
Efficacy	<p>Efficacy trial with standard of prevention incorporated.<sup>3</sup></p> <p>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.</p> <p>Evidence of broad coverage of genetic diversity of HIV-1 across geographies, populations and modes of transmission.</p> <p>Antibody combinations and/or multispecific formats, with antibodies targeting different epitopes in a complementary manner to achieve broad protection and to prevent viral escape.<sup>4</sup></p> <p>Efficacy maintained with repeated use.</p>	<p>Efficacy trial design should conform to relevant regulatory standards and be conducted with reference to the UNAIDS/WHO <i>Ethical considerations in HIV prevention trials (100)</i>. As outlined in this guidance document, researchers and trial sponsors should ensure access to a package of recommended prevention methods.</p> <p>While developers should aim to determine non-inferiority or superiority to current standard(s) of care, logistical challenges and cost barriers in conducting noninferiority and superiority trials are acknowledged. Appropriate trial design should be discussed with key ethical and regulatory stakeholders, including national regulatory agencies.</p> <p>Alternative trial designs may be needed to establish the value of specific agents for HIV prevention in the context of evolving standards of prevention.</p> <p>Trials should also conform to WHO <i>Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (124)</i>.</p> <p>Programmatic benefits – such as less frequent administration, increased acceptability, improved safety and improved cost-effectiveness – should be considered alongside efficacy.</p> <p>Sustained protection with repeated use should be evaluated based on long-term follow-up studies and post-introduction surveillance.</p> <p>High breadth of protection will be key to supporting sustained use across diverse geographies.</p> <p>Specimens should be collected during efficacy trials to support the identification of correlates of risk/protection and for breakthrough virus sequencing.</p> <p>Population-level data will be important in determining whether there is selection for resistance to specific antibodies over time.</p> <p>Transplacental and breastmilk transfer should be considered in product development.</p> <p>There may be a need to tailor mAb combinations for regional use by the prevalence of strains in different regions.</p>

3 If a correlate of neutralization titre is determined and accepted by regulators, this can potentially support alternative study design for next-generation products.

4 In preclinical studies, Xu and colleagues found that a tri-specific targeting the V1V2, MPER and CD4bs sites was highly potent and broadly neutralized 99% of HIV viruses when tested against >200 different HIV strains (56). The 10E8.2/iMab bi-specific antibody targeting the human CD4 receptor and the HIV-1 Env MPER neutralized 100% of circulating HIV-1 strains in a multiclade panel of 118 viruses (78).

Parameter	Preferred characteristic	Notes
Formulation/presentation	<p>WHO-defined recommendations on presentation, packaging, storage volume and disposal should be met, where applicable to mAbs (114).</p> <p>A single vial product is preferred.</p> <p>For infants, 0.5 ml per dose is preferred.</p> <p>For children aged 5 years or younger, 1 ml per dose or less is preferred (111).</p>	<p>For volumes &gt;2 ml, multiple injections are typically used (125). However, in clinical studies, target injection volumes of as high as 3 ml have been well tolerated and may be preferred over multiple injections (126). Further evaluation of preferences with respect to injection frequency, volume and site is needed.</p> <p>Other approaches to increase the volume that can be injected subcutaneously are being evaluated and may become available in the future.</p> <p>While IV infusion is not preferred (see route of administration), if used, best practices for IV administration should be followed (127).</p>
Dose regimen	<p>Administration every 3 months; longer may be preferable depending on the population and product characteristics.</p> <p>Fixed, non-weight-based dosing is preferred, with age-appropriate fixed dosing presentations for:</p> <ul style="list-style-type: none"> <li>- adolescents/adults</li> <li>- infants</li> <li>- neonates.</li> </ul> <p>Coformulation of mAb combination products is preferred.</p> <p>Single site, single injection is preferred but not required.</p>	<p>Less frequent administration may be preferred; however, additional evidence is needed on preferences for, and the potential benefits of, products with longer durations. Duration needs to be considered in the context of other attributes and product options as well as duration of the period at risk for transmission.</p> <p>Pharmacokinetic studies demonstrating half-life sufficient to support the schedule of administration are needed.</p> <p>Fixed, non-weight-based dosing, with stepwise age-appropriate adjustments can help accommodate growth while avoiding requirements for complex adjustments on-site.</p> <p>Antibody kinetics should be well characterized to ensure that subsequent doses are administered before the level of antibody drops below the threshold of protection.</p>
Co-administration	<p>Demonstration of favourable safety upon co-administration with an HIV vaccine or other antibody product targeting the HIV envelope protein to be used concomitantly.<sup>5</sup></p>	<p>Concomitant administration of mAbs for HIV prevention are not expected to interfere with immune responses to non-HIV vaccines; hence, it is anticipated that HIV mAbs may be administered with such vaccines.</p>
Route of administration	<p>Subcutaneous or intramuscular injection is highly preferred for use in LMICs.</p>	<p>Per defined criteria for prequalification, WHO specifies that an IV route of administration is not broadly suitable for programmatic implementation in LMIC settings (112).</p> <p>While IV administration might be suitable in some highly specific settings, it would significantly reduce the ability to deliver these products in most LMIC contexts and should be discussed with WHO in advance.</p>

