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CONFERENCE SUMMARY

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HIV Prevention in a Time of COVID-19: A Report from the HIVR4P // Virtual Conference 2021

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Abstract

The HIV Research for Prevention (HIVR4P) conference catalyzes knowledge sharing on biomedical HIV prevention interventions such as HIV vaccines, antibody infusions, pre-exposure prophylaxis, and microbicides in totality—from the molecular details and delivery formulations to the behavioral, social, and structural underpinnings. HIVR4P // Virtual was held over the course of 2 weeks on January 27–28 and February 3–4, 2021 as the coronavirus disease 2019 (COVID-19) pandemic continued to inflict unprecedented harm globally. The HIVR4P community came together with 1,802 researchers, care providers, policymakers, implementers,

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and advocates from 92 countries whose expertise spanned the breadth of the HIV prevention pipeline from preclinical to implementation. The program included 113 oral and 266 poster presentations. This article presents a brief summary of the conference highlights. Complete abstracts, webcasts, and daily rapporteur summaries may be found on the conference website (https://www.hivr4p.org/).

Keywords: HIV, HIVR4P, vaccine, antiretrovirals, microbicides, PrEP, South Africa, prevention, clinical trials, broadly neutralizing antibodies (bNAbs), TaSP

Introduction

The HIV Research for Prevention (HIVR4P) 2020 conference was planned, fittingly, to occur in the country with the highest number of new HIV infections each year, South Africa.[1] In August 2020, amidst a new pandemic, the International AIDS Society announced that HIVR4P would, for the first time, be postponed and conducted virtually. By the time HIVR4P // Virtual conference began at the end of January 2021, coronavirus disease 2019 (COVID-19) had infected ~100 million people (~1% of all humans) in its first year.[2] This is in stark contrast to the slow burning pandemic of HIV with 76 million people infected in four decades.[3] Because many pioneering investigators in HIV were simultaneously on the frontlines of the COVID-19 pandemic, the conference, for the first time, introduced an opportunity to discuss another pandemic.

The quick successes of the COVID-19 response were certainly aided by the platforms developed for HIV, and will in turn likely lead to learnings in HIV vaccine development. The HIV and COVID-19 syndemics will also undoubtedly impact the trajectory of both diseases over the next decade. The HIV prevention research community brought HIVR4P // Virtual to their homes and workplaces across different time zones. Survey results from conference delegates suggest that HIVR4P // Virtual may have been especially successful in broadening access to the conference among African researchers, implementers, and community advocates. In this article, we present the prominent ideas that emerged. Despite the challenges that were a feature of 2020, HIV research innovation, interventions, and implementations did not disappoint.

Vaccines and Antibody Infusions: Trials, Triumphs, and Tribulations

Decades of HIV vaccine research contributed to the prompt and adept development of COVID-19 vaccines

Multidisciplinary HIV vaccine research paved the way for the COVID-19 vaccine endeavor in at least two important ways. The first contribution is that existing expertise gained from the HIV field in structure-based reverse vaccine design[4] was galvanized into designing the stable prefusion spike immunogen used in the COVID-19 vaccines. Structure-based reverse vaccine design uses X-ray crystallography, which measures the angles and intensities of X-ray beams diffracted off of crystallized viral envelope spike when it is bound to an antibody derived from an infected person, to determine the structure. Once the binding site of the antibody is known, a complementary viral antigen is reverse engineered to serve as the basis of vaccine candidates.

Structure-based reverse vaccine design succeeded immediately to produce effective COVID-19 vaccines [Presentation PL01.01; Supplementary Table S1]. However, it has not yet delivered a highly effective vaccine against HIV, an infection with considerably more complicated challenges. Unlike COVID-19, antibodies elicited by HIV vaccines have not yielded protection in most human efficacy trials except for the partial and waning protection observed in the modified-intention-to-treat analysis of RV144.[5] The second contribution is that existing infrastructure and expertise at the HIV trial networks and the global HIV clinical trial sites allowed for COVID-19 vaccines to be tested with proficiency in clinical trials [Presentation PL01.01].

Infusions of VRC01 monoclonal broadly neutralizing antibody did not prevent HIV infection overall in the Antibody-Mediated Prevention trials, but viral sensitivity to VRC01 determined its protection efficacy

In natural HIV infection, antibodies that can disable most HIV strains (broadly neutralizing antibodies, bNAbs) develop after a couple of years in a minority of individuals.[6] The Antibody-Mediated Prevention (AMP) trials intravenously infused HIV-uninfected volunteers every 2 months with bioengineered copies of VRC01, an antibody that had been isolated in 2009 from a slow-progressing HIV-infected individual [Presentation RT03.01]. In preclinical studies, VRC01 demonstrated 70%–90% neutralization breadth measured against a panel of viruses in the laboratory [Presentation RT03.04].

Retention in AMP was ~96% for infusion visits, and participants stated a good trial experience [Presentation RT03.02]. AMP has been designed primarily to address the main question of whether a lower and higher dose of VRC01 monoclonal antibody can prevent HIV infection in diverse human and viral populations [Presentation RT03.03].

