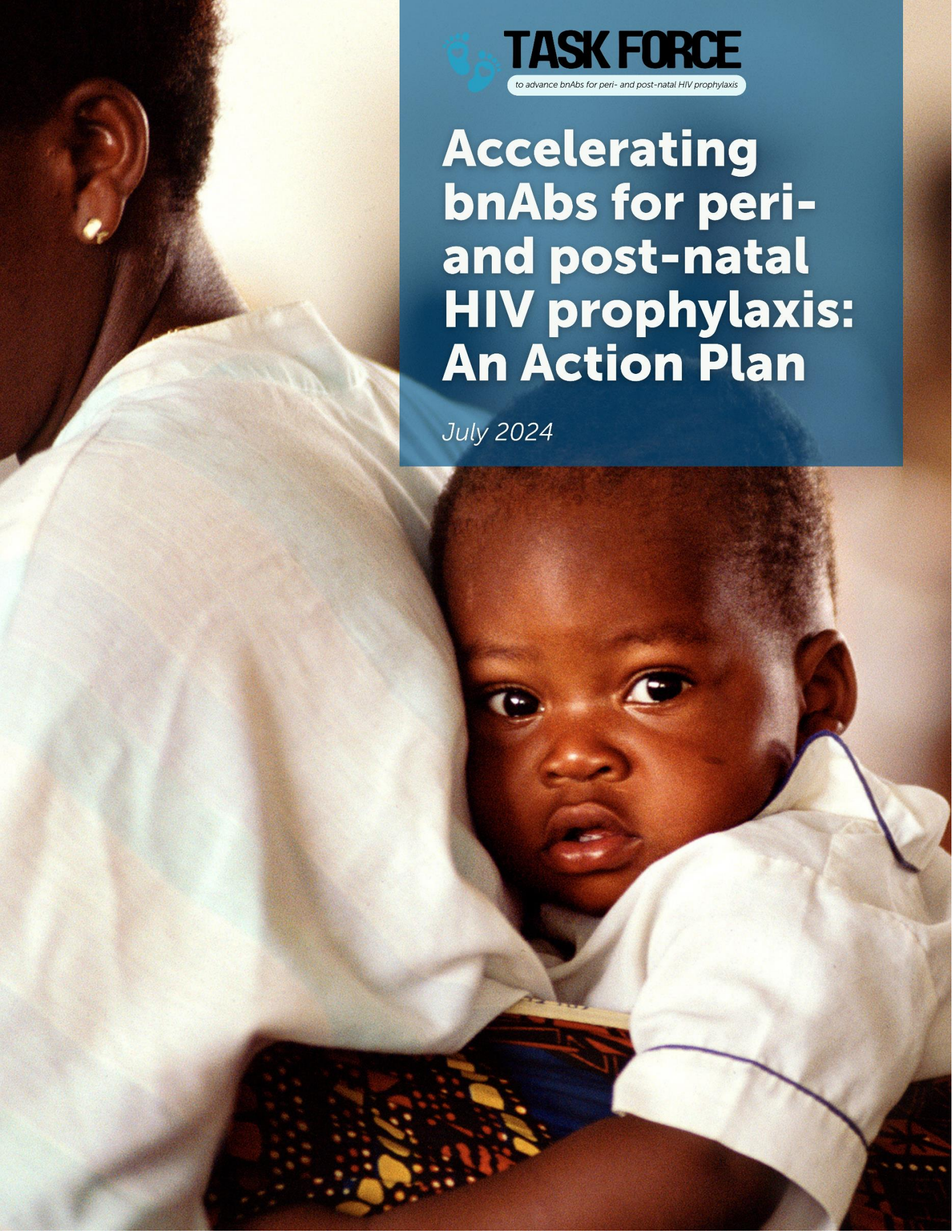

TASK FORCE

to advance bnAbs for peri- and post-natal HIV prophylaxis

Accelerating bnAbs for peri- and post-natal HIV prophylaxis: An Action Plan

July 2024

ON THE COVER

Mother and child. © Charlotte Raymond Photography 2011

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Participating Organizations


Acronyms

ADA – anti-drug antibody

ADCC – antibody-dependent cellular cytotoxicity

AMA - Africa Medicines Agency

AMP – Antibody-Mediated Prevention trial

ART – antiretroviral therapy

AVAREF – African Vaccine Regulatory Forum

ARV – antiretroviral

bnAbs – broadly neutralizing antibodies

CABs – Community Advisory Boards

CDMO – Contract Drug Manufacturing Organization

COGS – cost of goods sold

CRP – Collaborative Registration Procedure

EMA – European Medicines Agency

EU-M4all – European Union medicines for all

Fc – fragment crystallizable

FDA – Food and Drug Administration

GPP – Good Participatory Practice

HHS – Global HIV, Hepatitis, and STI Programme

IM – intramuscular

IV – intravenous

IVB – Immunization, Vaccines, and Biologicals Department

LMIC – low- and middle-income countries

mAb – monoclonal antibody

MPP – Medicines Patent Pool

nAbs – neutralizing antibodies

NHP – non-human primate

NRA – National Regulatory Authority

PD – pharmacodynamic

PEPFAR – President's Emergency Plan for AIDS Relief

PK – pharmacokinetics

PNP – post-natal prophylaxis

PT80 – predicted serum neutralization 80% dilution titer

RSV – respiratory syncytial virus

R&D – research and development

SC – subcutaneous

SHIV – simian human immunodeficiency virus

USAID – United States Agency for International Development

WHO – World Health Organization

Background

In 2023, 120,000 infants acquired HIV, contributing to 9% of new global infections in that year, despite comprising less than 2% of the population.[1] This disparity highlights infants' status as a "forgotten" high-risk group. Approximately 350 infants continue to acquire HIV each day, and about 1.2 million are exposed annually. Children accounted for 15% of all AIDS-related deaths in 2022, but comprised only 4% of people living with HIV.[2]

While antiretroviral (ARV)-based post-natal prophylaxis (PNP) for infants alongside antiretroviral therapy (ART) for pregnant and lactating people has significantly reduced peri- and post-natal HIV transmission, ART coverage among pregnant populations has levelled off at approximately 82% during pregnancy, leaving about 220,000 pregnant people living with HIV without ART coverage.[3] Additionally, adherence to ART during the postpartum period is known to be suboptimal, with rebound viremia in as many as 30% of breastfeeding people on ART[3-5].

These data highlight that while there are available interventions to reduce new infant infections, there remain implementation challenges with existing prevention modalities for pregnant and lactating people for a variety of complex social and structural reasons. These reasons include factors such as lack of knowledge of HIV status due to gaps in initial or repeat HIV testing during pregnancy and breastfeeding; maternal acquisition of HIV infection during late pregnancy or breastfeeding; challenges in retention in care and adherence to ARV therapy in the postpartum period; and challenges in administering daily ARV prophylaxis to infants in the 6-12 weeks following birth to reduce the risk of acquiring HIV.[6] To meet the commitments to end the AIDS pandemic in children, new strategies are needed to close this gap in the prevention of new pediatric HIV infections, particularly during the post-natal breastfeeding period.

In the last decade, biomedical research has identified broadly neutralizing antibodies (bnAbs) as a promising strategy to address gaps in the prevention of peri- and post-natal HIV transmission. Of the different products in development for HIV prevention ranging from oral pills, vaginal and rectal gels, and vaginal rings/inserts to long-acting injectables, bnAbs are one of only a few products currently being evaluated for use as neonatal and infant HIV prophylaxis. An array of bnAbs have now entered clinical trials, and newer, more potent, longer-acting options are in the pipeline.

There is mounting evidence from Phase 1 clinical trials testing several bnAbs and bnAb combinations that demonstrate their encouraging pharmacokinetics (PK) and safety profiles when administered subcutaneously to infants with peri- and post-natal exposure.[7, 8] Simian HIV (SHIV) models highlight the promising potential of bnAbs in both pre- and post-exposure HIV prophylaxis.[9, 10] The Antibody Mediated Protection (AMP) trials — which were conducted in cisgender women in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe, and in men who have sex with men and transgender men in Brazil, Peru, Switzerland, and the U.S. — provided proof of concept of the VRC01 antibody's efficacy (75%) against sensitive HIV-1 isolates. Nonetheless, the trials did not meet their primary endpoints and highlighted the importance of using bnAbs in combination to ensure increased potency and breadth.[11]

Given their strong safety profile and potential for long half-life, there is hope that bnAbs could help overcome gaps in preventing peri- and post-natal transmission of HIV, potentially providing months of protection during the period of highest transmission risk for infants, without the same adherence barriers that may arise from daily oral prophylaxis. Additionally, it is anticipated that given their strong safety profile, bnAb-based options could obviate concerns regarding toxicity and potential ARV drug resistance related to use of the same ARV-based options or drug classes for both treatment and prevention. Their lower dosing requirements could help support ease of administration and deployment and reduced cost of goods relative to adult bnAb products. Additionally, the ability to use common bnAb formulations for infant and adult populations could streamline supply chains and facilitate progression to infant studies by eliminating the need for distinct clinical supply across age groups.

