

HIVR4P 2016, Partnering for Prevention: Conference Summary and Highlights

Barbara L. Shacklett,¹ Cynthia A. Derdeyn,² Morenike Oluwatoyin Folayan,³ Raphael J. Landovitz,⁴ Colin Anthony,⁵ Anna-Janina Behrens,⁶ Thomas J. Hope,⁷ Elise Landais,^{8,9} Lorna Leal,¹⁰ Jeanne M. Marrazzo,¹¹ Lynn Morris,¹² Nelly Mugo,¹³ Kenneth Ngunjiri,¹⁴ Veronica Nosedá,¹⁵ Srinika Ranasinghe,¹⁶ Damien C. Tully,¹⁶ Yegor Voronin,¹⁷ Mitchell Warren,¹⁸ Constantinos Kurt Wibmer,¹⁹ Irene Y. Xie,²⁰ Gabriella Scarlatti,¹⁷ and Bargavi Thyagarajan¹⁷

Abstract

HIV Research for Prevention: AIDS Vaccine, Microbicide, and ARV-based Prevention Science (HIVR4P) was built on a growing consensus that effective HIV prevention requires a combination of approaches and that understanding, analyzing, and debating the cross-cutting issues that impact prevention research are all essential to combat the global HIV/AIDS epidemic. To that end, the biennial HIVR4P conference is dedicated to all biomedical HIV prevention research approaches, including HIV vaccines, microbicides, pre-exposure prophylaxis, and treatment as prevention. The HIVR4P 2016 conference was held in Chicago, Illinois (USA), on October 17–21, and included more than 700 scientific presentations and 21 satellite sessions covering the latest and most promising advances across the HIV prevention research field. The theme “Partnering for Prevention” represented the conference’s commitment to breaking down silos between research disciplines as well as between researchers, program developers, care providers, advocates, communities, and funders. Delegates spanning 42 countries attended the conference. One-third of those in attendance were early career investigators, which reflects a firm commitment to emerging researchers and ultimately to the goal of developing a sustainable scientific enterprise well into the future.

¹Department of Medical Microbiology and Immunology and Division of Infectious Diseases, Department of Medicine, School of Medicine, University of California at Davis, Davis, California.

²Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia.

³Department of Child Dental Health, Obafemi Awolowo University, Ile-Ife, New HIV Vaccine and Microbicide Advocacy Society, Lagos, Nigeria.

⁴Division of Infectious Diseases, UCLA Center for Clinical AIDS Research & Education, University of California, Los Angeles, California.

⁵Division of Medical Virology, Department of Pathology, Faculty of Health Sciences, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa.

⁶Department of Biochemistry, Oxford Glycobiology Institute, University of Oxford, Oxford, United Kingdom.

⁷Department of Cell and Molecular Biology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

⁸International AIDS Vaccine Initiative, Neutralizing Antibody Center, The Scripps Research Institute, La Jolla, California.

⁹International AIDS Vaccine Initiative, New York, New York.

¹⁰Hospital Clínic de Barcelona–IDIBAPS, Barcelona, Spain.

¹¹Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama.

¹²National Institute for Communicable Diseases, Johannesburg, South Africa.

¹³Center for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya.

¹⁴Department of Public and Community Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya.

¹⁵Planned Parenthood France/Le Planning Familial, Paris, France.

¹⁶Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Cambridge, Massachusetts.

¹⁷Global HIV Vaccine Enterprise, New York, New York.

¹⁸AVAC, New York, New York.

¹⁹Faculty of Health Sciences, Centre for HIV and STIs, National Institute for Communicable Diseases (NICD), of the National Health Laboratory Service (NHLS), University of the Witwatersrand, Johannesburg, South Africa.

²⁰National HIV and Retrovirology Labs, Department of Medical Microbiology and Infectious Diseases, JC Wilt Center for Infectious Diseases, Public Health Agency of Canada, University of Manitoba, Winnipeg, Canada.

This article presents a concise summary of highlights from the conference. For a more detailed account, one may find full abstracts, daily summaries, and webcasts on the conference website at hivr4p.org.

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Introduction

THE BIENNIAL HIVR4P CONFERENCE is the only global scientific meeting dedicated exclusively to biomedical HIV prevention research, including HIV vaccines, microbicides, pre-exposure prophylaxis (PrEP), treatment as prevention (TasP), and other prevention approaches. While detailed reporting of all meritorious presentations is beyond the scope of this summary, this review will briefly highlight presentations deemed to be of special interest.

The conference opened with a strong message by Ruxandra Draghia-Akli (European Commission), who reported that despite intensive prevention efforts the rate of new HIV acquisitions in Europe has not declined since 2005, with more than 29,000 new HIV diagnoses in Europe in 2014 alone.¹ Furthermore, the acquisition rate in Europe is currently increasing among men who have sex with men (MSM). According to UNAIDS, 36.7 million adults and children are living with HIV worldwide; this includes more than 25 million in Africa, 5 million in Asia, 2 million in Latin America, 1.5 million in eastern Europe/central Asia, and 2.4 million in western Europe and North America.² These data highlight the need for development of better prevention modalities and implementation strategies. France has been a leader in implementing PrEP, and demonstration projects are now ongoing in several other EU countries, but more work is clearly needed if we are to meet the ambitious goal outlined by UNAIDS of ending the AIDS epidemic by 2030.²

Providing Care to Vulnerable Populations: Complexities and Successes

Epidemiological evidence suggests that despite dramatic advances in HIV prevention sciences in recent years, decline in new HIV infections among adults has slowed alarmingly. There continues to be a critical need for increased uptake, access, and novel products and interventions. In addition, health disparities persist across populations. As outlined by Ambassador Deborah Birx, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) continues to support efforts to scale up HIV prevention and treatment programming globally, and is closely monitoring metrics at the level of individual country and region to support local successes, particularly in key populations (Abstract PL04.02³).

Youth and adolescents exhibit unique biological, behavioral, social, and structural challenges to HIV prevention. Sharon Achilles described hormonal transitions in adolescents and associated increased hormone-sensitive tissue vulnerability to infection (Abstract SY04.01³). Susan Rosenthal talked about prefrontal cortex development and the effect of "amygdala hijack" leading to high-risk behavior and/or limited or incorrect understanding of risk (Abstract SY04.02³). Youth community representatives Sydney Roberson and Kortez Davis shared their experience navigating sexual maturity, information acquisition, and risk, highlighting the challenges they faced. Together, these presen-

tations provided nuanced accounts of social and structural barriers in access to care and prevention that derail efforts to scale up the new generation of highly effective HIV prevention strategies.