VRC01 proved safe and tolerable, but overall did not have protection efficacy in both of its Phase 2b proof-of-concept trials: one among women at risk in Africa (HVTN 703/HPTN 081) and the other among men and transgender persons who have sex with men in the Americas (HVTN 704/HPTN 085) [Abstract HY01.01LB].[7]

In the laboratory, researchers estimated HIV sensitivity to VRC01 by first infecting TZM-bl cells once *in vitro* with pseudoviruses based on breakthrough HIV strains from the placebo and VRC01 groups, and then measuring viral neutralization titers. VRC01 could neutralize about a third of breakthrough viruses, with most from the placebo group. In a subset analysis estimating prevention efficacy by considering as endpoints only the breakthrough infections that had VRC01 sensitivity (80% inhibitory concentration, $IC_{80} < 1$ μg/mL), HIV incidence was lower in the VRC01 group compared with placebo recipients (estimated prevention efficacy 75.4%, 95% confidence interval: 45.5–88.9).

In summary, VRC01 could prevent HIV acquisition if one is exposed to VRC01-sensitive HIV [Presentation RT03.04]. These findings support researching the administration of multiple antibodies with a variety of neutralization profiles to prevent infection with HIV, a virus with

unparalleled diversity. This is being approached through a bispecific antibody or combination of antibodies (e.g., 3BNC117 plus 10-1074) [Presentation RT01.02]. A further discovery from AMP was that the *in vitro* serum neutralization titer was a predictive marker for *in vivo* prevention efficacy, similar to findings from the nonhuman primate (NHP) studies. The neutralization assays could be used to calibrate similar studies in future [Presentation RT03.04].

Implications of the AMP studies were deliberated throughout the conference. The field still needs to discover an efficacious antibody/regimen. Next-generation antibodies are optimizing the route and frequency of administration (VRC07-532LS allows for subcutaneous administration and has a longer half-life) and diversifying binding locations (M4008_N1 binds to the HIV-1 V3 crown region) [Abstract OA03].[7] There was also a presentation from an *in vitro* study about another consideration: how a naturally occurring antibody, IgA, could block the function of VRC01. Using samples from HIV-uninfected individuals, high levels of plasma IgA inhibited the function of some broadly neutralizing antibodies—VRC01, PGT121, VRC03, and 3BNC117—but not 10-1074 [Abstract OA01].[7]

Finally, because the VRC01 antibody did not prevent HIV acquisition overall, there are repercussions on the design of vaccines being developed to induce broadly neutralizing antibodies. Hypothetically, a vaccine aiming to induce only VRC01-like antibodies may be as nonefficacious as VRC01 itself.

Not to be discouraged, several strategies to improve the quality and function of vaccine-elicited VRC01 were presented at the conference. The first showed a vaccination strategy in the Vh1-2/LC mouse model to elicit VRC01-like antibodies able to neutralize the N276 glycan. This included a prime of naked or glycan-masked eOD-GT8 60-mer followed by gp120 cores with increasing glycan coverage and a final boost with BG505 trimer to increase breadth and potency [Abstract OA08.02].[7] Another intriguing strategy to boost B cell proliferation in germinal centers and activate B cells expressing desired unmutated VRC01-class heavy and light chains is the use of iv4/iv9 bispecific anti-idiotypic monoclonal Abs [Abstract OA08.05LB].[7]

Novel HIV vaccine candidates

Although much is still being learned about interactions between immune system components, and the maturation pathway from germline antibodies to broadly neutralizing antibodies are yet to be fully elucidated, current vaccine design is using systems vaccinology and bioinformatics to aid HIV vaccine design. A key challenge remains the rapidly evolving viral diversity.

Key vaccine strategies showcased at the conference are given in Table 1. Major themes in vaccine design were (1) harnessing messenger RNA to deliver HIV antigens, after the platform demonstrated successful emergency-use authorization for highly effective COVID-19 vaccination; (2) germline targeting, which is the induction of broadly neutralizing antibodies through vaccination, and (3) selective T cell vaccines that induce CD8 but not CD4 cells.

Back to Basics: Measure, Design, Test, and Repeat

Engineering next-generation antibodies for improved function

As made more apparent by the reported failure of VRC01 to effectively protect overall in the AMP trial,[8] next-generation broadly neutralizing antibodies with increased potency used in combination are likely to be the most promising way forward for the success of passive immunization strategies. However, it is encouraging that beyond this, there are approaches to improve the antibodies themselves. These do not only focus on neutralization but include Fc-mediated functions. Given the requirement for several broadly neutralizing antibodies to engage Fc receptors to provide optimal protection from HIV,[9,10] it was heartening to see groups grappling with the detailed Fc mechanisms and how to translate these into workable vaccine and passive immunization strategies.