5 Studies on mAb–vaccine interaction 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 the EMA and FDA covering the clinical development of RSV (respiratory syncytial virus) mAbs for prophylaxis neither requires nor suggests conducting coadministration studies with other vaccines, although the EMA guidance does include recommendations for development of RSV vaccines (FDA draft 2017; EMA 2018).

Parameter	Preferred characteristic	Notes
Product stability and storage	<p>It is preferred that mAbs should be stable at refrigerated condition (2–8°C) preferably for 2–3 years<sup>3</sup>;<sup>6</sup> a CTC product is preferred (128).</p> <p>Storage footprint should be minimized.</p>	<p>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.</p>
Registration, prequalification and programmatic suitability	<p>WHO prequalification is preferred.</p>	<p>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 <i>Collaborative procedure for accelerated registration of prequalified FPPs</i> (129). Close cooperation and coordination with WHO and with national and international regulatory authorities is highly important.</p> <p>Product attributes that support programmatic implementation and adherence – such as for extended duration of protection and tolerability – hold the potential to lower delivery costs and improve the real-world effectiveness of HIV prevention products.</p> <p>There may be benefits in aligning dosing schedule with other care-seeking time points, such as for injectable contraceptives or infant follow up visits. Engagement to understand the product preferences and needs of local decision makers and end users is important.</p>

ADAs: antidrug antibodies; ART: antiretroviral therapy; CTC: controlled temperature chain; IV: intravenous; PPCs: preferred product characteristics; mAbs: monoclonal antibodies; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; PWID: people who inject drugs; SRH: sexual and reproductive health; UN: United Nations; WHO: World Health Organization.

6 At the time of this publication, WHO is in the process of drafting guidance on the manufacture and quality control of mAbs and mAb fragments as well as regulatory considerations for the preclinical and clinical evaluation of mAbs for infectious diseases. Once available, these forthcoming guidance documents can be accessed at: [www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/guidelines-for-biologicals](http://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/guidelines-for-biologicals).

# Annex 1: Table of ongoing HIV vaccine trials

Trial	Product	Sponsor	Description	Phase	Estimated completion	Identifier
HVTN 706	Ad26.Mos4.HIV; Clade C and Mosaic gp140 HIV bivalent vaccine	Janssen Vaccines & Prevention B.V.	To evaluate the vaccine efficacy of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminium phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection.	3	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.	2B	Mar-23	NCT04066881
HVTN 118 IPCAVD-012	Ad26.Mos4.HIV biological; 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 Env-binding Ab responses.	2	May-23	NCT02935686
RV 305(A)	ALVAC-HIV AIDSVAX B/E	US 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.	2	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.	1/2	Oct-21	NCT04563377