Given their unique value proposition in infant populations and the potential for benefit in high HIV transmission areas, there is an urgent need for novel approaches to innovate and accelerate the clinical development pathway for bnAbs as peri- and post-natal prophylaxis. In February 2023, IAVI, the Desmond Tutu Health Foundation, and Advocacy for the Prevention of HIV/AIDS organized a technical

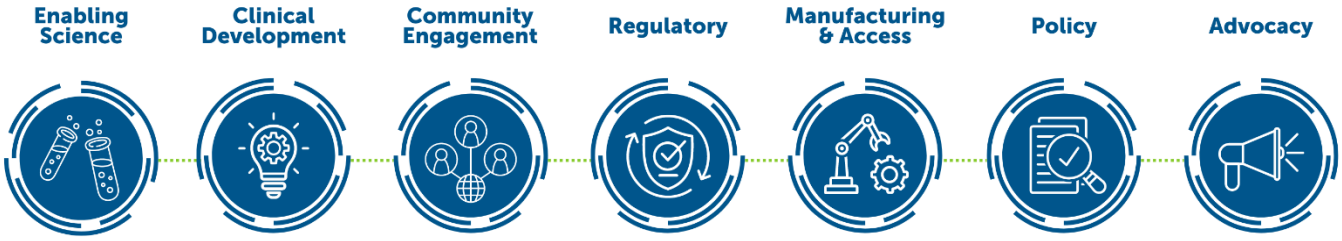
consultation in Cape Town, South Africa, with financial support from the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR), to inform the clinical development pathway for investigational bnAbs for the prevention of peri- and post-natal HIV acquisition. The goal of this consultation was to forge consensus and clarify the pathway for infant bnAb trials, while still early in development, with the aim of accelerating the clinical development pathway and incentivizing funders and manufacturers to invest in this neglected area.

Participants agreed that significant political will and resources would be needed to advance this ambitious agenda and that a coordinated action plan could help accelerate clinical development, regulatory approval, and broad access to bnAbs for peri- and post-natal HIV prophylaxis. This forward-looking action plan would need to address not only clinical trial design, but a range of intersecting supportive activities needed in the areas of enabling science, regulatory pathways, community partnership, advocacy, evidence for policy adoption, and pathways for broad supply and access to this potentially game-changing intervention.

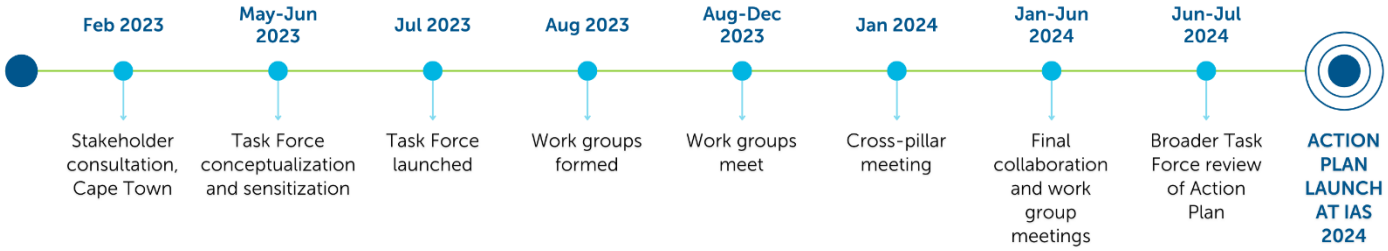
Introduction to Approach

Following the technical consultation in Cape Town in July 2023 with ongoing support from USAID and PEPFAR, a multi-stakeholder Task Force convened to develop an action plan that defines key recommendations, priority activities, and resources needed to accelerate the clinical development, licensure, and availability of bnAbs for peri- and post-natal HIV prophylaxis. The following Action Plan aims to facilitate coordinated efforts and strategic planning, while ensuring the required resources to advance bnAbs for use in infant HIV prophylaxis from early development through introduction and scale-up. By providing a succinct, consolidated roadmap outlining critical recommendations, prioritized activities, and necessary resources, it is anticipated that the Action Plan can galvanize action, foster collaboration, and help mobilize required resources end-to-end along the research, product development, and introduction continua.

Working together, this diverse group of Task Force members (see Appendix 1) guided the development of the Action Plan across seven pillars: 1. Enabling science; 2. Clinical development; 3. Regulatory strategy; 4. Community partnership; 5. Manufacturing and access; 6. Policy; and 7. Advocacy. Task Force contributors included more than 100 stakeholders from 49 organizations spanning 19 countries and four World Health Organization (WHO) regions, who brought multidisciplinary perspectives to the Action Plan's development, including community liaisons, advocates, ethicists, funders, industry representatives, access and voluntary licensing experts, parents, nurses, pediatricians, nonprofit product developers, program implementers, public sector representatives, regulators, researchers, statisticians, and representatives of United Nations agencies.



From August 2023 through June 2024, Task Force working groups met monthly to align on defined needs and key actions across the seven thematic pillars. The resulting Action Plan outlines 23 priority goals with associated concrete action steps to advance the ambitious agenda of accelerating the clinical development, regulatory approval, and broad access to bnAbs for peri- and post-natal HIV prophylaxis.



1. Enabling Science

The objective of the Enabling Science pillar was to define the key nonclinical and translational studies needed to facilitate efficacy trials for bnAbs for HIV prophylaxis in infants. Identified enabling science priorities include studies in the areas of virology, immunology, and non-human primate (NHP) models.[12]

Context setting:

Studies on the protective effectiveness of neutralizing antibodies (nAbs) in blocking mucosal or intravenous challenge with various SHIV strains in juvenile NHPs have been highly informative, helping to define challenge routes, pharmacokinetics *in vivo*, and protective doses using combinations of potent bnAbs.[13] Infant NHP studies have delivered findings in several key areas which suggest great promise for the use of HIV bnAbs as infant prophylaxis, as well as informing the potential for bnAbs to maintain tight control of infection after withdrawal of antiretroviral therapy when delivered for treatment in infants with HIV infection. This body of research has highlighted the following key takeaways:

1. Studies in infant macaques have identified a *defined potential window of opportunity* of 48 hours post-birth for bnAb post-exposure prophylaxis, resulting in viral clearance after high dose oral inoculation.[9, 10]
2. Studies have shown *success in prophylaxis during breastfeeding* with repeated bnAb dosing in a model that mimics repeated oral exposure.[14]
3. In infant macaques, there appears to be *less anti-drug antibody (ADA) response* than in adult macaque populations, especially when antibodies are delivered as a single bolus by the subcutaneous route; however, more data is needed on the occurrence of ADAs with combinations of bnAbs and engineered multi-specific bnAbs.[10][a]
4. Since there appears to be low or no ADA response to the bnAbs in very young macaques, it appears *possible to maintain long term (>1 year) expression of bnAbs in vivo* in nearly all infant macaques after vector-mediated gene delivery.[15]

A limitation of existing research is that the available virus panels to model the potency and efficacy of bnAb combinations to be used for prevention of peri- and post-natal transmission may not reflect the diversity and bnAb sensitivity of currently circulating viruses, and that the properties of viruses transmitted peri- and post-natally may differ in their bnAb sensitivity compared to sexually transmitted viruses.[16] Understanding of transmitted viruses from previous studies on peri- and post-natal transmission has been hindered by the technologies available at the time the studies were conducted. Older studies predominantly used single genome amplification as opposed to more contemporary deep sequencing technologies, which build upon earlier approaches by allowing for significantly improved sampling depth and characterization of circulating viruses. Virtually all the published studies on HIV transmitted to infants address clade C viruses, circulating in Eastern and Southern Africa, the Indian sub-continent, and parts of Asia. However, the current burden of peri- and post-natal HIV spans additional geographic regions (e.g. West and Central Africa, and South and Southeast Asia), where other clades of HIV are circulating, in particular, clades A, D, G, and recombinants thereof.[17-23] Characterization of transmitted infant virus sensitivity to maternal antibodies requires knowledge of the precise time of transmission, which is very difficult or impossible to ascertain in clinical studies.[24] However, transmitted infant virus sensitivity to bnAbs is important and within reach of technologies in hand. Future research should be informed and guided by the epidemiology of contemporaneous viruses being transmitted in regions of high peri- and post-natal transmission.

[a] ADA responses refer to antibodies that are generated following injection of a foreign protein into a recipient. They can result in enhanced clearance, reduced efficacy, or increased reactogenicity following immunization.

1.1. Defined need: Characterization of contemporary HIV-1 viruses transmitted peri-natally and through breastmilk in order to understand:

- The relative sensitivity or resistance of contemporary circulating viruses to specific bnAbs and bnAb combinations, and the potency of those bnAbs/bnAb combinations against peri- and post-natally transmitted viruses across multiple geographies; and
- The relationship between parental virus bnAb sensitivity and virus that is transmitted to infants, specifically whether bnAb-resistant viruses are transmitted to infants from a viremic birthing parent.

Lessons from this research will have high clinical relevance in guiding the selection of optimal bnAbs or bnAb combinations by defining the minimum number of bnAbs and minimum concentration for effective prophylaxis in specific geographies.

PRIORITY ACTIONS:

1.1a. Compiling a panel of peri- or post-natally transmitted viruses representing a breadth of geographies in which HIV is being transmitted.

1.1b. Sequencing transmitted viruses and characterizing their neutralization sensitivity.

1.1c. Evaluating leading bnAb combinations for neutralization of this virus panel to guide the selection of the most relevant bnAbs for infant passive immunization.

1.2. Defined need: Evaluating PT80 as a predictive biomarker of the prophylactic efficacy of bnAbs against HIV breastmilk transmission in infant NHP SHIV models.