With important implications for the AMP trial, Fc antibody variants of VRC01 and VRC07-523 with longer half-lives (M428L/N434S), typically used in clinical trials, showed differential distribution in the tissues of NHPs. This is despite these antibodies being clonally related and having the same Fc modifications. This may be a result of their differential Fc glycosylation profiles [Abstract OA01.01].[7] Similarly, Fc variants, that either enhance or deplete Fc receptor binding of the same parent antibodies, are also associated with unique cellular subsets. This suggests that not only will the mutations influence binding to Fc receptors as intended, but may also alter antibody localization and, therefore, availability in the mucosa.

Although it is clear that the Fc portion has impact on protection for broadly neutralizing antibodies through Fc effector function, it is emerging that it can also influence neutralization. To illustrate this, antibody subclass was shown to alter neutralization potency in an antibody lineage [Abstract OA08.01].[7] This suggests that subclass switching in concert with changes in the Fab portion may act as a mechanism of neutralization escape.

The association of Fc effector function with the RV144 vaccine efficacy and the formation of FcγR immune complexes is required for optimal Fc effector function elicitation.[11] Therefore, a computational method to predict levels required of different subclasses to achieve this was presented. In this model the biggest enhancement of function in RV144 was seen by increasing Fc receptor affinity for IgG1 antibodies, whereas enhancing binding to antigen had a limited effect on Fc receptor complex formation [Presentation SY01.05]. This gives the field insight into how to tune Fc effector function in a vaccine setting, likely through the elicitation of favorable Fc glycosylation.

In contrast, a study showing the success of single-chain variable fragments of broadly neutralizing antibodies used in combinations that do not have the Fc portion was reported [Abstract OA08.03].[7] Despite having a significantly reduced neutralization potency compared with the parent bNAbs, in combination these still showed remarkable potency and 100% breadth. These constructs have the added benefit of being cost-effective and suitable for adeno-associated virus-vectored immunoprophylaxis given their small size, suggesting their promise for targeted passive immunizations in difficult-to-reach tissues. However, the lack of Fc portion limits their potential targeted use only for prevention of HIV-1 acquisition.

Networking big data to inform vaccine design

The power of large and diverse data sets to examine multifaceted networks and accurately capture the complexity of the immune system was on full display. The interaction between different arms of the immune system is beginning to

Table 1. Novel HIV Vaccine Candidates

Vaccine strategy	*Vaccine*	*Results [conference presentation/abstract]*
Messenger RNA	HIVConsvM: mRNA lipid nanoparticle encoding a tetravalent antigen from conserved regions of HIV	In a preclinical model, polyfunctional T cell responses were observed [Abstract OA12.03][7]
Viral vectors	Vesicular atomatitis virus containing HIV-1 Env chimeras with or without SIV gag in absence of VSV-G and with or without the Ebola glycoprotein	Provides protection in macaques against low-dose cross-clade SHIVenv_SF162_P3 challenge [Abstract OA12.04LB][7]
	MVAGD5: Modified Vaccinia Ankara expressing clade C mosaic gag and Du151 envelope	In animals, MVAGD5 elicited neutralizing antibodies to Tier 1A and Tier 1B viruses but not to Tier 2 [Abstract OA12.05][7]
	Cytomegalovirus vector	Elicit effective early effector memory T cell responses: MHC-E restricted CD8 cell responses under viral genetic control. Phase 1 safety and immunogenicity trial for a spread deficient (Δpp71) HCMV/HIV vector is underway [Presentation SY09.03]
Protein subunit: native-like envelope trimers aiming to induce broadly neutralizing antibodies	ASO1B-adjuvanted eOD-GT8 60mer	IAVI G001, a Phase I trial of eOD-GT8 60mer, demonstrated safety and tolerability, and that 97% of vaccine-recipients produced VRC01-like antibodies [Presentation SY07.01]
	BG505 SOSIP.664, a Clade A gp140	The phase I clinical trial IAVI C101 is testing adjuvanted BG505 SOSIP.664 gp140 [Presentation SY07.03]
	ConM and ConS envelope trimers	In EAVI 2020-01, IgG and neutralizing antibodies were produced [Presentation SY07.04]
	ConMSOSIPv7, a Consensus M envelope trimer	ACTHIVE001 is enrolling [Presentation SY07.05]
Combinations	Clade C ALVAC plus clade C gp120 adjuvanted with MF59 versus aluminum hydroxide versus no adjuvant	In HVTN 107, an early-phase trial, co-administration of ALVAC+gp120+MF59 induced the highest antibody response rates and magnitudes. Alum-adjuvanted gp120 plus ALVAC downregulated early serum cytokine responses but MF59 induced sustained elevated serum cytokine levels [Abstract OA18.03].[7] Alum-adjuvanted gp120 administered in a prime/boost regimen with ALVAC reduced early systemic serum cytokine and chemokine responses to the vaccine, while MF59 induced a diverse immunomodulatory cytokine profile [Abstract OA18.02][7]
	Prime-boost Adenovirus 26 with synthetic mosaic antigens plus trimeric gp140 adjuvanted with aluminum phosphate	Efficacy trials HVTN 705 and HVTN 706 ongoing [Presentation SY09.01]
	DNA/SeV-CaV11	In rhesus macaques, induced Gag/Vif-specific CD8 but not CD4 T cells and protection against repeated intrarectal low-dose SIVmac239 challenge in 8 of 12 macaques [Abstract OA09.02]

be unraveled with the advent of high-throughput technologies and the machine-learning techniques to understand the relationship between data. Certainly, this has been particularly powerful in understanding responses postvaccination [Presentations SY08.04 and SY01.03].