Patrick Sullivan presented a newly developed database and online tools designed to analyze statistics of the HIV epidemic in the United States by zip code using parameters such as demographics, care access, commute distance, and Twitter data. Such databases can be utilized to identify risk groups and increase access to and/or retention in care. A new pipeline is being developed that will allow testing, assessment, and the delivery of treatment to occur remotely using telemedicine. This approach should increase access of vulnerable populations to healthcare (Abstract PL02.03³).

Understanding Risk of Acquisition Across Populations

Researchers presented epidemiologic estimates of risk and HIV prevalence in a variety of populations, including several marginalized communities. Wipas Wimonsate showed that HIV incidence among MSM and transgender women (TGW) at a Bangkok clinic was 5.3 infections per 100 person-years, peaking in 2011 and declining since that time (Abstract OA05.04³). Using data from the VOICE trial, Jennifer Balkus reported on a predictive score for HIV acquisition within 1 year. The method was validated with data from two other trials, and shows promise for application to PrEP scale-up (Abstract OA05.03³). Beatriz Grinsztejn presented data describing the HIV Care Cascade for TGW in Rio de Janeiro, Brazil. Of those with HIV infection, 90% had been previously tested, 65% were on antiretroviral therapy (ART), and 57% had an undetectable viral load (Abstract OA05.06LB³). Finally, Jocelyn Elmes presented meta-analysis and mathematical modeling to suggest that at least 16% of HIV infections in at-risk women in the United States might be due to anal intercourse (Abstract OA05.02³).

HIV Transmission Dynamics

In a deft display of multidisciplinary and translational science, Deenan Pillay described how insights into HIV transmission dynamics provide clues for accurate targeting of interventions on a population level. Carefully deployed synergies between epidemiologic data and the assessments of timing of HIV acquisition afforded by "molecular clocking" can help determine which intervention strategies may have the greatest impact (Abstract PL02.01³).

Although many aspects of HIV transmission can be effectively modeled using nonhuman primate models and *in vitro* systems, studying the earliest events at the mucosal surface presents unique scientific challenges. Julie Overbaugh reviewed our current understanding of the transmission "bottleneck," focusing on the distinct biological features of transmitted/founder (T/F) viruses. We now know that the window of opportunity for blocking viral dissemination is relatively short (1–2 days); this information is

critical for the informed use of treatment and prevention strategies (Abstract PL02.02³). New studies of international cohorts are also shedding light on the nature of T/F viruses. Gladys Macharia presented a study of transmitted viruses in 21 Kenyan MSM, conducted as part of the IAVI Protocol C cohort. Full-genome sequencing revealed that 38% of T/F viruses were cross-clade recombinants, suggesting frequent coinfection with more than one clade in this population (Abstract OA18.03³).

Bacterial vaginosis (BV), which is highly prevalent in sub-Saharan Africa, is associated with a significant increase in HIV acquisition. Ryan Cheu reported that neutrophils recruited to the female genital tract in response to BV-associated bacterial species express proteases that damage the epithelium. They also express PD-L1, a ligand for PD-1, potentially leading to altered T cell function in the female genital tract. Thus, in the context of BV, neutrophils may play an important role in enhancing susceptibility to HIV acquisition (Abstract OA05.05³). Adam Burgener showed that in the CAPRISA 004 study, certain species of vaginal bacteria could deplete tenofovir, potentially modulating PrEP efficacy (Abstract SY02.04³).

Gender differences in early immune responses, and how these differences may influence HIV transmission, are poorly understood. On average, women have elevated immune activation during chronic HIV infection, but early events are less well studied. Elina El-Badry and colleagues tracked early events following HIV infection in a Zambian cohort of serodiscordant couples. They found that compared to men, women had lower viral load, higher CD4 counts, and lower levels of activated CD8 T cells during the first year of infection. Linear discriminant analysis also revealed distinct innate immune responses for men and women (Abstract OA18.01³).

New Insights in Mucosal Biology: Target Cells and Opportunities for Intervention

The route of HIV transmission and nature of the initial target cells within mucosal tissues have important implications for early viral dissemination. In particular, immune cells and their activation profile can drive the infection process; however, these issues have been difficult to study due to challenges inherent in mucosal sampling. Compared to U.S. women, women in Zimbabwe had significantly more cervical CD4⁺, CCR5⁺, and CD69⁺ (activated) T cells in the genital tract, providing a relevant cell substrate for the virus (Sharon Achilles, Abstract OA15.01³). Marta Rodriguez-Garcia reported that dendritic cell subsets with HIV capture potential were found throughout the female reproductive tract. Viral capture occurred regardless of DC-SIGN expression, suggesting that receptors other than DC-SIGN may be involved in HIV acquisition in the female reproductive tract (Abstract OA15.03³). Mucosal challenge studies in rhesus macaques, utilizing a novel single-round dual-reporter lentiviral vector pseudotyped with a CCR5-tropic Env, identified Th17 cells as the predominant initial targets for HIV/SIV infection in both anorectal and vaginal mucosal tissues (Danijela Maric, Abstract OA02.01³).

The role of antibodies at mucosal surfaces was the focus of several talks. Maria Lemos found that certain broadly neutralizing antibodies (bNAbs) were capable of inhibiting viral

replication in outer and inner foreskin explants following HIV JR-CSF challenge. Interestingly, inner foreskin required higher concentrations of bNAb than outer foreskin, supporting the notion that inner foreskin is more difficult to protect from HIV acquisition *in vivo* (Abstract OA02.02³). Rosemary Bastian discussed the glycan-dependent formation of mucin/antibody complexes and documented an interaction between IgG and mucin MUC5AC, resulting in a multivalent complex consisting of eight IgG molecules binding to a single MUC5AC monomer. Compared to IgG alone, these complexes had enhanced antibody potency against HIV and increased binding to SOSIP gp140 trimers (Abstract OA07.03³).

Anthony Fauci, James Arthos, and Claudia Cicala presented recent work on a novel approach to fighting HIV persistence using a monoclonal antibody against $\alpha 4\beta 7$ integrin. This integrin is required for T cell trafficking to the gut, an important site of HIV infection and virus replication. The antibody can suppress viral rebound during ART interruption in SIVmac251-infected rhesus macaques. The new findings do not provide a “cure” for HIV, but they do demonstrate that in the macaque model treatment with $\alpha 4\beta 7$ antibody can reduce or in some cases completely suppress viral rebound following ART interruption and restore CD4⁺ T cells. Interestingly, this antibody (FDA approved as vedolizumab) is already used in humans for treatment of inflammatory bowel disease, and a small clinical trial is being undertaken by NIH to explore its use in HIV-positive persons.