Predicted serum neutralization 80% inhibitory dilution titer (PT80), a biomarker that integrates the neutralization potency of a bnAb with its serum concentration, has been proposed as a correlate of protection for bnAb-mediated protection against adult sexual acquisition of HIV-1. A growing body of preclinical and clinical evidence is being generated to help validate PT80 as a correlate of protection conferred by neutralization. The PT80 biomarker predicted preventive efficacy against bnAb-sensitive and resistant strains in adults passively immunized with VRC01 in the AMP trials.[25] The PT80 is also associated with bnAb protection in NHPs, with a similar PT80 needed to confer a given level of protection in humans versus NHPs, suggesting the suitability of the NHP model in studying biomarkers of efficacy.[26] However, as PT80 does not consider other effector functions associated with bnAbs, such as various fragment crystallizable (Fc)-mediated factors that may be important contributors to viral clearance through the action of immune cells, it may underestimate the overall impact of bnAb activity.

The difference in pathophysiology between sexual transmission and peri- and post-partum transmission has raised questions in terms of the ability to extrapolate targets from adult pre-exposure prophylaxis studies to infant transmission. Because the mucosal sites of viral transmission and immunological milieu differ between infants and adults, it is unclear whether PT80 has the same predictive value for protection of infants exposed to HIV during the peri- and post-partum periods through oral ingestion of breastmilk multiple times daily at a potentially lower viral titer, as for sexual transmission. Additionally, infants are exposed to both cell-free and cell-associated viruses in breastmilk, which may mean that different antibody functions are needed to prevent infant HIV acquisition. Further preclinical and clinical studies are also needed to determine whether the PT80 biomarker bridges to bnAbs used in combination and to bnAbs targeting epitopes on the HIV envelope other than the CD4-binding site targeted by VRC01.

Evaluating PT80 as a predictive biomarker of the prophylactic efficacy of bnAbs against breastmilk HIV transmission in a SHIV model can inform understanding with respect to PT80's reliability as a correlate of protection, support identification of the level of antibody titers needed for protection, and elucidate the mechanisms of protection against breastmilk transmission. The overall impact of PT80 in predicting the efficacy of a bnAb, or a combination of bnAbs, may be complicated by the effect of maternal antibodies

which may also contribute to the overall protection or susceptibility of infants through competition for similar HIV epitopes.

PRIORITY ACTIONS:

1.2a. Carrying out studies in infant NHPs evaluating PT80 as a predictive biomarker, ensuring a range of study arms to assess different key variables toward the optimization of a bnAb regimen for infant prophylaxis, including evaluating:

- A single bnAb as well as combinations of bnAbs targeting different HIV epitopes.
- Challenges with single SHIVs as well as with swarms of SHIVs to increase the information gained and to evaluate the dynamic range of the serum neutralization biomarker.
- Frequent and repeat challenges through the oral route to replicate the real-world conditions of virus exposure during breastfeeding.

1.2b. Evaluating the extent to which serum neutralization titers can be predicted using *in vitro* neutralization and PK data.

1.3. Defined need: Continued discovery and advancement of bnAbs to nurture a pipeline of products that align with preferred characteristics (see Box 1), including optimal combinations for therapeutic as well as prevention indications.

There is a need to expand efforts to discover and optimize the next generation of bnAbs. In addition to post-natal prophylaxis, there is a broader potential use for antibodies in treatment to induce remission in infants living with HIV. From the treatment perspective, bnAbs combined with ART could potentially maintain virus suppression through the first year of life, which has been shown to reduce overall infant mortality.[27] Delivery of two bnAbs to infants in Botswana who were long-term ART suppressed was well-tolerated, and repeated bnAb administration resulted in suppressed viremia during 24 months of ART interruption.[28, 29] Infants living with HIV can be identified and treated to achieve viral suppression immediately after infection.[8, 30-33] The resulting HIV reservoir in this population is likely to be smaller and less diverse, which increases the likelihood of demonstrating a functional cure. Expanding the potential indications for use from prevention to treatment and functional cure/remission can maximize the impact of bnAbs, while also expanding their potential market to help bolster commercial viability.

PRIORITY ACTIONS:

1.3a. Discovery and optimization of new bnAbs, including with Fc-mediated functions for therapeutic indications.

1.3b. Identification of optimal combinations of bnAbs to be included in both infant prophylaxis and in early HIV treatment regimens.

1.3c. Exploring the potential of bnAbs to reduce or eliminate the virus reservoir through Fc-mediated antibody effector functions (e.g., antibody-dependent cellular cytotoxicity [ADCC] to kill HIV-infected cells) in virally suppressed infants who initiate immediate treatment.

2. Clinical Development

The objective of the Clinical Development pillar of the Task Force was to define the key actions needed to accelerate the clinical development of bnAbs for use in infant peri- and post-natal HIV prophylaxis. This includes defining criteria for advancing bnAb combinations, ensuring optimal staging of trials, and addressing study design considerations at each stage of clinical development.

Context setting:

A need for novel approaches to clinical trials has been identified to ensure feasibility and address ethical considerations for trials assessing bnAbs in the context of prophylaxis alternatives that are largely efficacious when used as directed (in the context of well-controlled clinical trials) but are difficult to implement in real-world settings. Given the strong safety profile and potential for benefit in high HIV transmission areas, there is strong rationale and community support (see Section 4) for deploying novel approaches to accelerate the clinical development pathway for bnAbs as peri- and post-natal prophylaxis to eliminate neonatal and infant HIV acquisition.

2.1. Defined need: Identifying and advancing bnAbs and bnAb combinations that meet criteria for high impact in the highest prevalence settings.

In addition to being efficacious and safe, bnAb and bnAb combinations prioritized for advancement should be affordable, readily deployed, broadly protective against circulating strains in high HIV prevalence settings, and have a product profile that is acceptable to communities.[34] (See Box 1 for key criteria to inform prioritization of antibody combinations.)

Box 1: Key criteria for prioritization of bnAb combinations

- Breadth of activity against the majority (>70%) of circulating strains across many regions, in the context of programmatic benefits that might improve ease of administration.
- Potent and long-acting regimens that achieve prophylactic levels with low doses and infrequent administration.
- Highly concentrated bnAbs to enable a volume that can be delivered through intramuscular or subcutaneous injection at a volume of 1 ml or less per injection.
- A stable formulation that has storage and shelf-life requirements feasible for distribution in low- and middle-income countries (LMICs), ideally without cold chain requirements.
- The ability to scale production for commercial supply, including products with good manufacturability and yield, conducive to large-scale manufacturing and low cost per gram of product.
- Affordability, facilitated by low cost of goods sold (COGS) and commitments to accessibility in high prevalence settings.
- Acceptable to communities in high prevalence and incidence settings, and aligned with criteria as outlined in the *WHO preferred product characteristics for monoclonal antibodies for HIV prevention* guideline document.[34]

Based on antibodies identified thus far, achieving the breadth necessary for high efficacy will likely require a combination of complementary antibodies for optimal coverage and to mitigate against escape. As noted in Section 1.1, further insight into the sensitivity of peri- and post-natally transmitted viruses to antibody activity will be key to discerning the optimal combination with the minimum number of bnAbs and *in vivo* concentration necessary for effective prophylaxis in specific geographies. In addition, the following key actions are recommended to inform the selection of bnAbs for advancement:

PRIORITY ACTIONS:

2.1a. Manufacturability assessments to help support prioritization of candidates with a viable pathway to commercial scale production and low cost of goods (see Section 5).

2.1b. Thermostability studies to advance formulations that can be stored at 2-8 degrees Celsius or in lyophilized form for ease of supply chain, distribution, and storage in a range of settings, including those with resource limitations.

2.1c. Mobilizing adequate resources to support the seamless end-to-end progression of bnAb combinations that align with prioritization criteria.

2.2. Defined need: Advancing strategies for rapid progression toward a licensed indication for peri- and post-natal HIV prophylaxis.

Traditionally, investigational products are tested for safety and efficacy in adults and adolescent populations before they are evaluated in children. Infant populations are altogether often excluded from clinical development or included only after a significant delay.

To accelerate the evaluation of bnAbs in infant populations, key learnings can be derived from earlier Phase 1 infant safety studies, including the value of close collaboration with adult protocol teams to ensure a seamless transition from adult to infant safety studies. Planning priorities include coordinating manufacturing runs for clinical trial material to ensure ample supply for both adult and infant studies; ensuring adult trials include comparable (intravenous, subcutaneous, or intramuscular) routes of administration to facilitate their subsequent evaluation in infant studies; and rapid readout of initial adult safety data to accelerate infant safety trial initiation.[7, 35][b]

Alongside bnAbs, a growing number of monoclonal antibodies (mAbs) directed to other infectious agents are being evaluated for use in infant populations, yielding important learnings that can inform future clinical development strategies for HIV bnAbs in infant PNP. The field of HIV peri- and post-natal prophylaxis may benefit from precedents set in the product development process for other mAbs, such as nirsevimab and Synagis (palivizimab) for respiratory syncytial virus (RSV) prevention, the latter of which was only ever tested in 62 healthy adults and progressed promptly to clinical development in infants (see Box 2).[36]

[b] A precedent has been set for pediatric bnAb studies to be initiated on the basis of safety and PK data from dozens rather than thousands of adults and based on a minimal post administration follow up period from a single dose (e.g. 28 days).

PRIORITY ACTIONS:

2.2a. Harnessing learnings from the clinical development of other mAb-based products used as passive immunization in infants and from earlier Phase 1 trials of bnAbs in infants to accelerate progression from Phase 1 adult studies directly to infant studies.