In particular, relationships between innate, adaptive, demographic, and microbiome responses were used to define responders and nonresponders in two different HIV vaccine trials [Presentation SY01.01]. Genes, associated with bacterial diversity before vaccination, were correlated with the development of neutralizing antibodies and were found to be biomarkers of responders in the second trial. This provides the opportunity to define non-responders and potentially alter dosage to result in a desired vaccine response.

The ability of vaccines to train innate cells, including monocytes, dendritic cells, and neutrophils, was also studied using these integrated methods in a modified vaccinia virus Ankara vaccine regimen in NHPs [Presentation SY01.03]. Responses were dependent on the vaccine schedule and the route of administration, and innate immune cells were phenotypically more mature/activated suggesting they were more

equipped to respond to revaccination. The unappreciated role of natural killer cells in the response to bacille Calmette-Guerin vaccination in infants and revaccination in adolescents, also highlighted the cross-talk of the innate and adaptive immune response and the strength of integrated studies [Presentation SY03.2].

In addition, the detailed analysis of the antibody response to immunization of NHPs with NFL trimer required the examination of large data sets to understand the expansion of 180 clonotypic lineages. Completed by combining single B cell sequencing of antibody heavy chains with high-throughput bulk repertoire sequencing and antibody lineage tracing analysis, this study highlighted that achieving high levels of somatic hypermutation with repeated boosting leads to functional antibody improvements, even in minimally expanded lineages [Presentation SY08.02].

T cells in COVID-19 and HIV

Although the role of T cells in HIV dysregulation is well described, studies expanded on their role as HIV therapeutic intervention, function in tissues as well as their somewhat diminished response in severe COVID-19 infection.

Despite T cells being the major target of HIV infection, a study made use of novel chimeric antigen receptor T cells transduced with 4-1BB and CD28 domains and further engineered to protect them from HIV infection that were then shown to prevent CD4 depletion [Abstract OA20.02].[7] In the hunt for reliable T cell markers, T follicular regulatory cells are difficult to separate from T follicular helper cells and a study presented novel biomarkers (DPP4 and FCRL3) of cells from lymph nodes as well as PBMCs [Presentation SY06.01]. This opened up the possibility of a more mechanistic study of these cells.

Similarly, although the $CD8^+$ T cell role in HIV infection is well understood, it was reported that most HIV-specific $CD8^+$ T cells in tissues display tissue-resident memory-like phenotypes and those found in the lymph node from elite controllers, in which they are increased, efficiently suppress HIV [Presentation SY08.03]. Their low presence in the cervix in precancerous conditions may also suppress the cell-mediated immune response to HIV [Abstract OA20.04].[7]

In vaccination, the cellular mucosal responses including alterations to $CD4^+$ T cells elicited by additional late boosts to the RV144 ALVAC-HIV/AIDSVAX B/E prime/boost intramuscular vaccine regimen (RV306) were discussed [Abstract OA22.02].[7] These late boosts induced increases in alpha-4 beta-7 integrin expression on CD4 T cells indicative of homing to tissues as well as increases in viral-specific Th17 cells and IgA plasmablasts. This compartmentalization of the quantity and quality of the immune response upon vaccine administration between the periphery and mucosa is imperative to understand for future vaccine regimens.

In a much-anticipated illustration of how HIV research infrastructure enabled quick translation to COVID-19, immunological memory that included antibodies, B cells, and T cells was shown to extend to at least 8 months post-SARS-CoV-2 infection. Type 1 and 3 interferon (IFN) responses were very much delayed in severe infection leading to a particularly stunted T cell response. Despite this, 50% and 95% of infected individuals had detectable SARS-CoV-2-specific $CD8^+$ and $CD4^+$ T cells, respectively, at 8 months postinfection [Presentation SY08.01]. Of importance, receptor binding domain antibodies were not predictive of the T cell response, suggesting that serology tests would not be able to reflect T cell function. T cells targeted almost 1,000 different epitopes with M, N, and spike proteins only accounted for 11%–27% of $CD4^+$ responses, further corroborating that antibody targets are not immunodominant for T cells [Presentation SY08.05].

Transmission at the mucosa

Clearly, understanding the site and the mechanism of the initial viral transmission in different population groups is imperative to the advent of new catered prevention strategies, and was therefore a major theme of discussion at the conference.

One such population group is neonates and infants. The importance of not taking our eyes off of preventing mother-to-child HIV transmission was highlighted as a remaining concern of clinical significance. There is a need to utilize many of the prevention strategies already in place for adults to further curb the spread of HIV in infants. Broadly neutralizing antibodies passively administered within 24 h after birth in NHPs successfully eliminated simian-human immunodeficiency virus (SHIV) viral reservoirs [Presentation PL02.01]. There is also progress toward harnessing the dynamics of early-life immunity to elicit neutralizing antibodies by vaccination in infants.