In SIV-infected macaques, pretreatment with $\alpha 4\beta 7$ antibody resulted in a modest reduction in plasma viral load after SIV challenge, but led to a profound reduction in gut proviral DNA load and highly significant delay in disease progression (Abstract OA07.02³). Blocking $\alpha 4\beta 7$ in naive macaques before infection led to substantial protection from low-dose mucosal challenge with SIVmac251 and minimal CD4⁺ T cell loss in breakthrough infections (Abstract SY02.01³). These data support the role of $\alpha 4\beta 7$ integrin in HIV/SIV transmission. Indeed, in the context of the CAPRISA 004 tenofovir (TFV) gel trial, Aida Sivro showed that levels of $\beta 7$ “high” cells at the time of acquisition were significantly higher in cases compared to controls (Abstract OA07.01³).

Microbicides: Drug and Hormone Levels

The delivery of chemoprevention agents at the genital site of infection is attractive because this approach has the potential to deliver high doses of anti-HIV products with limited systemic toxicity. In addition, the use of topical microbicides can be discreet and does not require disclosure to the partner. Sharon Hillier discussed recent progress in topical prevention science, including microbicide rings and technologies such as films, gels, on-demand tablets and enemas that will help broaden the range of possibilities for administering ARVs to mucosal surfaces. Multipurpose products delivering ARVs in combination with contraceptives are also being developed, and are likely to be of great interest to women of childbearing age (Abstract PL03.03³).

Many who study ARV-based prevention remain concerned that failures of such interventions may select for resistant viral variants, complicating subsequent ARV treatment. This is of particular interest in the case of the dapivirine (DPV) ring, as resistance to DPV could compromise response to

efavirenz-based first-line therapy in resource-limited settings. Urvi Parikh presented data on ASPIRE/MTN-020, finding no difference in rates of NNRTI-associated mutations in a study of seroconverters exposed to active DPV in vaginal rings compared to placebo (Abstract OA03.03³). Kathleen Vincent showed that pod-intravaginal rings (IVRs) containing tenofovir disoproxil fumarate (TDF) alone as well as both TDF and emtricitabine (FTC) were safe and had favorable pharmacokinetics (PK) in humans and sheep during short-term use (Abstract OA06.04³). Andrea Thurman discussed a study to assess four prototypes under development for on-demand topical microbicide inserts (CONRAD 134). These prototypes are being developed in response to user feedback from earlier studies. Optimized prototypes disintegrated faster and had enhanced acceptability over first-generation products, and this platform warrants further development (Abstract OA06.05³). Jonathon Holt presented data suggesting very low potential for DPV to impede the PK activity of levonorgestrel (LNG) if coformulated. Similarly, studies showed no indication that LNG would inhibit the activity of DPV (Abstract OA06.06³).

A nuanced complexity in the field of topical prevention is the interaction between ARV-based preparations, the hormonal milieu, and the vaginal microbiome, and how this may affect susceptibility and drug PK. Andrea Thurman presented data from CONRAD 124, in which TFV levels were assessed in pre- and postmenopausal women using TFV gel. In the premenopausal group, there were no differences in local or systemic PK when comparing follicular to luteal phase. However, postmenopausal women had lower plasma TFV compared to premenopausal women. This difference was reversed with topical estradiol treatment (Abstract OA04.01³). Ekaterina Taneva presented data extending the finding that the vaginal microbiome can modulate topical ARV PK/PD, which may have implications for microbicide drug choice (Abstract OA04.02³). Irina Zalenskaya, looking for a mechanism by which certain hormonal contraceptives that have been associated with increased acquisition of HIV may contribute to disease susceptibility, reported that depot medroxyprogesterone acetate downregulates genes involved in keratinocyte differentiation, stratum corneum maintenance, and tight junctions, leading to decreased epithelial integrity (Abstract OA04.04³).

Understanding Adherence in Microbicide Trials

The challenges of ensuring adherence to prevention products have plagued virtually all prevention modalities in efficacy studies. Topical preparations pose unique challenges to adherence measurement, as systemic levels are often not achieved, which necessitates creative and novel methods to measure product use in a study. Alex Carballo-Dieguez presented results of MTN-017, a Phase 2 expanded safety and acceptability crossover study of two products delivered in three regimens: reduced glycerin 1% TFV (RG-TFV) gel applied daily or on-demand (pre- and postcoitally); and oral FTC/TDF taken daily. The team found good acceptability and high adherence ($\geq 80\%$) to the rectal microbicide gel for both regular and on-demand use, suggesting a rectal microbicide gel could be an alternative for those uninterested in daily oral PrEP should efficacy be demonstrated (Abstract OA20.01³).

Barbara Mensch compared objective measures of adherence such as plasma DPV levels and residual drug in used

rings in the ASPIRE/MTN-020 trial with self-reports of ring use. Based on objective measures, nonadherent women, particularly those ages 18–21, significantly overreported their use of the ring. Among those who reported never removing the ring, up to 22.9% had biological measures indicating nonadherence. Importantly, women ages 18–21 were more likely than older women to remove the ring during the study, which may account for the ring's apparent lower effectiveness in younger women (Abstract OA20.02³).

PrEP Provision, Adherence, and Use

Noel Gordon Jr., a PrEP advocate, gave the audience a frank and personal illustration of the HIV epidemic profile in the United States, how it disproportionately affects young black gay men and TGW, and the successes and challenges of PrEP access. He noted that PrEP can be a transformative tool for linking sex and HIV prevention, because it removes the anxiety associated with the prospect of HIV transmission for those who are HIV negative; just as TasP addressed this same concern for those who are HIV positive. PrEP, however, also brings new challenges that research needs to address, such as the increasing risks for sexually transmitted infections (resulting from absent or inconsistent condom use) and the concerns of stigma associated with PrEP use (a structural barrier). Access to PrEP is disproportionately skewed toward white and older persons, rather than toward those demographic groups most affected by the epidemic (Abstract PL03.02³).

San Francisco, California, is successfully scaling up PrEP for at-risk communities. Susan Scheer estimated that 12,500 San Franciscans are now on PrEP, including about 30% of HIV-negative, at-risk MSM; this is close to the stated goal of 15,000 by 2017. Some groups, including younger people, African Americans, women, and TGW have not yet been adequately reached by PrEP, although outreach efforts to these groups are increasing (Abstract OA24.03³). Little data exist on PrEP rollout in sub-Saharan Africa. Robinson Karuga identified barriers to PrEP use among Kenyan MSM. These include social stigma, inconvenience, and cost. Encouragingly, overall acceptability was $>80\%$ despite these barriers (Abstract OA24.02³). U.S.-based providers are still conflicted regarding PrEP's role in the prevention armamentarium. Sarah Calabrese performed a survey of U.S. medical students and identified biases in their willingness to offer PrEP to MSM patients. Paradoxically, students were most likely to offer PrEP to patients with the *lowest* risk of HIV infection; for example, those with high condom use or those in a monogamous relationship, implying that personal biases related to condom use, monogamy, and heteronormative sex can interfere with provision of optimal PrEP services (Abstract OA03.05³). Dominika Seidman reported in a Northern California survey of more than 1900 cisgender women seeking family planning services and found low rates of CDC-defined PrEP eligibility and also low rates of PrEP knowledge, and disappointing rates of interest in learning about PrEP (Abstract OA16.04³).