2.2b. Establishing a robust package of nonclinical evidence to inform and facilitate clinical development pathways (see Section 1), including PK/pharmacodynamic (PD) modeling to determine antibody trough levels likely to be protective for antibody combinations, evolving dosing needs with infant's rapid growth during the first 6-12 months of life, and related injection volume implications.[37, 38]

2.2c. Fostering coordination of efforts across research groups and networks working to advance bnAbs for peri- and post-natal prophylaxis to support collaboration in advancing Action Plan recommendations.

Box 2: Strategies from nirsevimab and earlier pediatric bnAb development programs that can inform infant PNP pathways

- Recruitment of all neonates in high seroprevalence/sero-incidence areas to capture infants in the stages when maternal or infant infection status is unknown and to pave the way for vaccine-like use.
- Consenting mothers during pregnancy, in advance of delivery, to facilitate enrollment.
- Ensuring potential co-administration with routine immunization during the breastfeeding period on the basis of safety data in the absence of interference data.
- Ensuring adult trials include comparable (intravenous [IV], subcutaneous [SC] and/or intramuscular [IM]) routes of administration to facilitate their subsequent evaluation in neonate (IV) or infant studies (SC or IM).
- Rapid readout of initial adult safety data to accelerate infant safety trial initiation.
- Direct initiation of infant studies following adult safety studies without pediatric age de-escalation from older children based on their limited prospect for benefit compared to use for PNP.
- Bridging to approval in pre-term and high-risk neonates from data from full-term neonates.
- Coordinating manufacturing runs to ensure ample supply of clinical trial material for both adult and infant studies.
- Leveraging the broad and well-defined safety database accrued for both bnAbs for HIV prevention and a broader range of non-HIV antibodies to validate rapid progression from adult to infant safety studies.

2.3. Defined need: Accelerating strategies for efficacy evaluation of bnAb combinations.

Some have asserted that HIV transmission through breastfeeding could potentially be reduced using a single long-acting bnAb with extended breadth, high potency, and effector properties (ADCC, phagocytosis) against circulating HIV strains in specific settings, a hypothesis that will be assessed in forthcoming research.[39, 40] However, as with adults, it is postulated that a combination of complementary antibodies may be required to achieve optimal coverage, especially in high subtype diversity settings and to restrict escape if infection does occur.[11, 34]

The standard path to regulatory approval for an investigational product involves evaluating the efficacy of individual products first, then in combination. Both European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) guidance identify scenarios in which co-development may be warranted as an alternative to monotherapy-based development, including where there is a strong biological rationale for the use of a combination, a full non-clinical characterization of the activity of both the combination and the individual new investigational drugs has been completed, and there is a compelling reason why new investigational drugs cannot be developed independently. This includes scenarios in which "monotherapy for the disease of interest leads to resistance," or "one or both of the agents would be expected to have very limited activity when used as monotherapy" — both conditions that are hypothesized to apply in the case of HIV preventive bnAbs in infants, based on results from the AMP trial.[41, 42] The actual impact of bnAbs in infants, who are suggested to have lower viral loads and decreased viral complexity, however, remains to be established.

As with ARV-based options, viral evolution and the emergence of resistance will necessitate continually expanding the pipeline of novel antibodies and antibody combinations. Staggered timelines for Phase 1 data availability in adults and for manufacturing of sufficient clinical supply for both adult and infant trials complicate efforts to simultaneously line up combination bnAb regimens for progression into infant PNP trials.[c]

PRIORITY ACTIONS:

2.3a. Generating evidence to facilitate the co-development of bnAbs in combination, including a full non-clinical characterization of the neutralizing activity of both individual bnAbs and bnAb-based combinations against circulating viruses in high prevalence settings (see Section 1.1).

2.3b. Defining strategies to rapidly integrate new bnAbs into combinations as they become available, including exploring the potential for adaptive trial designs for late-stage efficacy evaluations that enable opening new arms for optimized and novel bnAbs as they become available.[d]

2.4. Defined need: Exploring clinical trial designs that would enable use of bnAbs as an alternative to, instead of an add-on to, standard of care for peri- and post-natal HIV prophylaxis.

Adding long-acting bnAbs and bnAb combinations as an adjunct to standard of care can ensure an added layer of protection for infants in scenarios in which there are gaps in coverage due to non-initiation or non-adherence to either maternal ART or infant ARV-based prophylaxis. Nonetheless, being able to use bnAbs as an alternative rather than an add-on to ARV-based options would support programmatic implementation and reduce costs. Ethical requirements to offer standard of care to study participants preclude head-to-head evaluation of bnAbs and bnAb combinations without infant ART prior to demonstration of the relative efficacy of the bnAbs. In this context, there is a need to explore study designs that could facilitate rapid progression to the use of bnAbs in lieu of — rather than on top of — ARV-based infant prophylaxis.[e]

[c] As more effective prevention modalities are developed, comparison studies to evaluate new interventions will require very large sample sizes to demonstrate superiority or non-inferiority. Ultimately, innovative trial designs and investment in establishing surrogate markers that can streamline efficacy evaluation and regulatory pathways can greatly facilitate efficacy evaluation of future bnAbs (See Sections 1.2 and 2.3).

[d] For late-stage studies, ensuring a clear scientific rationale for integration of additional arms, including the need to ensure regimens with adequate breadth and coverage of circulating strains, will be important, as will early engagement to ensure buy in from communities, regulators, and funders.

[e] Because it will be difficult to know early on whether we are providing the bnAb to an exposed but uninfected infant (requiring prophylaxis) or an infant who was already infected and requires treatment, there is a need to evaluate bnAbs as treatment in the neonatal period.

Currently, in most settings, infant prophylaxis is only provided to known HIV-exposed infants or HIV-exposed infants viewed as being at high risk of HIV acquisition (e.g., based on maternal viremia or short duration of maternal ART) for a recommended period of 6-12 weeks or less in some settings. There is no indication for general population-level administration of prophylaxis (e.g., administration to all neonates as opposed to restricted to known HIV-exposed neonates and infants), even in settings of generalized HIV risk. An approach that enrolls all neonates born to persons living with HIV as well as non-HIV exposed neonates throughout the breastfeeding period in a high prevalence and incidence setting could enable demonstration of the independent efficacy of bnAbs and bnAb combinations amongst neonates and infants who are newly HIV-exposed during the breastfeeding period (born to mothers who become infected post-natally) among infants exposed to HIV after completion of the 6-12 week infant PNP period. Robust assessment of sample size considerations, guidance from both regulators and ethicists, and community consultations will be needed to inform trial design for such full birth cohort strategies.

PRIORITY ACTIONS:

2.4a. Exploring trial designs that can facilitate the demonstration of bnAbs and bnAb combinations' independent efficacy, including:

- "All-comer" neonatal enrollment strategies.
- Powering studies to assess the preventive efficacy of bnAbs and bnAb combinations in infants who continue to breastfeed after completion of the 6–12-week infant PNP period.[f]
- Examining efficacy in infants born to mothers with HIV with inconsistent ART usage, documented by drug levels.

[f] This study design will need to account for and generate data on the transfer of bnAbs in breastmilk if there is continued maternal use of bnAbs.

3. Community Partnership

The objective of the Community Partnership pillar of the Task Force was to employ a good participatory practice (GPP) approach to stakeholder engagement throughout the product development process to build trust within communities, ensure clear and consistent communication of progress with trials, and establish alignment on ethical aspects of the product development process.[43]

Context setting:

Community stakeholders, defined as the end users of a product and their networks, are critical to the product development pathway. Their knowledge, beliefs, attitudes, behaviors, wants, preferences, and needs should inform product design, clinical development plans, and strategies for the commercialization and introduction of products. Community input and engagement can also support uptake, once products are introduced.

As part of its early establishment, GPP has been anchored to the clinical development phase, with less focus on other key stages of the product lifecycle. GPP guidelines offer guidance on stakeholder engagement approaches from the early phase of clinical development through to access. However, in practice, the GPP body of work has often been initiated with protocol development at the start of clinical trials and has ended with trial results dissemination, with limited strategies occurring outside of the clinical development phase. This imbalance has entrenched funding models for community engagement within the clinical trial phase, making it difficult to justify or advocate for broader participatory practices. Additionally, tying community engagement to trial settings can restrict engagement to communities in countries and local settings where the trials are conducted. This design relies heavily on Community Advisory Boards (CABs) which have historically been the primary engagement conduit between researchers/trialists and communities.

3.1. Defined need: Early and sustained partnership with communities to create a product development ecosystem that is for communities and by communities.

While product developers rely on end-users to test, buy, and use their products, communities are rarely seen as partners throughout the end-to-end development pathway and there is a lack of standardized approaches to community partnership. Even when communities are brought into discussions, often these engagements are not geared toward them and efforts to make scientific content accessible to broad audiences are limited. Community engagement activities need to be evaluated and, where applicable, re-designed for each phase of the product development pathway and contextualized, as needed, to specific settings. A paradigm shift from community engagement to community partnership from conception through introduction is required. This will require recognizing communities as active collaborators and decision-makers in the product development process.

PRIORITY ACTIONS:

3.1a. Harnessing community inputs along the end-to-end discovery to introduction pathway, building on the Community Working Group of the Task Force and linking with the mAbs Advisory Board (see Section 7.1b) to harness community inputs along the end-to-end discovery to introduction pathway.

3.1b. Translating scientific and Action Plan content into concise and easy-to-understand key messages and research literacy tools, co-developed by community members and tailored to each stage of development. This includes the creation of materials and dissemination strategies adapted to diverse audiences and contexts.[44]

3.2. Defined need: Harnessing community-driven evidence generation to inform the product development continuum.

While GPP guidelines lay out a standard framework for engaging communities in preparation for, during, and after clinical trials, even earlier and more systematic engagement of community stakeholders and sustained partnership can build goodwill and result in products that are better suited for the communities they are intended to serve.