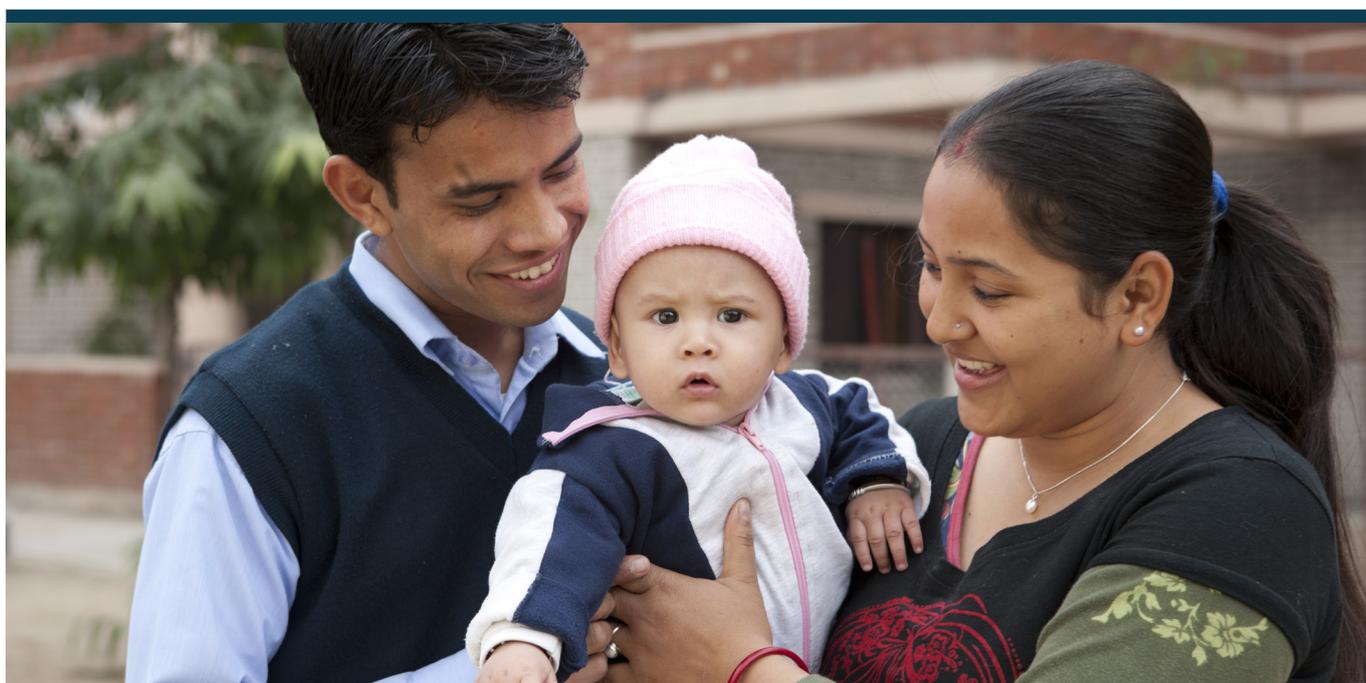
Trial	Product	Sponsor	Description	Phase	Estimated completion	Identifier
HVTN 117 (TRAVERSE)	Ad26.Mos.HIV biological, Ad26.Mos4.HIV biological, Clade C gp140	Janssen Vaccines & Prevention B.V.	To assess the safety and tolerability of the 2 different vaccine regimens: (1) priming with trivalent Ad26.Mos.HIV 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.	1/2	Apr-23	NCT02788045
HVTN 121	AIDSVAX B/E	NIAID	To evaluate the breadth and potency of HIV-1 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.	1b completed	Sep-20	NCT03618056
G001	eOD-GT8 60mer vaccine;#859	IAVI	To assess the safety, tolerability and immunogenicity of eOD-GT8 60mer vaccine, adjuvanted.	1	Jan-20	NCT03547245
VRC 018	VRC-HIVRGP096-00-VP (Trimer 4571)	NIAID	To assess whether the vaccine Trimer 4571 is safe and well tolerated, and to study immune responses to it.	1 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.	1 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.	1	May-20	NCT03699241

Trial	Product	Sponsor	Description	Phase	Estimated completion	Identifier
HVTN 106	MVA-CM-DR;#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 an MVA-CMDR vaccine that may boost the immune response to the DNA vaccines in healthy, HIV-uninfected adults.	1 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.	1	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.	1	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.	1	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.	1	May-22	NCT04177355