Previous PrEP studies have indicated that younger individuals and some race/ethnicity groups are more likely to have challenges achieving levels of TDF/FTC adherence anticipated to provide high levels of protection. Interventions to support adherence in these populations, which are also

disproportionately affected by HIV, are sorely needed. Albert Liu presented interim baseline and overall adherence data from the EPIC study, which uses a randomized design to test a PrEP adherence intervention for young MSM and TGW in Chicago. Encouragingly, drug level data from dried blood spots suggested overall high rates of TDF/FTC adherence over 48 weeks of follow-up. African American and uninsured participants were less likely than other groups to attain protective levels; however, encouragingly, a majority of participants in all subgroups did achieve protective tenofovir-diphosphate (TFV-DP) levels (Abstract OA16.01³). Maria Pyra presented adherence data from the Partners-PrEP open-label extension study in East Africa, showing high rates of adherence among HIV-negative women in sero-different partnerships (Abstract OA16.02³). Douglas Krakower reported on Fenway Health's cohort of over 600 PrEP initiators between 2011 and 2014, and found that unplanned PrEP discontinuation was associated with HIV seroconversion, as were African American race, identifying as transgender or trans-feminine, having an HIV-uninfected partner, and having mental health and/or substance abuse issues (Abstract OA16.06³).

As PrEP use becomes better understood, an important research gap remains regarding the safety of TDF/FTC PrEP for pregnant women and their fetuses. Clearly, any safety concerns would need to be balanced against the risk of HIV acquisition during pregnancy or breastfeeding. Kenneth Mugwanya tested whether the components of Truvada, when taken as PrEP by lactating HIV-uninfected women, are excreted into human milk and absorbed by breastfeeding infants. The team found that infants are exposed to minimal concentrations of TFV and FTC, suggesting PrEP can safely be used as part of HIV prevention by breastfeeding women (Abstract OA03.02³).

Although PrEP is highly protective when taken as prescribed, no prevention strategy achieves 100% efficacy. As a sobering reminder of this fact, Howard Grossman described a case of seroconversion despite apparent consistent daily TDF/FTC PrEP use, in this case with multidrug-resistant virus. Phylogenetic analysis suggested that the source of the multiclass drug-resistant virus was not the patient's virally suppressed HIV-infected partner, but was likely one of two casual partners (Abstract OA03.06LB³). This represents the second such report of breakthrough HIV infection as a result of transmitted resistance despite consistent adherence to PrEP (CROI 2016 Abstract 169aLB⁴).

ARV PK and Pharmacodynamics

ARV distribution in mucosal tissues is heterogeneous, and ratios of active drug metabolites in target tissues have important implications for drug efficacy. Angela Kashuba reminded the audience that a single, ideal surrogate marker of PrEP efficacy is yet to be defined. That is, it remains unclear if plasma, peripheral blood mononuclear cells (PBMCs), or tissue drug levels are the best predictor of HIV protective efficacy (Abstract SY03.01³).

There is much excitement about long-acting injectable preparations of antiretroviral agents. Two such agents are in advanced phases of clinical development: cabotegravir, a long-acting integrase inhibitor, and rilpivirine, a long-acting, second-generation NNRTI. We also learned at CROI 2016 about eFda (MK-8591), a novel NRTTI with a prolonged intracellular half-life (CROI 2016 Abstract 98⁴). Cabote-

gravir is being evaluated for PrEP in HPTN 083, the Phase 3 efficacy study comparing long-acting injectable cabotegravir to daily oral TDF/FTC for prevention of HIV acquisition among MSM and TGW (Myron Cohen, Abstract PL01.01³). While human-similar doses of long-acting injectable rilpivirine (RPV LA) did not prevent vaginal transmission of wild-type or NNRTI-resistant HIV in a BLT-mouse model (Zandrea Ambrose, Abstract OA06.01³), there is still interest in the product, as well as new delivery systems in development.

Peter Anderson provided insights into how measures of short- and long-term adherence can be combined to inform our understanding of adherence as well as global patterns of product use and effectiveness (Abstract SY03.03³). Julie Fox provided an important perspective on PK/PD studies, showing that sampling from men and women in all genital compartments is well tolerated and acceptable. She also emphasized that menstrual cycle stage and hormonal status should be incorporated into the PK/PD study design for female subjects. Ivana Massud showed similarities between plasma, PBMC, and genital tract PK in a macaque model of lamivudine (3TC) dosing. Anticipating efforts to replace FTC with 3TC in TDF-containing PrEP, future nonhuman primate (NHP) challenge studies are planned (Abstract OA06.03³). As 3TC is available generically, and TDF is soon to be available generically, these results are eagerly anticipated. TDF/3TC, already available as a generic fixed-dose combination in some resource-limited settings, would provide a reduced cost option for PrEP. Jim Turpin discussed a recommendation for accelerated complementary animal and human studies in PK/PD modeling efforts, and observed that not all animal-modeled interventions have realized their promise in human trials. He also described a potential solution to address this need using BLT mice and nonhuman primates.

Passive Immunization with Broadly Neutralizing Antibodies

Passive administration of bNAbs for HIV prevention is already being tested in two Antibody Mediated Prevention (AMP) trials conducted by the HVTN and HPTN (Larry Corey). Enrollment for HVTN 703/HPTN 081 (sub-Saharan African women) and HVTN 704/HPTN 085 (North and South American MSM) is proceeding well. In addition to revealing more about passive antibody protection against HIV in humans, results from the AMP studies may also provide a benchmark for vaccine development in terms of serum antibody levels that may be protective.

John Mascola provided an overview of bNAbs currently under development, including a long half-life variant of VRC01, improved bNAbs directed toward the CD4 binding site, and trispecific antibodies. Current efforts are focused on improving existing bNAbs in three important ways: increasing their potency (meaning smaller doses and lower cost); increasing their breadth of coverage; and increasing their half-life within the body. The monoclonal 3BNC117, described by Nussenzweig and colleagues, appears to delay viral rebound in humans during treatment interruption.⁵ In a study comparing maternal to infant viruses in cases of peripartum transmission, all but one of the viruses from the 14 infants studied were resistant to autologous maternal plasma, yet sensitive to VRC01 bNAbs, suggesting that passive immunization with VRC01 may be very effective in preventing

peripartum mother-to-child transmission (Amit Kumar, Abstract OA18.02³). It can be envisaged that administration of bNAbs to the newborn may also be effective in preventing breast milk transmission.