PRIORITY ACTIONS:

3.2a. Garnering and building upon lessons learned from past GPP implementation to develop strategies for engaging communities further upstream in the product development process, to inform early thinking about product characteristics and research priorities, as well as downstream, to inform roll-out strategies.

3.2b. Designing end-user research to understand the social, psychological, behavioral, and structural factors that influence communities' health decisions and preferences to shape clinical trial design, preparation for introduction, and implementation practices.[45]

3.2c. Developing an evidence-based, community-led and validated roadmap with recommendations for how to ensure communities are engaged as meaningful partners along the end-to-end product development continuum.

4. Regulatory Strategy

The objective of the regulatory pillar was to define pathways for regulatory approval, including potential clinical and future immuno-bridging approaches for demonstrating efficacy, and to plan for engaging the global regulatory community to reach consensus on regulatory pathways for bnAbs in peri- and post-natal HIV prophylaxis.

Context setting:

Less than 10% of antibody-based products approved in the U.S. and Europe are authorized for use in Africa.[46] Delays in regulatory filing, the complexity of biologics, lack of mutual recognition across regulatory authorities, lengthy review processes, and cost have hindered access to mAb-based innovations in LMICs.[47-49] Although pathways to licensure for mAbs and mAb-based combinations exist, there is a lack of uniformity across countries in the procedures and requirements that underlie their regulation.

Various collaborative mechanisms have emerged intending to streamline regulatory processes, increasing reliance amongst regulatory authorities, and strengthening the capacity of national regulatory authorities to evaluate, approve, and monitor new interventions, including the Africa Vaccines Regulatory Forum (AVAREF), WHO prequalification, the EU Medicines for All (EU-M4all), and WHO Collaborative Registration procedures. These existing processes and forthcoming institutions, such as the African Medicines Agency (AMA), may help mitigate differences in application requirements, timelines, and information requests across countries while building experience in the regulation of complex biologics amongst National Regulatory Authorities (NRAs). Alongside broader efforts to strengthen regulatory convergence and capacity, efforts are needed to engage regulators early and comprehensively on a product-specific basis to understand the chemical manufacturing and controls, nonclinical, and clinical evidence required to support and facilitate eventual product applications and approvals.

4.1. Defined need: Harnessing learnings from complementary disease and product areas to inform regulatory pathways for bnAbs.

Key learnings can be gleaned on clinical development strategy and regulatory pathways from related products including a) antibody-based products for treatment and prevention of other infectious diseases (e.g. SARS-CoV-2, RSV); b) combination-based products (e.g. HIV, tuberculosis); and c) other prophylactic interventions (e.g. HIV prevention trials for long-acting agents). Harnessing these learnings can help to ensure streamlined and efficient clinical development pathways for bnAbs for peri- and post-natal prophylaxis.

PRIORITY ACTIONS:

4.1a. Identifying product development areas with precedents that can inform regulatory pathways, building upon the initial efforts of the Task Force.

4.1b. Consolidating lessons learned on key study design approaches (see Section 2.2a) from parallel disease and preventive areas to inform regulatory strategies.

4.2. Defined need: Early regulatory engagement to guide and accelerate regulatory pathways for bnAb-based PNP products.

Early engagement with regulatory agencies from the regions in which pediatric HIV is most prevalent should be prioritized to define appropriate regulatory pathways for a future bnAb-based preventive regimen. During clinical development, two specific types of regulatory advice are important for approval of bnAb-based products:

- *General scientific advice on cross-cutting topics* that apply to the field of PNP and the use of bnAbs for infant peri- and post-natal prophylaxis, including strategies to streamline clinical development pathways and address unique ethical considerations emerging in infant PNP trials.
- *Product-specific scientific advice* sought by individual sponsors to help inform the clinical development strategy for specific bnAbs or bnAb combinations.

PRIORITY ACTIONS:

4.2a. Identifying the regulatory authorities and technical groups that should be engaged during the bnAb product development process, including AVAREF, EMA, the FDA — through the PEPFAR/Tentative Approval pathway, the WHO Prequalification team, the WHO Paediatric Regulatory Network, and national regulators in countries in which infant HIV acquisition is highly prevalent, as well as in the country of manufacture, which is important for subsequent regulatory filings.

4.2b. Pursuing opportunities for early scientific advice on clinical development plans for specific bnAb combinations. This includes seeking advice on specific study design approaches, as well as on nonclinical evidence that could help support and accelerate clinical development in infants. AVAREF, the EMA, and the FDA/PEPFAR each have pre-submission scientific advice mechanisms that should be pursued.

4.2c. Generating a catalogue of questions broadly pertinent to bnAb infant prophylaxis trials, building upon the work of the Task Force. Priority topics include required safety data and follow-up intervals and outcomes; strategies for future potential immuno-bridging approaches (see Section 2.3) to infer the efficacy of these antibodies in lieu of clinical disease endpoint efficacy studies, once an approved bnAb or bnAb combination with demonstrated efficacy is available; potential requirements to enable concomitant use with vaccines used in routine childhood immunization; and future strategies to accelerate pathways for biosimilar development.

4.2d. Convening a regulatory workshop or workshops, building on the Cape Town consensus meeting, bringing together regional regulators, ethicists, researchers, product developers, statisticians, and community representatives for alignment and skill building on cross-cutting topics broadly relevant to the regulation of bnAb-based regimens, and to pressure test and gather joint inputs into clinical development plans.

4.3. Defined need: Evidence frameworks to move toward immuno-bridging approaches.

Validating a surrogate marker of protection derived from bnAbs used in passive immunization studies that demonstrated clinical efficacy is an important priority for the field and could facilitate clinical development by supporting the informed selection of bnAbs/bnAb combinations and paving the way for potential future clinical immuno-bridging studies of bnAbs using such identified 'surrogate endpoints.' Greater use of *in vitro* pharmacodynamic markers, when available, to infer effectiveness and other supportive nonclinical and clinical data for 'bridging' of effectiveness from an already licensed reference product could streamline clinical development pathways, decrease required trial sizes, and potentially facilitate regulatory agencies' approval of future bnAbs, reducing costs and timelines (see Section 1.2).[50, 51] These surrogate markers could enable more rapid evaluation of new bnAbs based on the same platform

technology as the reference product as the pipeline evolves and as viral evolution necessitates novel combinations. The use of surrogate markers could also accelerate eventual biosimilar development and help bridge to demonstration of clinical benefit in special populations, such as preterm infants with underlying health concerns that might complicate clinical evaluation.

Establishing a surrogate marker will likely increase the size of clinical trials designed to validate the marker, and validation through more than one trial may be required, which will be costly. Over time, however, investment in identifying a surrogate marker would likely be cost-saving, enabling the conduct of immuno-bridging studies and accelerating the clinical development pathway for future bnAb-based products.

PRIORITY ACTIONS:

4.3a. Identifying lessons from the validation of other surrogate markers across disease areas to help inform strategies to establish a surrogate endpoint, including lessons from the AMP study and clinical immuno-bridging strategies applied in other disease areas (e.g. SARS-CoV-2).[51]

4.3b. Seeking input from regulators on the consolidated evidence base for use of PT80 as a potential biomarker and enlisting their guidance in designing forthcoming clinical trials in pediatric populations using bnAbs with an eye toward further validation of this surrogate endpoint for future pediatric trials.

4.3c. Advocacy to support the establishment of a surrogate marker (see Section 7.4) by convening additional dialogue across researchers, product developers, civil society, funders, and regulators to define an evidentiary pathway and invest resources to support the establishment of the PT80 as a surrogate marker of bnAbs efficacy.

4.4. Defined need: Strengthening regional capacity and innovative pathways for regulation of bnAb-based products.

Agencies with extensive experience in the regulation of biologics, such as the U.S. FDA and EMA, together with the WHO Prequalification of Medical Products Programme, have established mechanisms that could be leveraged to support other national regulatory authorities in reviewing the dossiers for regulatory approval of bnAbs. Leveraging platforms for joint reviews and strengthening regulatory networks with mutual recognition — through platforms such as the AMA/AVAREF and WHO's Collaborative Registration Procedure (CRP) — could also facilitate faster and broader approval of new bnAbs, while helping strengthen regulatory capacity.[52] Concerted efforts are needed to expand these collaborative platforms and to ensure they are being utilized for forthcoming bnAb-based products.

PRIORITY ACTIONS:

4.4a. Leveraging pathways such as EU-M4all to accelerate approval and strengthen regulatory capacity for bnAbs for use in LMICs by facilitating joint assessments in collaboration with WHO, relevant NRAs, and experts, using the alternative listing procedures for WHO prequalified products, and sharing assessment reports.[53, 54]

4.4b. Securing marketing authorization for other mAb-based products of high public health impact that have already been prequalified, albeit in non-ID disease areas such as trastuzumab and rituximab, to build experience in high HIV prevalence regions in the regulation of mAbs by using the WHO CRP to pave the way for accelerated registration of future bnAb-based products.

5. Manufacturing and Access

The objective of the Manufacturing and Access pillar was to define the key actions to occur in parallel with the end-to-end product development and introduction continuum to ensure low cost of goods, sustainable and affordable supply, and timely and broad access to bnAbs for infant PNP.