Trial	Product	Sponsor	Description	Phase	Estimated completion	Identifier
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.	1	Jun-22	NCT04844775
HIV-CORE 006	ChAdOx1.tHIV-consv1, MVA.tHIV-consv3 and MVA.tHIVconsv4	University of Oxford	To test three experimental HIV vaccines in healthy adults.	1	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.	1	Oct-22	NCT04607408
IHV01 and A244/AHFG	IHV01 and A244/AHFG with and without ALFQ	US 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.	1	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.	1	Oct-22	NCT03220724
ACTHIVE-001	ConM SOSIPv7 gp140	Academisch Medisch Centrum – Universiteit van Amsterdam	To determine the safety profile of the native-like HIV-1 envelope vaccine ConM SOSIPv7, adjuvanted with MPLA liposomes.	1	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.	1	Dec-22	NCT04842682

Trial	Product	Sponsor	Description	Phase	Estimated completion	Identifier
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.	1	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 and VRC-HIVRGP096-00-VP (Trimer 4571).	1	Apr-24	NCT03878121

Ab: antibody; AHFG: aluminium hydroxide fluid gel adjuvant; ALFQ: Army Liposomal Formulation adjuvant; ANRS: French Agency for Research on AIDS and Viral Hepatitis; EHVA: European HIV Vaccine Alliance; Env: envelope; GLA-SE: glucopyranosyl lipid adjuvant-stable emulsion; HVTN: HIV Prevention Trials Network; IAVI: International AIDS Vaccine Initiative; LSHTM: London School of Hygiene & Tropical Medicine; MPLA: monophosphoryl lipid A; MRC/UVRI: Medical Research Council/Uganda Virus Research Institute; MVA: modified vaccinia virus Ankara; MVA-CMDR: multigenic, recombinant modified vaccinia virus Ankara; nAb: neutralizing antibody; NIAID: National Institute of Allergy and Infectious Diseases; TLR: toll-like receptor.



Photograph courtesy of IAVI/Charlotte Raymond Photography

## Annex 2: Table of ongoing nonvaccine HIV prevention trials

Method	Product	Sponsor	Description	Route	Phase	Estimated completion	Identifier
Long-acting ARVs	Islatravir	Merck	Once-monthly oral dose; being studied also as an annual implant	Oral and subdermal implant	3/ 2 planned for implant	Trials on hold	NCT04003103; NCT04644029; NCT04652700
	Cabotegravir	NIAID (ViV Health-care, 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 (IM)	3	May-22	NCT03164564; NCT02720094
	Tenofovir alafenamide	CAPRISA/Oak Crest	Sustained-release tenofovir alafenamide subdermal implant	Subdermal implant	1/2	Dec-22	PAC-TR201809520959443
	Lenacapavir	Gilead	Subcutaneous, twice-yearly injection	Injection (subcutaneous)	3	Apr-27	NCT04925752

Method	Product	Sponsor	Description	Route	Phase	Estimated completion	Identifier
mAbs	PGDM1400, VRC07-523LS, PGT121	IAVI	PGDM1400 mAb alone or combination of PGDM1400 mAb + PGT121	IV infusion	1	Apr-20	NCT03205917
	VRC07-523LS	NIAID	IV infusion of VRC07-523LS	IV infusion	1	Dec-20	NCT03735849; NCT03387150
	3BNC117-LS	Rockefeller University	3BNC117-LS administered as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or IV infusion	1	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.	IV infusion	1	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 IV infusion	1	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 IV infusion	1/2A	Dec-21	NCT04173819
	VRC-HIVMAB091-00-AB (N6LS)	NIAID	VRC-HIVMAB091-00-AB (N6LS) with or without recombinant human hyaluronidase PH20 given at a 4-month interval	Injection (subcutaneous) or IV infusion	1	Dec-21	NCT03538626
	VRC01, VRC01LS, VRC07-523LS	NIAID	Monthly injections of VRC01, VRC01LS or VRC07-523LS in HIV-1-exposed infants	Injection (subcutaneous)	1	Jan-22	NCT02256631