Frances Priddy described a promising strategy to make passive immunization with bNAbs more durable. She provided an update on vectored immunoprophylaxis, an approach using a benign vector to deliver antibody genes into long-lived human cells. If successful, this approach could reduce or eliminate the need for multiple injections since the antibody would be produced within the recipient's own body (Abstract SY05.03³). Therapeutic successes have been reported with a similar approach in treatment of hemophilia B,⁶ and the first human safety trials are currently ongoing (IAVI A003/CHOP HVDDT 001). Alternative routes of administration of bNAbs are also being explored: VRC01 produced in tobacco plants and delivered to rhesus macaques in pod-intravaginal rings (Pod-IVRs) is released in a controlled and sustained manner (John Moss, Abstract OA06.02³) with favorable safety and PK findings. Challenge studies in NHP are planned and will provide hints on efficacy.

Human Vaccine Trials

Georgia Tomaras presented an overview of cellular and humoral responses to vaccination in the RV144 trial, showing that the reduced risk of acquisition involved multiple components of cellular and humoral immunity, as well as host genetics (Abstract PL01.02³). Nicole Frahm presented data demonstrating that COMPASS scores, a new summary metric of T cell polyfunctionality, were inversely associated with HIV risk in the RV144 trial.

In a related update, the first trial of the Pox Protein Public Private Partnership (P5), designated HVTN 100, with Clade C inserts and protein, tested in 252 low-risk individuals in South Africa, has successfully passed all four "go/no go" criteria. This Phase 1/2 follow-up trial to RV144 conducted across multiple sites in South Africa has paved the way for HVTN 702, a Phase 2b/3 trial based on a modified RV144 regimen. The vaccine was changed to include Clade C HIV-1 immunogens and a different adjuvant, and will be tested in a distinct at-risk population. This is the first large-scale HIV vaccine trial to be launched since RV144 7 years ago.

A priority is to improve the magnitude and durability of antibody responses in immunized human subjects. RV305 and RV306, two follow-on studies to RV144 (Lindsay Wieczorek, Abstract OA22.03³), were deployed to study persistence of the immune response to the immunization schedule. In RV305, participants received a greatly delayed 5th boost of ALVAC-HIV/AIDS VAX[®] B/E, 6–8 years after the 4th immunization. In RV306, participants received the RV144 regimen with additional boosting at different intervals where a 5th boost was done much earlier, at 48, 60, or 72 weeks. Tier 1 NAb responses observed in RV144 could be significantly improved by additional boosting. Also, increased activation and proliferation of NK cells were observed (Michael Eller, Abstract OA14.03³), suggesting a model in which vaccination stimulates and expands NK populations, consistent with recent reports of NK memory-like capacity. Carolina Herrera suggested that mucosal tissue explants may provide better tools to assess protection than

measurements from peripheral blood, citing data showing that ALVAC-HIV and AIDS VAX B/E elicited different cytokine responses in mucosal tissues compared to blood (Abstract OA14.01³).

Giuseppe Pantaleo presented on behalf of the HVTN 096/ EV04 team comparing different priming strategies to optimize HIV vaccine responses. Their Phase 1 study assessed safety and immunogenicity of coadministration of AIDS-VAX B/E gp120 proteins during priming with either NY-VAC or DNA candidate vaccines expressing Clade C Env, Gag, and Pol-Nef. The team did not observe neutralizing antibodies against Tier 2 viruses; however, coadministration of gp120 proteins with DNA or NYVAC during priming resulted in earlier induction and higher magnitude and durability of protective V1V2 antibody responses. DNA priming induced more potent T cell responses (Abstract OA11.06LB³). In the HVTN 094 trial, which tested the GeoVax DNA/MVA VLP vaccine using GM-CSF as an adjuvant with either two or three MVA boosts, antibody responses were generally directed toward gp41 and were durable for 12 months, while gp120 responses decayed more rapidly (Susan Buchbinder, Abstract OA22.02³). Increasing the number of MVA boosts to three improved antibody magnitude and durability, and future studies will test the addition of a protein boost.

Holly Janes gave an update on cell-mediated immune responses in the HVTN 505 Phase 2b vaccine efficacy trial, which was stopped early due to the lack of efficacy. HIV-specific CD4⁺ T cell responses showed no association with HIV infection risk; however, among vaccine recipients, higher HIV-specific CD8⁺ T cell magnitude, summed across HIV proteins, was strongly associated with lower HIV infection risk. Furthermore, high Env-specific CD8⁺ T cell polyfunctionality was also inversely associated with risk. The investigators speculate that this association might be due to an unknown factor related to natural resistance or susceptibility to HIV infection. Additional studies will be required to further probe this possibility (Abstract OA17.03³).

Antibody Epitopes and Env Immunogenicity

In the late 1990s, the goals of neutralizing antibody-based HIV vaccine design included presenting an intact mature HIV Env oligomer as an immunogen, increasing its immunogenicity, and learning real-world lessons from antibodies that potently neutralize primary viruses. An overview of progress, including better understanding of Env structure and variation, characterizing bNAb responses in natural infection, and elucidating the basic biology of B cells and T follicular helper (Tfh) cells, was presented by Dennis Burton. The field now has a good structural view of the native Env trimer, the major targets of bNAbs have been mapped, and numerous bNAbs have been recovered that are up to 1,000-fold more potent than the first-generation bNAbs. In the next phase of research, immunogen design, development of better/sequential immunization regimens, and iterative approaches will be critical to develop an immunization strategy that will ultimately provide "steering" of the immune response toward protection (Abstract PL03.01³).

Insights into developmental pathways utilized by bNAbs, viral escape, and characterization of the Env epitopes recognized are extremely valuable for guiding rational vaccine

design. Devin Sok showed that most bNAbs targeting the high mannose patch, including three new lineages, commonly recognize an important part of the CCR5 coreceptor binding site on gp120. These antibodies are therefore less effective at neutralizing CXCR4-tropic viruses (Abstract OA01.01³). Nicole Doria-Rose presented the coevolution of virus and antibodies during acute infection, and mapped multiple MPER-targeting neutralizing antibody lineages, providing new insight into the development of MPER-directed bNAb development (Abstract OA01.02³). Penny Moore explored the ontogeny of bNAbs, focusing on factors such as viral diversity and the rate of viral escape that drive the development of breadth. An earlier study showed that gradual, rather than rapid, accumulation of Env escape mutations drove breadth in donor CAP256. Interestingly, the presence of autologous Tier 2 NABs during infection does not predict development of breadth. Env glycan “holes” typically elicit strain-specific antibodies during infection. Despite being confronted with diverse options for continued maturation over the course of infection, these lineages often do not mature toward breadth. This finding suggests that similar dead ends in bNAb development may be encountered following vaccination (Abstract SY08.04³). Indeed, John Moore showed that immunization of rabbits with SOSIP trimers based on different Env variants consistently elicited NABs targeting distinct glycan holes, limiting the activity of these NABs to mainly the autologous virus (Abstract SY08.03³).