Context setting:

With promising bnAbs for HIV prevention and mAbs for a broader range of infectious disease priorities on the horizon, overcoming barriers to access in LMICs will be critical. Weak economic incentives, business models that are misaligned with global health needs, high development and manufacturing costs, and gaps in end-to-end funding for mAb-based interventions all contribute to access inequities.[55]

Manufacturing of mAbs is more complex than manufacturing small molecules, involving a larger number of steps and specialized input materials, workforces, and facilities. These factors contribute to an overall higher (COGS) for mAbs than for small molecule products; however, COGS for mAbs are decreasing with the optimization of product profiles for increased potency and half-life (thereby minimizing the doses and volumes needed), antibody engineering and selection to improve manufacturability, innovations in mAbs manufacturing (reducing manufacturing costs), and large-scale production (supporting economies of scale). Concerted efforts are needed to address factors with an impact on the affordability and scalability of supply to catalyze timely and equitable access to bnAbs in the pipeline.

5.1. Defined need: Defining the key access measures needed at each stage of product development, from early discovery through launch, to ensure prompt bnAbs accessibility:

This includes defining upstream activities to ensure product profiles support ease of delivery in LMICs; manufacturing process optimization to support low COGS and ease of technology transfer; and public health-driven intellectual property, voluntary licensing, and business model strategies.[56]

PRIORITY ACTIONS:

5.1a. Defining, adequately resourcing, and implementing enablers that could facilitate the establishment of viable commercial models for bnAbs in PNP, leveraging insights and best practices from other relevant initiatives, including the IAVI, Unitaid, Medicines Patent Pool (MPP), and Wellcome supported initiative to advance Novel Business Models for Accessible mAbs in LMICs, and the IAVI, Africa CDC, and Wellcome supported initiative to promote a sustainable supply and demand ecosystem for mAbs-based products in Africa.[57] This includes strategies for ensuring robust technology transfer with sharing of process know-how, expert human resources, and access to key materials such as cell lines to accelerate voluntary licensing strategies.[56]

5.1b. Creating a compendium of access provisions to govern research, manufacturing, and commercialization agreements, including contractual requirements to ensure affordability; prompt, broad, and equitable availability; and sustainable supply strategies, building on previous initiatives such as MPPs Long-Acting Therapeutics Patents and Licences Database (LaPal) [58] compendium and the Global Healthcare Innovation Alliance Accelerator guide (see Box 3).[59]

Box 3: Access provisions to govern research

- Prioritizing regulatory filings in affected regions and with NRAs operating at maturity level 3 and 4 (as benchmarked against WHO Global Benchmarking Tool) to ensure quality and facilitate adoption, financing, and procurement in a broader range of countries.[60]
- Advancing strategies to ensure adequate, quality-assured supply that meets demand, including through voluntary licensing and technology transfer provisions.
- Establishing equitable allocation plans for products.
- Securing pricing strategies for bnAbs that ensure both affordability and sustainability.
- Ensuring strategies and resources are in place to support the rapid distribution, deployment, and scale-up of products.

5.2. Defined need: Evaluating the relative impact of innovative manufacturing platforms and technologies on lowering COGS and advancing prioritized strategies.

Several novel technologies and platforms are being explored to reduce the cost of mAbs. This includes alternatives to currently-used mammalian cell-based expression platforms — such as bacteria, yeast, fungi, and plant-based approaches — that are promising, but in early development. The use of perfusion bioreactors and continuous processing, as opposed to batch processing, alongside product optimization and other novel technology platforms are also being explored to bring down costs. The high cost of implementing experiments to test different strategies means they are generally piloted individually on a small scale, and in a manner that precludes head-to-head comparison across strategies to determine relative yield and COGS.

Investment in comparative testing of COGS-lowering strategies is being advanced by the Biomedical Advanced Research and Development Authority for mAbs for medical countermeasures through the Division of Research, Innovation, and Ventures initiative.[61] Building upon this model, further investment in the comparative evaluation of novel approaches to bring down manufacturing costs is needed.

Ensuring manufacturing processes are as streamlined as possible (e.g., in terms of cell culture and purification) can help make bnAbs in a particular preventive combination more platform-able, facilitating scale-up to achieve volume-based efficiencies and technology transfer, including to regional manufacturers. Ensuring streamlined processes will require proactive planning and coordination.

Manufacturing optimization strategies that involve specialized technologies could introduce complexity that impacts the ease of scalability and technology transfer. The interlinked goals of manufacturing process optimization and manufacturing scale-up must therefore be carefully managed.

PRIORITY ACTIONS:

5.2a. Aggregating the existing evidence base on the time-to-market, relative impact on COGS and scalability, bridging potential, intellectual property considerations, and voluntary licensing provisions that could impact accessibility for novel manufacturing process optimization approaches.

5.2b. Incentives for manufacturing technology innovators and vendors to develop alternate low-cost technologies, raw materials and consumables.

5.2c. Establishing and adequately resourcing a manufacturing optimization consortium that invests in head-to-head testing of different optimization strategies for a portfolio of prioritized bnAbs.

5.2d. Examining the implications of innovations in bnAb production on technology transfer, human resource needs, equipment requirements, and overall feasibility of biosimilar production, including exploring the trade-offs between optimization agendas and those strategies aimed at creating streamlined/large-scale processes to gain efficiencies.

5.3. Defined need: Ensuring novel commercialization models and voluntary licensing strategies for bnAbs support prompt and broad accessibility and supply sustainability in settings where infant HIV acquisition is high.

Prioritizing sustainable, quality-assured, and affordable supply is key to ensuring that manufacturing, commercialization, and rollout strategies for HIV prevention innovations, including bnAbs, are equitably accessible to populations in LMICs. Potential voluntary licensing, manufacturing, and commercialization models to deliver these goals have been articulated by a growing number of global health stakeholders and include partnership strategies to reduce timelines to availability of innovations in LMICs, strengthen sustainable regional supply capacity, ensure production is scaled to sustainably meet market needs, and ensure return on investment is balanced with access and affordability considerations.[55, 56, 62, 63] Delivering on the vision of equitable access to innovations will require a renewed focus on defining innovative models that overcome barriers to public and private sector collaboration.

PRIORITY ACTIONS:

5.3a. Refining understanding of the potential market size and demand for bnAbs, not only for use in infant prophylaxis but inclusive of the broader adult HIV prevention market and potential HIV treatment and remission indications, in the context of an evolving pipeline of interventions that now includes long-acting ARVs.[64] Improved characterization of the HIV bnAbs market can help define the business case for outreach to manufacturers while informing manufacturing scale-up and access strategies.

5.3b. Assessing the innovation and manufacturing landscapes for bnAbs/mAbs, including for pipeline products, to identify potential commercialization and manufacturing partners to potentially supply bnAbs in LMICs at scale. This includes innovators and biosimilar manufacturers engaged in noncommunicable disease mAbs as well as those based, or with a footprint in, key geographic regions of relevance, including LMICs with high HIV burden.

5.3c. Early engagement of private sector partners to define strategies to accelerate the affordable supply of bnAbs in LMICs, building upon the IAVI, Unitaid, Wellcome, and MPP *Novel Business Models* initiative. This includes exploring voluntary licensing and tech transfer, second brand, and other novel approaches to lower the barriers to timely private sector engagement in LMIC access agendas.

5.3d. Performing scenario planning to assess the manufacturing capacity that would be needed to meet projected LMIC demand and the relative tradeoffs across different manufacturing models to deliver the required supply (see Table 1). This includes a more robust analysis of the COGS and overall cost implications for different approaches, and of mitigating measures needed to ensure their effectiveness.

5.3e. Identifying and mobilizing funding for market shaping and push mechanisms that could reduce risk and incentivize private sector investments in bnAb manufacturing and commercialization in LMIC markets. This includes ensuring mechanisms to support financing and procurement pathways through pooled mechanisms, and upfront investment to ensure adequate supply to progress seamlessly through clinical development, and from clinical to commercial manufacturing scale-up.

5.3f. Requiring clear and transparent information-sharing and public health-friendly voluntary licensing terms for innovations benefiting from public and philanthropic funding and encouraging other innovators to follow similar access-friendly commitments.

Table 1: Illustrative bnAbs manufacturing models

Manufacturing model	Potential access enablers	Potential access risks
Centralized manufacturing hub (e.g., through a contract drug manufacturing organization [CDMO])	• Large-scale production to drive cost efficiencies • Leveraging standing manufacturing capacity to save facility capital expenditures • Flexible business model conducive to change-over strategies and that enables pivoting across a diverse product portfolio to ensure optimized utilization	• Anti-competitive/monopolistic conditions potentially created, if not mitigated through strong access provisions and cost transparency • Skill-based and intensive process could require protracted technology transfer timelines, particularly if utilizing a specialized process and if working with a less seasoned CDMO • More profitable campaigns prioritized by CDMO, contributing to unpredictability/risk in securing manufacturing slots and supply interruptions • Requires enlisting a marketing authorization holder to take on accountability and financial ownership (including upfront investment) and other non-manufacturing tasks required for commercialization (e.g., pharmacovigilance, product recall systems, regulatory filings, tendering, distribution).
Competitive model in which originator company voluntarily licenses bnAbs to multiple biosimilar manufacturers and provides technology transfer	• Competition supports lowest sustainable price • Supply security fostered by diversification • Opportunity to leverage expertise of biosimilar companies experienced with mAbs technologies • Potentially conducive to a model for building regional supply capacity for bnAbs and other mAbs as a technology platform (e.g., through a hub and spoke model)	• Need to recoup capital expenditures for multiple manufacturing facilities could contribute to higher costs • Sustainability risk if volumes inadequate to sustain commercial manufacturing at multiple sites • bnAbs skill-based and intensive manufacturing process could require protracted technology transfer timelines, particularly if utilizing a specialized process and if working with a less seasoned biosimilar manufacturer
Small-footprint/ modular manufacturing models	• Lower facility/overhead expenditures • Ease of decentralization, conducive to regional supply models • Amenable to small batch manufacturing to meet local needs	• Low-volume manufacturing contributes to higher cost per gram • Difficulty meeting high volume supply needs • Specialized trained workforce may be needed but difficult to sustain with a low-volume/on-demand model • Licensing terms of originators of portable/modular technology platforms could potentially add to costs in a manner that counteracts cost-savings • Potential complexity for manufacturing platforms that do not yet have authorized products associated with them

6. Policy

The objective of the Policy pillar of the Task Force was to anticipate the evidence needed for potential inclusion of bnAb-based PNP into future normative global clinical guidelines.