Impressively, immunization of infant NHPs with BG505-SOSIP trimers showed the development of neutralization. A similar vaccination strategy in human infants, HVTN135 is planned using the HIV envelope immunogen, CH505. There are also significant differences in disease progression between neonates and infant NHPs, with T cell response being largely nonexistent in newborns, who failed to mount any significant antiviral responses, rapidly developing pathogenesis [Abstract OA20.03][7] indicating the need to continue to probe the immune system at these different stages of life.

Risk factors for infection and the profile of cells initially infected were also in the spotlight. After 48 h, Th17 were some of the earliest cells infected in NHPs following rectal challenge [Abstract OA22.03].[7] Surprising was the predominance of HIV infection in the heart, currently under investigation. Genital epithelial cells were shown to differentially transcytose X4 and R5 HIV-1 viruses linked to the regulation of their respective receptors and type 1 IFN responses [Abstract OA22.01][7] underscoring the potential to manipulate this for prevention. Risk of infection was associated with the luteal phase of menstruation in NHPs [Abstract OA22.04][7] and the increased density of HIV target cells in foreskin tissue after sex likely as a result of coating of the penis with IL-8 rich cervicovaginal secretion [Abstract OA22.05].[7]

Poor disease progression was noted in men who have sex with men and individuals with STIs who showed the transmission of the highest number of transmitted/founder viruses and efficient cell-to-cell spread. Lactic acid, a metabolite produced by beneficial Lactobacillus species in the female genital tract, was likely to aid in preventing HIV infection through its anti-inflammatory and epithelial barrier integrity enhancing properties *in vitro*[12] [Presentation SY06.04].

In addition to risk factors, the assessment of transmission pathways in communities is indispensable for guidance on

where to focus prevention. HIV transmission is primarily within the bounds of communities known to each other. Men between the ages of 25 and 35 years transmit HIV four times more than women within transmission clusters [Presentation PL03.01]. Likely as a result of higher viral load, most HIV transmissions are driven by recently infected individuals with ~40% transmission occurring within the first year after infection.

Understanding viral latency to cure HIV

As the old adage goes, prevention is likely better than cure, but with ~40 million infections worldwide the cure of HIV is an important goal. Interventions to kill already infected cells included a combination of neutralizing and non-neutralizing antibodies that was found to be effective in the clearance of reactivated cells latently infected with neutralization-resistant viruses through antibody-dependent cellular cytotoxicity (ADCC) [Abstract OA14.01].[7] Elimination of infected cells through this same cytotoxic mechanism could be achieved by novel Ab-like molecules fused to domains 1 and 2 of soluble CD4, enabling the opening of the trimer. This allows for potent ADCC-mediating antibodies to target sites previously inaccessible to them [Abstract OA01.05LB].[7]

Mechanisms of HIV latency, including the role of $CD8^+$ T cells and noncytolytic mechanisms that appear to maintain the latent reservoir in $CD4^+$ T cells, may affect the effectiveness of interventions using latency reversing agents [Abstract OA14.02].[7] In addition, cell-to-cell transmission may promote HIV latency but may be targeted by sphingosine-1-phosphate (S1P), which reduces total and integrated HIV-1 DNA in $CD4^+$ T cells and reduces the proliferative state in these cells [Abstract OA14.04].[7]

Antiretrovirals: Where Do We Stand?

New technologies to close-in on the moving target

Winnie Byanyima [Presentation PL01.02] reflected that although there was encouraging progress toward reducing HIV-related mortality, we have missed the 2020 HIV targets.[13] COVID-19 has highlighted the fragility of the HIV response, emphasizing the need for increasing efforts to reach the 2030 targets. Although scientific progress has been phenomenal, Byanyima highlighted inequality as one of the major challenges in achieving our goals; specifically, the most vulnerable populations need affordable access for scientific innovations to be made meaningful.

The ambitious new UNAIDS target is for 95% of people at risk of HIV acquisition using combination prevention by 2025.[14] With the targets for favorable societal environments met, 430,000 HIV-related deaths will be averted and 2.6 million new infections will be prevented. Strengthening the provision of HIV prevention, and reducing stigma and discrimination will put us on the path to End AIDS by 2030.

Four large Treatment as Prevention (TaSP) studies found that Universal Test and Treat has had a modest impact on incidence [Presentation PL04.01]. This may, in part, be owing to studies not being powered to detect moderate reductions in HIV risk. In addition, the models were not age stratified, which is important, because sexual activity is higher in younger ages and antiretroviral therapy (ART) coverage is higher in older ages. These findings highlight the importance of targeted efforts to increase HIV testing and linkage to care, and support retention in care to promote viral suppression.

Accordingly, there were a number of new technologies with promising findings. Sinead Delaney-Moretlwe [Presentation PL02.03] summarized preexposure prophylaxis (PrEP) options currently in the research pipeline. Important considerations include the following: what the users want, cost, coverage, and clinic access as well as what drug and delivery mechanisms are available.