Almost all bNAb Env epitopes involve glycans through direct binding and/or accommodation. Therefore, a better characterization of the Env glycan shield is critical for immunogen design. Katie Doores (Abstract SY08.02³) and Anna-Janina Behrens (Abstract OA21.03³) presented important data from their studies aimed at characterizing the nature of glycans at individual sites, while Jason Yolitz presented an interesting result showing that non-neutralizing CH58 (not glycan-dependent) and broadly neutralizing PG9 (glycan-dependent) V2-apex antibodies recognize Env proteins originating from different cellular processing pathways (Abstract OA01.05³).

Harry Gristick presented a crystal structure of natively glycosylated BG505 Env SOSIP trimers in complex with two bNAbs, one of which binds to the CD4 binding site and has unusual CD4 mimetic properties. This new antibody, IOMA, is similar to VRC01, but has a CDRL3 that is eight amino acids in length, which is more common than the five amino acid CDRL3 found in VRC01 and therefore may be viewed as an easier path for bNAb development via vaccination (Abstract OA09.06LB³). Kelly Lee shared data on Env structure from hydrogen/deuterium exchange mass spectrometry, a method that allows probing of protein structure under native conditions. Data from this approach and other analytical methods revealed that Env trimers from different strains have different levels of structural plasticity, challenging our understanding of what constitutes a prefusion native trimer. These findings also have implications for the antigenicity of different Env preparations (Abstract SY08.01³).

Preclinical Immunization Approaches to Induce Humoral Immunity

Testing rational vaccine design strategies in animal models includes immunization of human Ig locus transgenic (Ky-

rab) mice with germ line-targeting immunogens, which effectively select for VRC01 precursors despite a very low frequency of these B cells (Devin Sok, Abstract OA08.02³). Marit van Gils presented data on immunization of macaques with Env BG505 SOSIP trimers as a starting point for iterative vaccine design. Remarkably, vaccination elicited antibodies that targeted the same glycan holes that were previously identified as targets for NABs in rabbits; these also showed a level of overlap with epitopes recognized by bNAbs, suggesting the potential to mature toward breadth (Abstract OA08.01³).

New approaches to increase breadth of the antibody responses are under investigation. Sequential immunization of rhesus macaques with Envs derived from subject CH505, who developed the bNAb lineage designated CH103, was presented by Barton Haynes. Immunization with these Envs induced some Tier 2 neutralization activity, mainly in one macaque; studies are underway to better understand the antibody response elicited in this animal (Abstract SY01.01³).

Vaccine studies using heterologous Ad/MVA vectors with mosaic inserts and trimer gp140 Env protein boost are aimed at increasing vaccine coverage of global HIV isolates. In rhesus macaques, the addition of a protein boost to vaccination with heterologous Ad/MVA vectors with mosaic inserts increased protection against SIV (Hanneke Schuitemaker). Several follow-up studies are underway, with the goal of expanding breadth/clade coverage, balancing cellular and humoral responses, and defining correlates of protection in nonhuman primates. Frank Wegmann discussed a candidate HIV-1 vaccine regimen against SHIV-SF162P3 in rhesus macaques. Six groups were given different boost components for a prototype Ad26 (alone or in combination with MVA mosaic and/or Clade C gp140), including one placebo group. Boosting with MVA-mosaic induced high HIV-1-specific cellular responses. Ad26/Ad26+gp140 regimens provided 94% pre-exposure risk reduction against SHIV challenge (Abstract OA11.05³). Analogously, a pediatric vaccine to prevent oral transmission of HIV-1 through breast milk (Bonnie Phillips, Abstract OA11.02³) was studied. Infant macaques were given MVA with either HIV Env or SIV Gag/Pol, HIV Env protein, or all three (on either a regular schedule or an extended interval). All regimens induced antibodies specific for a variety of HIV Env epitopes and clades. IL-2 production by Tfh cells was elevated in the protein-only group in lymph node and spleen, and intestinal B cells specific for gp120 were detected in the extended interval group.

Cellular Immune Responses to Vaccination

Several ongoing vaccine studies in NHP that aim to induce cellular immune responses were described. Andrew McMichael presented a collaborative study in which a mosaic vaccine delivered by ChAdOx1 prime and MVA boost primed T cell responses with high breadth and magnitude in NHP. The monkeys are yet to be challenged, with results anticipated in 2017 (Abstract SY06.01³). Louis Picker presented an update on the CMV vector-based HIV vaccine, which has shown approximately 55% efficacy in ~160 vaccinated NHP. Control is binary (all or none), occurs early, and over time the virus appears to be completely eradicated from tissue compartments. Notably, the vector induces unconventional CD8⁺ T cells restricted by MHC class II or

MHC-E. Future studies will aim to determine which of these unconventional responses are responsible for immune control. Currently, translation of CMV vectors to HCMV/HIV vectors suitable for human clinical testing is scheduled for late 2017/early 2018 (Abstract SY06.03³).

The role of germinal centers and Tfh cells in vaccine response was underscored by several presentations. Rama Amara presented data demonstrating the induction by vaccination of follicle-homing, CXCR5⁺, SIV-specific CD8⁺ T cells. These cells express many of the genes associated with Tfh cells, migrate to germinal centers, and can restrict virus replication in Tfh. In addition, they may also give rise to extrafollicular CXCR5⁺ CD8⁺ T cells (Abstract OA17.04³). Sudhir Kasturi showed that a combination of novel ligands for TLR4, 7, and 7/8, delivered using synthetic nanoparticles, strikingly enhanced the magnitude, quality, and durability of humoral and cellular immune responses to protein antigens in mice and macaques. These ligands elicited robust induction of Tfh cells with striking persistence of Env-specific plasma cells in bone marrow and draining (iliac) lymph nodes (Abstract SY07.01³). Hendrik Streeck described a small population of peripheral IL21-secreting CD4⁺ T cells that resemble Tfh cells transcriptionally, phenotypically, and functionally (Abstract SY07.02³). Afam Okoye presented data on the “dark side” of germinal centers and how B cell follicles can act as sanctuary sites that allow persistent productive infection in SIV elite controllers (Abstract SY07.03³).