Context setting:

There is currently no precedent for the adoption of bnAbs into HIV treatment and prevention guidelines globally; and, while selected non-HIV mAbs have been integrated into global or national policy, timelines from regulatory approval to adoption into policy or procurement guidance have often been protracted.[65] Early identification of policy-related research priorities and a clear definition of engagement pathways can help mitigate delays in transitioning from regulatory authorization to adoption and impact. Leveraging WHO-convened processes to foster alignment among stakeholders will be important to help define these policy-related research priorities (see Section 4.4).

6.1. Defined need: Defining the evidence required for potential inclusion of bnAb-based infant PNP into WHO guidelines.

Issuance of WHO policy guidance is a precursor to the inclusion of products in many national and international financing and procurement mechanisms and is an important catalyst of country adoption for HIV prevention innovations. The WHO guidelines review process involves rigorous evaluation of scientific evidence as well as consideration of data on risk and benefits, acceptability and equity considerations, feasibility, and cost-effectiveness. To enable prompt potential inclusion of bnAb-based HIV PNP into guidelines upon marketing authorization, the following priority actions are needed.

PRIORITY ACTIONS:

6.1a. Convening expert consultations to review the current evidence on the use of bnAbs-based PNP and identify evidence gaps for normative guidance development.

6.1b. Collating evidence on bnAbs in the pipeline for use in PNP and on current standards of care to ensure timely consideration of peer-reviewed data for guidelines revision.

6.1c. Developing a research roadmap that summarizes the state of policy-related evidence and maps forward-looking research priorities.

6.2. Defined need: Clarifying pathways and advancing a coordinated strategy for global policy development for bnAbs and other mAb-based products.

Given the intersection of cost, product profile, feasibility, acceptability, and supply considerations that inform decisions to adopt innovations, cross-cutting, and integrated evidence-generation strategies are needed to support policy recommendations. Within the WHO, the Immunization, Vaccines, and Biologicals (IVB) Department and the Department of Global HIV, Hepatitis and STI programmes (HHS) have spearheaded early product development guidance on the Preferred Product Characteristics for HIV preventive bnAbs and other mAb-based products based on broad stakeholder consultation.[34, 66, 67] Under the guidance of the Strategic Advisory Group of Experts on Immunization, WHO IVB is also evaluating the potential integration of RSV mAbs into routine immunization programs for use in passive immunization. In parallel, WHO has now prequalified multiple biosimilar mAbs, including rituximab and trastuzumab for cancer therapy, and tocilizumab, an anti-inflammatory for use in COVID-19 therapy.[68, 69] The WHO has also issued guidelines on the nonclinical and clinical evaluation of mAbs for the prevention or treatment of infectious diseases[70], and several mAbs have been added to the WHO Essential Medicines List.[69]

At the end of 2023, WHO's Science Division kicked off efforts to enable innovation and access to mAbs-based solutions across diseases by forming a dedicated mAbs WHO Task Team to facilitate internal and external engagement across the product life cycle. More recently, WHO's HHS programme, in collaboration with the Global Accelerator for Paediatric Formulations, has convened experts to discuss the state of evidence on the potential use of bnAb-based PNP in infants exposed to HIV with the anticipated release of key outcomes by the end of 2024. In parallel, evidence reviews to inform potential revision of PNP recommendations are being initiated.

PRIORITY ACTIONS:

6.2a. Defining a coordinated strategy to promote timely evidence generation and equitable access to HIV bnAbs and other mAbs-based technologies, under the auspices of WHO's recently formed mAbs Task Team by:

- Working in collaboration with and building upon the complementary efforts of partners and Task Force counterparts (see Sections 2, 5, and 6), defining gaps and priority actions for WHO and global stakeholders on prioritization, manufacturing optimization, product development, regulation, market shaping, and advocacy for mAbs-based innovations.
- Leveraging WHO's platform and network of regional offices to convene consultations aimed at fostering consensus on evidence needs and disseminating research findings across a broad range of global and country-level stakeholders.

6.3. Defined need: Supporting evidence generation and implementation research and defining policy pathways for timely country adoption of improved options for PNP, including bnAbs, once authorized for use.

Evidence to support policy adoption for improved PNP options may differ by country. Factors such as baseline standards of care, perceived stigma, implementation strategies, programmatic suitability, budget impact, and willingness to pay differ depending on context. Decision-making drivers may also vary by context, with some countries placing a premium on the generation of evidence in local populations and others relying heavily on global guidance to inform country policies. Improved understanding of national policy pathways, baseline practices, and infrastructure, and evidence requirements is important to support country decision-making processes for forthcoming bnAb-based PNP options.

PRIORITY ACTIONS:

6.3a. Performing baseline assessments to understand current policies, practices, and infrastructure for implementation of PNP.

6.3b. Mapping country adoption pathways, decision-making drivers, and evidence requirements to support policy adoption of bnAbs for infant PNP, working in close collaboration with health ministries, maternal and child health stakeholders, providers, and local communities.

6.3c. Mobilizing resources to support the generation of additional targeted country-level evidence to support policy determinations based on identified priorities.

6.3d. Reviewing implementation research and scoping optimal delivery models including integration of bnAb interventions into routine child health and immunization programs.

7. Advocacy

The objective of the Advocacy pillar was to advance an advocacy agenda that makes progress toward full financial, political, programmatic, and policy commitments across all stakeholders for an end-to-end pathway to support for bnAbs to reduce peri- and post-natal HIV transmission.

Context setting:

HIV bnAbs are a promising option to potentially address peri- and post-natal HIV acquisition in infants, with a unique and valuable use case, as the HIV prevention landscape continues to evolve. mAbs represent a fast-growing area of product development and show promise in tackling non-communicable and infectious diseases. However, while the landscape for antibodies is expanding, significant barriers to the development, financing, and scale-up of HIV bnAbs for LMICs are anticipated and must be overcome to ensure equitable global access. With research showing promising advances and almost 20 different bnAbs in the pipeline, forward-looking thinking is needed to ensure adequate funding to bring promising candidates to the finish line and to chart an end-to-end pathway for access. With a focus on LMICs, product affordability and suitability will be imperative. Working with key stakeholders in critical countries, regions, and globally will be vital to cultivate the buy-in, accountability, and resources needed to advance bnAbs for infant PNP.

7.1. Defined need: Empowering well-informed and motivated transnational coalitions of civil society and communities to co-develop and deliver Action Plan commitments.

There is a need to develop an end-to-end accountability framework with civil society and communities at the core to ensure a person-centered approach to bnAbs development, launch, introduction, and roll-out. This includes addressing stigma, discrimination, and legal and policy barriers to availability and uptake.

PRIORITY ACTIONS:

7.1a. Implementing a community and civil society engagement strategy, linking with existing global, regional, and national initiatives, such as Africa Reach, the Global Alliance to End Pediatric HIV, the Community Working Group (see Section 3), and the Shot at Life advocacy initiative.[71-73] As part of this strategy, implement a learning agenda to increase bnAbs literacy, visibility, awareness, and eventual demand creation to enable meaningful inclusion and active partnership to support decision-making.

7.1b. Establishing a global bnAbs/mAbs Advisory Board, which coordinates with existing HIV CABs and leverages other disease platforms to advance advocacy for the development of bnAbs and mAbs that are suitable, affordable, effective, and accessible, with a focus on LMICs.

7.2 Defined need: Engaging LMIC governments to mobilize support for PNP bnAbs.

Governments and their Ministries of Health and Ministries of Finance are often only engaged late in the product development process, missing the opportunity to inform research agendas and garner political will, resulting in medical innovations that fall short of meeting public health needs in LMICs. With finite resources and competing health priorities, proactive efforts are needed to engage government stakeholders to build awareness, solicit and respond to questions on bnAbs, mobilize domestic co-financing, provide required evidence for policymaking, and support pathways for inclusion of suitable and affordable PNP bnAbs in the toolbox for HIV prevention in LMICs.

PRIORITY ACTIONS:

7.2a. Mobilizing critical resources to address funding gaps, track, and report on development pipeline progress (see Section 5.3b), and highlighting the prospective health and economic benefits of effective, suitable, and affordable bnAbs for PNP in various contexts.

7.2b. Facilitating engagement between national governments and the Task Force to ensure evidence is in place to support local decision-making and to co-develop needs assessments, budget estimates, training modules, and protocols for integrating PNP bnAbs into national HIV programs, once authorized for use.

7.2c. Developing a product introduction and scale-up roadmap as part of HIV National Strategic Plans, including target commitments paired with an accountability framework that tracks progress and gaps in access to bnAbs in LMICs.