Method	Product	Sponsor	Description	Route	Phase	Estimated completion	Identifier
	PGT121.414.LS VRC07-523LS	NIAID	PGT121.414.LS administered alone and in combination with VRC07-523LS via IV infusion or subcutaneous injection	Injection (subcutaneous) or IV infusion	1	Feb-22	NCT04212091
	SAR441236 (VRC01-10E8v4-PDGM-1400-LS)	NIAID	Tri-specific bNAb, SAR441236, given as an IV infusion	IV infusion	1	Feb-22	NCT03705169
	iMab/10e8v2.0	Aaron Diamond AIDS Research Center	Bi-specific Ab 10E8.4/iMab given as either a subcutaneous injection or IV infusion	Injection (subcutaneous) or IV infusion	1	Apr-22	NCT03875209
	PGT121, VRC07-523LS, PGDM1400	IAVI	Ab combinations, including PGT121 + VRC07-523LS and PGT121 + VRC07-523LS + PGDM1400	IV infusion	1/2A	Oct-22	NCT03721510
	CAP256V2LS, VRC07-523LS and PGT121	CAPRISA	CAP256V2LS alone and in combination with VRC07-523LS and PGT121	Injection (subcutaneous) or IV infusion	1	Aug-21	PAC-TR202003767867253 CAPRISA 012B
	PGT121 and VRC07-523LS	CAPRISA	VRC07-523LS and/or PGT121 administered subcutaneously	Subcutaneous injection	1 (completed)	Oct-19	PAC-TR201808919297244
Microbicides	Dapivirine	NIAID	Dapivirine gel administered rectally	Gel (rectal)	1 (completed)	Dec-18	NCT03393468
	Dapivirine	International Partnership for Microbicides	Fast-dissolving dapivirine vaginal film	Film (vaginal)	1	Dec-18	NCT03537092; NCT01548560
	Tenofovir alafenamide and elvitegravir	CONRAD	Combination vaginal insert containing tenofovir alafenamide and elvitegravir	Insert (vaginal)	1	Mar-19	NCT03762772
	Tenofovir	Johns Hopkins University	Tenofovir enema	Enema (rectal)	1 (completed)	May-19	NCT02750540
	DuoGel	Johns Hopkins University	IQP-0528 1% gel administered rectally	Gel (rectal)	1 (completed)	Jun-19	NCT03082690
	OB-002H	Orion Biotechnology	Vaginal and rectal gel containing OB-002H	Gel (vaginal and rectal)	1 (completed)	Aug-20	NCT04791007

Method	Product	Sponsor	Description	Route	Phase	Estimated completion	Identifier
	Griffithsin	University of Pittsburgh	Q-Griffithsin (Q-GRFT) enema	Enema (rectal)	1	Feb-21	NCT04032717
	Tenofovir	University of Pennsylvania	Tenofovir rectal douche	Douche (rectal)	1	Apr-22	NCT04686279
Multipurpose prevention products	MB66	Mapp Biopharmaceutical, Inc.	mAb-based vaginal film for HSV and HIV prevention	Film (vaginal)	1 (completed)	Jul-18	NCT02579083
	Griffithsin and Carrageenan	Population Council	Griffithsin and Carrageenan, non-ARV-based microbicide gel	Gel (vaginal)	1 (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)	1 (completed)	Apr-19	NCT03408899
	Dapivirine and levonorgestrel	International Partnership for Microbicides	Silicone matrix vaginal ring with 3-month duration containing DPV + LNG	Intravaginal ring	1 (completed)	Oct-19	NCT03467347
	Tenofovir and levonorgestrel	CONRAD	Tenofovir/levonorgestrel polyurethane, 90-day intravaginal ring	Intravaginal ring	1	Apr-20	NCT03762382
	TDF/FTC and levonorgestrel and ethinyl estradiol	Population Council	Overencapsulated dual-prevention pill containing TDF/FTC combined with levonorgestrel and ethinyl estradiol	Oral		Jan-23	NCT04778514

Ab: antibody; ARV: antiretroviral; bNAb: broadly neutralizing antibodies; DPV: dapivirine; Env: envelope; HPV: human papillomavirus; HSV: herpes simplex virus; IAVI: International AIDS Vaccine Initiative; IM: intramuscular; IV: intravenous; LNG: levonorgestrel; mAbs: monoclonal Abs; NIAID: National Institute of Allergy and Infectious Diseases; TDF/FTC: tenofovir disoproxil fumarate and emtricitabine.

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