Revisiting the Concept of Sterilizing Immunity

Several experimental results led to discussion of the concept of “sterilizing immunity” and whether “sterilizing” means total absence of viral infection. Carolyn Williamson presented data on recently transmitted viruses from the CAPRISA acute infection cohort, posing two questions: first, did 1% TFV gel, which decreased the risk of HIV-1 acquisition, select for viruses with higher transmission potential; second, does inflammation, which increases the risk of HIV-1 acquisition, reduce viral selection, enabling transmission of less “fit” viruses? Data revealed that viruses from TFV recipients were, in fact, more consensus like and had higher transmission indices than those from placebo recipients. Furthermore, preinfection genital inflammation was strongly associated with transmission of less infectious viruses. Thus, situations in which the selection bottleneck is made more stringent, that is, microbicide use, appear to favor acquisition of “fitter” virus, while situations in which the bottleneck is reduced, that is, through genital inflammation, allow acquisition of both fit and less fit viruses (Abstract RT01.01³).

Gustavo Kijak described viral evolution dynamics in recently infected subjects from high-risk cohorts in East Africa and Thailand (RV217). He described two intriguing phenomena: first, the emergence of rapid CTL escape within a few days; second, the presence of minor viral variants that subsequently displaced the dominant virus population, apparently due to better replicative fitness and greater resistance to type I IFN, despite greater dependence of the dominant variant on $\alpha 4\beta 7$ integrin binding (Abstract RT01.02³). Dan Barouch presented data challenging the current paradigm of “sterilizing immunity”: in 25 adult rhesus macaques, low levels of viral RNA and DNA were detected in distal tissues for 7 days postintra-vaginal challenge with SHIV-SF162P3 despite in-

travenous infusion of a fully protective dose of bNAbs PGT121, although the virus appeared to be completely cleared by day 10 postchallenge.⁷ These data demonstrate that following mucosal challenge, HIV-1-specific bNAbs can mediate protection by clearing early viral foci in distal tissues, rather than by true “sterilizing immunity,” which is generally understood to mean complete blockade of viral infection.

Creating Frameworks for Successful Implementation and Translation of Research

One of the main frameworks for the successful implementation of HIV prevention research is the regulatory oversight provided by ethics review committees. Efforts by countries conducting clinical trials focus on streamlining the ethics review process and addressing barriers that cause delays with protocol review processes. Jane Humprey Mashingia discussed an initiative of the East African Community (EAC), an intergovernmental organization of six partner countries: Tanzania, Kenya, Uganda, Rwanda, Southern Sudan, and Burundi, to address this challenge. The initiative, called the East African Community Medicines Regulatory Harmonization (EAC-MRH) Program, aims to harmonize the regulatory framework for registration of medicinal products and regulation of clinical trials in partner countries, thereby reducing complexities and delays often associated with these critical steps (Abstract OA13.01³). The EAC-MRH program is one of six African medium-term subregional programs. Boitumelo Mokgatla described a secure web-based platform that has been developed to improve the capacity of African countries to conduct ethics reviews in a standardized, efficient manner. The platform is currently being used by 29 centers in 8 African countries and has significantly improved research protocol submission, review, and approval process (Abstract OA13.04³). Laura Marie Lazar (Abstract OA13.05³) highlighted the importance of prioritizing African countries for HIV prevention research funding showing that in 2015, 740,277 of the total 868,101 participants in HIV prevention clinical trials were from Africa. Unfortunately, funding for African scientists remains poor despite the huge investment in global HIV prevention research between 2000 and 2015 (available online at www.hivresourcetracking.org).

The efficacy of voluntary medical male circumcision (VMMC) in reducing HIV transmission among males had previously been established.^{8–11} However, innovative implementation strategies were needed to realize the impact of VMMC as a successful intervention method. Karin Hatzold described how her team used a market segmentation strategy to identify three segments of the target population prioritized for VMMC. Using a human-centered design approach, demand was created for VMMC services to accelerate VMMC uptake in Zimbabwe (Abstract RT04.02³). John Stover evaluated the impact of a VMMC program in Kenya by using three models to quantify the benefits of VMMC. He estimated that 21,000 to 33,000 infections may have been averted between 2008 and 2015. In addition, the VMMCs already performed will continue to avert future infections throughout the sexually active lifetimes of the study populations (Abstract OA24.01³). Bertran Auvert noted that for young people 18 years and younger at Orange Farm, South Africa, VMMC increased from 9% in 2008 to 61% in 2011 and to 87.5% in

TABLE 1. HIV PREVENTION CLINICAL TRIALS THAT ARE DESCRIBED IN THIS CONFERENCE SUMMARY

Trial	Intervention	Phase	Strategy	Trial sites	Population	Status
AMP study HVTN 703/ HPTN 081	Antibody infusion	2b	Intravenous infusion of human mAb, VRC01	Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe	Women, ages 18–50	Ongoing
AMP study HVTN 704/ HPTN 085	Antibody infusion	2b	Intravenous infusion of human mAb, VRC01	Brazil, Peru, Switzerland, United States	Men and transgender persons, ages 18–50	Ongoing
ASPIRE/ MTN-020	Vaginal ring	3	Dapivirine ring	Malawi, South Africa, Uganda, Zimbabwe	Women, ages 18–45	Completed Jun 2015
CAPRISA 004	Vaginal microbicide	2b	1% TFV gel	South Africa	Women, ages 18–40	Completed Dec 2009
CONRAD 124	Vaginal microbicide	1	1% TFV gel	United States	Women, ages 21–89	Completed Oct 2014
CONRAD 134	Vaginal insert		Placebo vaginal inserts	United States	Women, ages 18–50	Completed Mar 2016
EPIC	Technology for PrEP		PrEP technology for PrEP adherence support	United States	Men, ages 18–29	Ongoing
HPTN 078	Behavioral		Enhancing recruitment (via deep chain respondent-driven sampling), linkage to care and treatment	United States	Men (MSM) ages ≥16, HIV+, and not virally suppressed	Ongoing
HPTN 083	PrEP	3	Injectable cabotegravir LA for PrEP	Argentina, Brazil, India, Peru, South Africa, Thailand, Vietnam, United States	Men (MSM) and transgender women, ages ≥18	Ongoing
HVTN 094	Vaccine	1	GEO-D03 DNA prime, modified MVA boost	United States	Men and women, ages 18–50	Completed Jan 2016
HVTN 096/EV04	Vaccine	1	NYVAC prime, NYVAC + VaxGen gp120 B/E boost	Switzerland	Men and women, ages 18–50	Completed Dec 2014
HVTN 100	Vaccine	1/2	ALVAC prime, bivalent sub-type C gp120/MF59 boost	South Africa	Men and women, ages 18–40	Ongoing
HVTN 505	Vaccine	2b	DNA prime, rAD5 boost	United States	Men and transgender persons, ages 18–50	Completed Apr 2013
HVTN 702	Vaccine	2b/3	ALVAC prime, bivalent sub-type C gp120/MF59 boost	South Africa	Men and women, ages 18–35	Ongoing
IAVI A003/CHOP HVDDT 001	Antibody coded by AAV vector	1	Recombinant AAV vector delivering PG9 antibody	United Kingdom	Men, ages 18–45	Ongoing
MTN 017	PrEP, microbicide	2	Oral FTC/TDF and rectal tenofovir RG 1% gel	Peru, Puerto Rico, South Africa, Thailand, United States	Men and transgender persons, ages ≥18	Completed May 2015
Partners-PrEP	PrEP	3	Oral TDF, FTC/TDF	Kenya, Uganda	Serodiscordant heterosexual couples, ages 18–65	Completed Oct 2010
RV144	Vaccine	3	ALVAC prime and VaxGen gp120 B/E boost	Thailand	Adults, ages 18–30	Completed Jun 2009
RV217	Early Capture HIV Cohort Study (ECHO)		Prospective natural history study following high-risk volunteers	Kenya, Tanzania, Thailand, Uganda	Men and women, ages 18–50, at high risk for HIV-1	Ongoing
RV305	Vaccine	2	Late boost of ALVAC and/or VaxGen gp120 B/E	Thailand	RV144 trial participants, ages ≥18	Ongoing
RV306	Vaccine	2	Combinations of ALVAC and/or VaxGen gp120 B/E	Thailand	Men and women, ages 20–40	Ongoing
VOICE/ MTN 003	PrEP, microbicide	2b	Oral TDF, oral TDF-FTC, or 1% TFV vaginal gel	South Africa, Uganda, Zimbabwe	Women, ages 18–45	Completed Aug 2012