Trials among cisgender women and pregnant women using daily oral emtricitabine/tenofovir alafenamide fumarate are in the pipeline, as well as a phase I trial using a topical TAF insert combined with elvitegravir. Long-acting cabotegravir (CAB LA) has been shown to be safe and effective in cisgender men, transgender women, and cisgender women in the HPTN 083 and HPTN 084 trials and gives an adherence advantage with the 8-weekly injections. After a single intramuscular injection, CAB LA was well tolerated and was detected in all tissues relevant to HIV acquisition, demonstrating that long-acting CAB may be an effective single PrEP agent [Abstract OA04.03].[7]

In a study investigating the relative efficacy of daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and CAB LA, CAB LA was superior to TDF/FTC [Abstract HY01.02LB].[7] Women in the CAB LA group had an 89% lower risk of infection where weekly CAB injections likely had adherence advantage over daily oral TDF/FTC. CAB is also being developed for use in implants and microarray patches (MAP) with positive results from preclinical studies.

Although participants preferred the smallest possible size MAP for ease of use and being discrete, some participants said they would accept larger patches with longer duration, between 1 and 3 months [Abstract OA04.01].[7] The benefits of using the MAP included reduced clinic visits, increased agency, reduced stigma, and reduced burden on the health care system. Alexandra Minnis [Abstract OA06.04][7] evaluated the acceptability of multipurpose prevention technologies by heterosexual couples. In general, women wanted to involve their partners in their decision. Most preferred oral tablets that needed to be taken for a longer duration of about a month. The study underscored the need for a diverse mix of choices to accommodate couples' needs.

An 8-week CAB reservoir implant in rhesus macaques found that the CAB implant demonstrated highly reproducible findings, an excellent safety profile, and no leakage [Abstract OA04.04].[7] High pharmacokinetic (PK) levels were detected for up to 16 weeks and no adverse events at either 4 weeks or 3 months.

Islatravir has high potency to inhibit the reverse transcriptase to suppress HIV-1 and drug-resistant variant replication and has a 190-hour (1 week) half-life after oral administration, making it a long-acting oral agent. Sharon Hillier's [Abstract OA04.05LB][7] PK results showed that the lowest dose of Islatravir that provided full protection to rectally challenged macaques and full antiviral efficacy in humans living with HIV. Islatravir trough concentrations for 60 and 120 mg doses were above the prespecified PK thresholds (0.5 pmol/10^6 PBMCs), demonstrating that there is leeway for missed doses.

Finally, Ivana Massud [Abstract OA04.02][7] shared findings on the safety and efficacy of long-acting polycaprolactone PrEP against vaginal SHIV in six pigtail

macaques versus eight controls. Seven of the controls were infected after a median of four challenges. All six macaques in the treatment condition remained uninfected after 6 weeks and until the 4-month follow-up. An *ex vivo* pharmacological profile of tenofovir (TFV) and TAF in human foreskin tissue found greater potency of TAF than TFV against penile HIV transmission.

Mucosal immunology, microbiology, and HIV susceptibility

Eric Armstrong [Abstract OA19.01][7] reported data from participants receiving treatment during the phase 2b randomized placebo-controlled trial of LACTIN-V (Lactobacillus crispatus CTV-05). Treatment with LACTIN-V reduced recurrence of bacterial vaginosis and increased L. crispatus CTV-05 colonization. LACTIN-V may represent a novel strategy to reduce HIV risk among women. When inserted vaginally, a silk fibroin platform encapsulating HIV inhibitors, including lectin Griffithsin (Grft), readily dissolved and released Grft [Abstract OA19.04LB].[7] Tissue biopsies were fully protected against *ex vivo* SHIV infection. Focus groups with men and women indicated a preference for silk inserts over oral PrEP because it allows for spontaneous protection in a more attractive, relatable packaging.

Participants reported rectal delivery of dapivirine (DPV) gel through a vaginal applicator and coital stimulation device were easy to use [Abstract OA16.03].[7] Rectal application of DPV 0.05% gel was both safe and acceptable to HIV negative male and female adults and PK results showed detectable median DPV levels in both plasma and rectal fluid [Abstract OA16.05].[7]

PrEP is here: Considerations to achieve continued use

AVAC's Global PrEP Tracker [Abstract OA11.01][7] indicates that PrEP initiations have increased sixfold from 102,446 in 2016 to 651,586 in 2020. Annual growth, however, has slowed, with total PrEP initiations globally (928,750) falling short of UNAIDs' target of 3 million. This slower than anticipated uptake [Abstract OA11.03][7] and retention [Abstract OA11.04][7] indicates a need for investment in demand-generation based on user preferences [Abstract OA11.02][7]. Integrated STI and PrEP services with asymptomatic testing among PrEP users may be beneficial [Abstract OA16.01].[7]

Reframing adherence

WHO estimates 50% adherence to long-term medication, with high health and economic cost of nonadherence [Presentation SY05.01]. Adherence rates vary between patients and within the same patients over time and across treatments, and nonadherence may be a norm, not an exception. Because subjective measures of adherence are less reliable, there may be benefits to pharmacological adherence assessment, including pharmacy refill data, automatic compilation of dosing history data, electronic monitoring, and ingested sensor devices [Presentation SY05.04].