7.3. Defined need: Ensuring global health actors take proactive measures to advocate for and adequately resource priorities as articulated in the Action Plan and to guarantee equitable access to bnAb innovations in a manner that advances LMIC health security.

The practices of developers and manufacturers significantly influence global access to new medical innovations, and if not managed appropriately, can result in high prices and products tailored for high-income settings, which widen access gaps in LMICs. Commercialization efforts tend to target high-income countries and intellectual property is too often managed in a manner that creates barriers to biosimilar market entry and affordable access. To enable the development of bnAbs that are affordable and suitable for LMICs and support their prompt scale-up to meet public health needs, access considerations should be integrated throughout the end-to-end development pathway.

As part of this access agenda, concerted efforts are needed to expand regional manufacturing of bnAbs and to ensure a supportive financing and procurement ecosystem. This includes the integration of antibodies into national essential medicines lists, health insurance schemes, and regional and/or global pooled procurement mechanisms.

PRIORITY ACTIONS:

7.3a. Mobilizing support to expand research and development (R&D), manufacturing, and deployment of bnAbs in LMICs through advocacy for recommendations outlined across the Action Plan.

7.3b. Ensuring broad stakeholder participation in advocating for Action Plan priorities, involving high-income and LMIC governments, multi-laterals, donors, developers, development finance institutions, regional and global health actors, manufacturers, civil society stakeholders, and community representatives.[74-76]

7.3c. Working in collaboration with country stakeholders to advance bnAbs that align with “target access profiles” for PNP and to advocate for transparent price sharing across countries to support affordable and sustainable target prices.

7.4. Defined need: Agreeing upon and ensuring adherence to key milestones in the time-to-population pathway by global health actors, developers, manufacturers, and regulators.

LMICs are often the last in line to reap the benefits of medical innovations. On top of the entrenched inequity in market-based approaches to innovation and delivery, barriers such as funding gaps along the R&D continuum, protracted normative guideline setting, manufacturing and supply challenges, delays in quality assurance and registration, and slow uptake of guidelines further contribute to a lack of timely access and availability to innovations in LMICs. A unified, transparent, and ambitious end-to-end time-to-population pathway with milestone commitments across all stakeholders could help ensure that scientific innovation leads to equitable and timely impact. This end-to-end pathway will be key to facilitating stakeholder ownership of and responsibility for an accelerated timeline to broad access while outlining the responsibilities of each party to adhere to transparent and pro-access practices and conditions.

PRIORITY ACTIONS:

7.4a. Setting targets, stage gates, and monitoring mechanisms to ensure adequate resourcing and on-time progress along the product development and time-to-population pathways to bnAbs accessibility. In the case of stalled progress, advocating for safeguards to ensure pathways to access.

7.4b. Mobilizing funding to support civil society and communities in implementing this advocacy agenda, carrying out community-led monitoring and evaluation, and holding stakeholders accountable for the implementation of access commitments.

7.4c. Working alongside the Regulatory and Policy Pillars to hold product developers, technical agencies, regulatory agencies, governments, and other global health actors accountable to ensure product submission and registration in high prevalence countries; accelerate review and decision timelines, while not compromising quality; and to establish normative guidance and to ensure its prompt dissemination within countries.

Conclusions

Meeting global targets to reduce peri- and post-natal transmission of HIV requires providing communities, parents, providers, and health systems additional options for infant PNP. Today, the landscape of HIV is changing, with exciting longer-acting prevention tools, such as Cabotegravir and Lenacapavir, on the market or the horizon. However, measures that focus on pregnant and breastfeeding people and their infants have so far been insufficient to end new HIV infections in infants.[77]

Ensuring additional strategies to close gaps in the HIV prevention cascade for infants is both an ethical and public health imperative. Measures as outlined in this Action Plan can build the preclinical, clinical, and policy evidence; establish the regulatory pathways; and advance the manufacturing, access, advocacy, and community partnership strategies needed to accelerate the development, availability, acceptability, accessibility, and widespread adoption of bnAbs as a complementary strategy for PNP.

This Action Plan details the priority needs and the concurrent actions required to advance this goal. It harnesses the perspectives, experiences, and expertise of leading experts and key constituencies from around the world with the aim of galvanizing action and mobilizing both the political will and resources that will be required. If successful, it is anticipated that bnAbs for the prevention of peri- and post-natal prophylaxis can serve as a trailblazer, providing proof of concept and forging pathways for broader mAbs access in LMICs. Moreover, the Task Force's approach of integrated, multisector priority setting early in research and development can hopefully serve as a model for priority-setting across a broader range of innovation areas.

Box 4: Proposed Action Plan for bnAbs for HIV PNP
Enabling Science 1.1. Characterization of contemporary HIV-1 viruses transmitted peri-natally and through breastmilk. 1.2. Evaluating PT80 as a predictive biomarker of the prophylactic efficacy of bnAbs against HIV breastmilk transmission in infant NHP SHIV models. 1.3. Continued discovery and advancement of bnAbs to nourish a pipeline of products that align with preferred characteristics, including optimal combinations for therapeutic as well as prevention indications.
Clinical Development 2.1. Identifying and advancing bnAbs and bnAb combinations that meet criteria for high impact in the highest prevalence settings. 2.2. Advancing strategies for rapid progression towards a licensed indication for peri-natal and post-natal prophylaxis. 2.3. Accelerating strategies for efficacy evaluation of bnAb combinations. 2.4. Exploring clinical trial designs that would enable use of bnAbs as an alternative to, instead of an add on to, standard of care for peri- and post-natal HIV prevention.
Community Engagement 3.1. Early and sustained partnership with communities to create a product development ecosystem that is for communities and by communities. 3.2. Harnessing community-driven evidence generation to inform the product development continuum.
Regulatory Strategy 4.1. Harnessing learnings from complementary disease and product areas to inform regulatory pathways for bnAbs. 4.2. Early regulatory engagement to guide and accelerate regulatory pathways for forthcoming bnAb-based products. 4.3. Evidence frameworks to move toward immuno-bridging approaches. 4.4. Strengthening regional capacity and innovative pathways for regulation of mAb-based products.
Manufacturing and Access 5.1. Defining the key access measures needed at each stage of product development, from early discovery through launch, to ensure prompt bnAbs accessibility. 5.2. Evaluating the relative impact of innovative manufacturing platforms and technologies on lowering the cost of goods and advancing prioritized strategies. 5.3. Ensuring commercialization models and voluntary licensing strategies for bnAbs support prompt and broad accessibility and supply sustainability in settings where infant HIV acquisition is high.
Policy 6.1. Defining the evidence required for potential inclusion of bnAb-based infant PNP into WHO guidelines. 6.2. Clarifying pathways and advancing a coordinated strategy for global policy development for bnAbs and other mAb-based products. 6.3. Supporting evidence generation and implementation research and defining policy pathways for timely country adoption of improved options for PNP, including bnAbs, once authorized for use.
Advocacy 7.1. Empowering well-informed and motivated transnational coalitions of civil society and communities to co-develop and deliver Action Plan commitments. 7.2. Engaging LMIC governments to mobilize support for PNP bnAbs. 7.3. Ensuring global health actors take proactive measures to advocate for and adequately resource priorities as articulated in the Action Plan, and to guarantee equitable access to bnAb innovations in a manner that advances LMIC health security. 7.4. Agreeing upon and adhering to key milestones in the time-to-population pathway by global health actors, developers, manufacturers, and regulators.

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Declarations of Interest

The following authors would like to declare their affiliations with, or involvement in, organizations or entities with financial or non-financial interests in the subject matter discussed in this Action Plan:

Lynne Mofenson has served as a consultant for WHO on issues related to the safety of antiretroviral drugs for the prevention of vertical HIV transmission.

Esteban Burrone, Aditi Das, Lobna Gaayeb, Ike James, Sébastien Morin and Manuele Piccolis are employed by the Medicines Patent Pool (MPP), a non-profit organization backed by the United Nations that negotiates public health driven voluntary licenses with pharmaceutical innovators with the aim of accelerating access to patented medicines in LMICs. The topic of this document relates to access to bnAbs for HIV PNP, which could be facilitated by voluntary licensing and technology transfer through MPP.

Anja Van der Westhuizen, Katerina Chapman, Ethel Makila, George Owino, Jon Heinrichs, Marion Gruber, Shelly Malhotra, and Vincent Muturi-Kioi are employees of IAVI, a nonprofit product development partnership whose pipeline includes HIV prevention products, including bnAbs.

Ana Puga, Annie Buchanan, Peter Leone, Ralph De Masi, Shaun Mellors, Christine Lampkin, Josephine Osikena, Nneka Nwokolo, and Lionel Tan are employees of ViiV Healthcare, whose pipeline includes HIV treatment and prevention products, including ARV and antibody-based options.

Ameena Goga and Philippe Van de Perre are part of the SAMRC-sponsored PedMAb study, a Phase 1 study evaluating the safety and PK of two bnAbs in newborns, and the SAMBULELO study evaluating one bnAb in newborns. Both studies were awarded in 2018-2020.

Elizabeth McFarland is a chair/co-chair/member of IMPAACT protocol teams that evaluate the safety and PK of several bnAbs in newborns, infants, and children and has served as a consultant on the use of bnAbs in infants for WHO workshops and seminars.

Coleen K. Cunningham is the protocol Chair for IMPAACT P1112, a Phase 1 study evaluating the safety and PK of three monoclonal antibodies in HIV-exposed infants and P2037, a Phase 1 study of two monoclonal antibodies HIV-exposed infants.

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