2015. Among adults, however, there was a need to institute additional innovative interventions, including financial incentives to compensate for time lost, to reach 80% uptake over the same period (Abstract OA24.05³).

Several presenters shared best practices in programmatic efforts aimed at HIV prevention, including those that facilitate integration of HIV-related services into routine health-care delivery programs. Susan Allen presented a national plan for couples' voluntary HIV counseling and testing (CVCT) in Zambia. She discussed replication of a successful Rwandan CVCT project in Zambia. Critical elements for the project's success include active engagement of the couple, providing transport and time reimbursement for couples, performance-based payment for community volunteers, and payment of designated government clinic staff (Abstract OA13.06³). Alexandra Hoagland reported on a program that successfully recruited local women with access to a long-acting reversible contraceptive (LARC), trained them to promote LARC among their peers, and thereby increased overall demand for LARC in the community (Abstract OA23.01³). Mubiana Inambao presented data on the effectiveness of a program providing integrated HIV prevention and family planning services for couples in Zambia. This program trained more than 250 nurses in LARC insertion and more than 390 couples testing/family planning counselors in a total of 55 urban clinics. Collectively, more than 120,000 couples received services, exceeding the initial targets and successfully averting numerous HIV infections and unintended pregnancies (Abstract OA23.03³).

HIV Care Continuum

The challenges of successfully implementing the HIV prevention/treatment cascade were the focus of several presentations. Rudy Patrick reported on the testing and care continuum in Washington, DC, using National HIV Behavioral Surveillance (NHBS) data collected from 2007 through 2015. The HIV testing and care continua can often highlight gaps and disparities in testing and care within populations at risk. Although engagement in care and ARV use has significantly increased in 2015 for certain groups, such as people who inject drugs, important gaps remain (Abstract OA10.01³). Etienne Karita discussed work with female sex workers (FSW) in Kigali, Rwanda, a population with an estimated HIV prevalence of 45%. Encouragingly, nearly all (~98%) FSW in Kigali have been tested and know their HIV status, use of ARVs is nearly universal, and approximately 80% of FSW on ARV have suppressed viral load (Abstract OA10.02³).

Ivan Balan reported on studies to determine acceptability of rapid HIV tests for screening potential sexual partners, such as a recently developed smartphone dongle-based "lab on a chip" that uses microfluidics to perform an ELISA for both syphilis and HIV using a finger prick blood sample. Over 80% of those surveyed to date (MSM and TGW who regularly engage in unprotected receptive anal intercourse) indicated they would likely use such a test (Abstract OA10.03³). Kate Mitchell discussed a mathematical modeling study to assess the potential impact (in terms of reduction in HIV incidence) of viral suppression among HIV-positive MSM in Baltimore as part of the HPTN 078 trial. The model found that large increases in viral suppression are needed to achieve moderate

reductions in HIV incidence in this setting. However, achieving current U.S. targets for diagnosis, retention in care, and viral suppression by 2020 is projected to reduce HIV incidence by approximately 50% (Abstract OA10.04³).

Closing Messages

In the last several years, enormous progress has been made in the realm of HIV prevention, ranging from treatment to prevent ongoing secondary transmission to the protective efficacy of daily oral TDF/FTC PrEP. However, realizing the full potential of these interventions will require careful collaboration between researchers, public health practitioners, government systems, funders, clinicians, and stakeholders.

As presented at this conference, basic science investigations are continuing to elucidate HIV transmission dynamics and the nature of the earliest host/virus interactions at mucosal surfaces. Novel interventions are being developed to block these interactions using monoclonal antibodies and/or antiretrovirals. Prevention modalities are expanding to include new technologies and delivery systems, including injectable and topical products, which will broaden the repertoire of choices available to men and women at risk. Furthermore, multipurpose tools are being developed to deliver ARVs in combination with contraceptives to women of child-bearing age. Together, these approaches hold great promise for the future.

Access to HIV prevention modalities, diagnostics, and care is generally increasing worldwide; however, barriers persist in access to prevention and care among vulnerable populations worldwide. Efforts to document adherence in PrEP and microbicide trials have increased our awareness of the challenges faced by at-risk populations. Although a wide range of prevention strategies and products now exist, efforts to disseminate these technologies cannot succeed without sustained commitment by government, industry, NGOs, and community partners.

Ongoing prevention studies currently include two Phase 3 trials involving antibody-mediated prevention (HVTN 703/704 and HPTN 081/085). These are the first HIV trials to directly test the efficacy of intravenously delivered monoclonal antibodies. Another ongoing trial, HPTN 083, will assess the efficacy of injectable long-acting cabotegravir as PrEP. Results from these trials, as well as other vaccine and microbicide studies planned for the next 3–5 years, are awaited with cautious optimism, and are expected to shape the future of HIV prevention science moving into the next decade (Table 1). Some of these studies and other advances in biomedical HIV prevention research will be presented in the next HIVR4P conference to be held from October 22 to 25, 2018, in Madrid, Spain.

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Address correspondence to:

Bargavi Thyagarajan
Global HIV Vaccine Enterprise
64 Beaver Street No. 352
New York, NY 10004

E-mail: bthyagarajan@vaccineenterprise.org