Gcobisa Madlolo [Presentation SY05.02] (recipient of Omolulu Falobi award 2018) presented the perspective of a PrEP user who revealed that it was not easy to start on PrEP. She eased into the PrEP journey by finding a PrEP ''buddy'' for motivation, used phone reminders and adherence cards. Moreover, improving knowledge, decreasing the cost of obtaining PrEP, addressing stigma and encouraging social support can support adherence [Presentations SY05.02 and SY05.03].

Achieving the unfulfilled promise of prevention of mother-to-child transmission

Philippa Musoke [Presentation SY02.01] presented the progress toward the elimination of mother to child transmission (MTCT), defined as <20,000 infant infections by 2020 and elimination by 2030. Although elimination of MTCT is feasible and some countries are well on their way, this goal requires >90% of mothers with HIV to be on treatment.

In South Africa, the national lockdown had seen a significant reduction in clinic headcount under the age of 5 years, indicating a need for community strategies to encourage continued antenatal care and ART uptake and adherence during pregnancy [Presentation SY02.03]. Multilateral engagement with community leaders, state policymakers, and those who use health care services can offer strategic opportunities to address access inequality [Presentation SY02.03]. Finally, passive antibody prevention in HIV-exposed infants demonstrates that the approach is acceptable, no safety concerns are apparent, and is likely to be cost-effective [Presentation SY02.04].

Addressing the Global HIV Pandemic Through Social Science, Implementation, and Advocacy Efforts

Presentations in the areas of implementation, social science, and advocacy advanced the discussion of how we situate our work in the context of successes and challenges in addressing the global HIV pandemic; how we understand the barriers and facilitators of getting broad and sustained uptake of HIV prevention and treatment services; and how we address these challenges in light of intersectional identities and the need for tailored service provision.

The presentations touching on this area acknowledged the importance of context in determining the success of prevention at the population level; the heterogeneity of resources, risks, and access to prevention tools; the corresponding need for a robust set of PrEP formulations and approaches; the need to include the diverse perspectives and people in the formulation and testing of prevention approaches; and the ongoing barriers, including stigma and COVID-19, to realizing the promise of prevention at the population level.

Global successes, opportunities, and contexts

Plenary presentations set the stage broadly by celebrating our collective successes in reducing new HIV infections, increasing coverage of ART for people living with HIV, and growing PrEP programs. But many of those same presentations acknowledged that even with declining new infections and increasing treatment, we are still not on the trajectory to meet global prevention targets.

Winnie Byanyima started the conference [Presentation PL01.02] with a passionate call for us to celebrate the milestone of the lowest HIV-related annual deaths since 1989 while acknowledging that we are failing in our response. She

encouraged us to see the global epidemic through an ''inequality lens'': although there are broad successes in reducing HIV transmissions in some settings, like Eswatini, Thailand, Vietnam, and among gay men in London, in many other places the conditions that permit such progress—access to health care without discrimination and significant funding for HIV prevention are lacking.

What shapes the differences in contexts that give rise to varying success in prevention programs, and how can we promote contexts that favor prevention successes? The answer, Dr. Byanyima suggested, was ''science and rights.'' Even within the set of prevention tools, there can be differences in intervention coverage. For example, an analysis of data from 38 countries [Abstract OA02.03][7] illustrated variation in progress of national programs toward UNAIDS HIV elimination targets. For annual HIV testing, the coverage was relatively high in many countries in the South of Africa, but was lower in central and Western Africa. For condom use indicators, coverage was uniformly low. Most significantly, the trend models suggested that no African country evaluated was on a trajectory to meet UNAIDS 2030 targets for either HIV testing or condom use.

Heterogeneity of resources, risks and access

A major theme of the presentations related to the heterogeneity of resources, risks, and access to prevention tools. Some prevention tools, like a testing platform [Abstract OA02.01][7] to distinguish new HIV diagnoses into recent and nonrecent infections, offer insights that could be used to target prevention resources toward groups where infections have occurred in the prior year (in North Carolina, among younger people), are not in general use. Risks for HIV infection are also still heterogeneous: the high HIV infection risks of female sex workers [Abstract OA02.04],[7] cisgender men transgender women who have sex with men [Abstract OA02.05LB],[7] and people living in HIV core transmission areas [Abstract OA02.02][7] are high.

Limitations in access to HIV prevention tools was described along two axes: first, the need for more options and choices for HIV prevention, especially noted as a need for young women [Presentation PL04.03], and second, with respect to long distance to clinics as a barrier [Abstract OA07.02].[7]

Need for robust PrEP tools and programs for service provision

These diverse needs and limitations to access were reflected in calls for a more robust set of choices for PrEP formulations and approaches. Data from >600 men who have sex with men (MSM) in the United States described awareness of and interest in event-driven PrEP (ED PrEP): $\sim$40% of survey respondents were aware of ED PrEP, and $\sim$1 in 5 expressed a preference for ED PrEP over daily use [Abstract OA07.03].[7] In terms of approaches, Wafaa El-Sadr reviewed multiple dimensions of choice, including efficacy, safety, convenience, access, privacy, duration of protection, types of protection, and costs [Presentation PL04.02]. For young women in Kenya and South Africa, monthly or bimonthly injections for PrEP were preferred.

The themes of heterogeneity and prevention choices highlight the need to include the diverse perspectives and people in the formulation and testing of prevention approaches. Presentations throughout the conference used different types of research designs to bring forward the reasons that people start, discontinue, or avoid PrEP. A presentation on PrEP ''journeys'' based on qualitative data to focus on decision-making, relational aspects of decisions to start PrEP, and mechanisms for resilience to mitigate mistrust, suspicion of gossip [Abstract OA07.02].[7]

Another presentation emphasized that PrEP programs might assume that all potential PrEP users share a common goal of reducing the risk of HIV infection, whereas for adolescent girls and young women (AGYW), primary goals may be more aligned with relationship management [Presentation SY10.04]. In Thailand, the Tangerine Clinic provides prevention services in the context of a broader range of health services, including hormone services, for trans people [Presentation SY10.02]. In this same theme, recognizing multiple prevention and service needs of people who inject drugs (PWID) was discussed as a critical need [Presentation SY10.05].

Ongoing barriers to implementing prevention

Ongoing barriers to promoting PrEP and sustaining PrEP clients on therapy spoke to a deeper and more stubborn set of challenges. Stigma was discussed as a barrier to both HIV prevention efforts and to serving MSM living with HIV; the influence of stigma spans the globe and was specifically discussed in the United States and in Ghana [Presentation SY10.01]. Gossip about PrEP use was described as a threat to PrEP persistence in the Eastern Cape of South Africa; women who used PrEP and disclosed to multiple people were less vulnerable to the ill effects of gossip on the PrEP persistence [Abstract OA07.04].[7]

Gender-based violence and intimate partner violence were identified as factors that might discourage PrEP uptake and undermine PrEP persistence for AGYW [Abstract OA07.05LB].[7] Access to PrEP was an issue for some, especially in more rural areas [Abstract PE01.31].[7] COVID was also reported to play a role in lowering PrEP uptake and persistence through multiple mechanisms, including disruption of infectious disease clinical programs and inducing anxiety and other mental health issues that interfered with starting or maintaining PrEP.

Meaningful involvement of impacted populations

A cross-cutting issue was the involvement of impacted populations in research and implementation studies. One presentation highlighted the importance of improving the inclusion of key populations, including female sex workers, PWID, men who have sex with men, and trans people, in prevention research globally. PrEP research with PWID was noted to be an especially underrepresented area of work [Presentation SY10.05]. This might mean having the voices of AGYW in decision-making processes around health programs, or the provision of sustainable resources for AGYW-led interventions and local responses.

Across populations with needs for HIV prevention services, the concepts of agency and autonomy were cited as determinants of successful, effective, and sustainable programs. Leadership by members of impacted populations in the development of research agendas and programs was

identified as a critical step to improve the impact of programs to reduce HIV risk and promote engagement in care for those living with HIV [Presentation PL04.03].

Concluding Messages

The COVID-19 pandemic upended the world in a matter of months, rendering an in-person HIVR4P impossible even after a several-month delay. Serendipitously, the COVID-19 pandemic spurred innovation and dispersed conference content, enabling more expansive participation than ever before. Certainly, the level of ongoing HIV research including engineering of antibodies for improved protection, the mining of large data sets for vaccine design, and the discovery of unexpected roles for cell types in HIV disease despite the COVID-19 pandemic illustrated the resilience of HIV researchers. It also highlighted the failure of our collective imaginations: we were not prepared for global economies, supply chains, and travel to be largely shut down and essential services for HIV and other communicable and noncommunicable diseases to be seriously curtailed. However, the emboldened global response that has been marshaled against COVID-19, and because of COVID-19, has created opportunities for HIV prevention to benefit.

If tens of billions of dollars can be mobilized to support the rapid development of multiple vaccines for SARS-CoV-2 in months, not years, can a similar level of investment be mobilized for accelerated HIV prevention research and development? Can the same type of highly parallelized, global vaccine efficacy trials that worked so well for COVID-19 be used to more quickly test and iterate on HIV vaccine candidates? Critically, can the global health community do better in delivering the fruits of this science to have public impact, and ensure that ART-mediated prevention is available to all who might benefit, and not follow the same inequitable access that the world is now seeing with COVID-19 vaccines? These questions, and others like them, will undoubtedly be a poignant topic of discussion in subsequent HIVR4P conferences as the responses to both viruses evolve throughout the next decade, and perhaps much longer.

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Supplementary Material

Supplementary Table S1

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