HPTN 2022 State of the Network

Myron S. Cohen, MD
Wafaa El-Sadr, MD, MPH
Principal Investigators, HPTN

HPTN
HIV Prevention Trials Network

ANNUAL MEETING
2022

Priority Areas as per RFA (2020-2027)

HPTN HIV Prevention Trials Network

Identify **novel ARV-based methods and delivery systems** for HIV prevention

Develop **multi-purpose technologies (MPTs)** for HIV prevention as well as for contraception, prevention of other STIs

Evaluate **broadly neutralizing antibodies (bnAbs)** alone or in combination that prevent HIV acquisition, in collaboration with the HVTN

Design and conduct population-specific **integrated strategy studies** that combine biomedical, socio-behavioral and structural interventions for HIV prevention to maximize their effectiveness

Scientific Aims

- **Develop new biomedical interventions:**
  - *Novel ARV methods & delivery systems*
  - *Multi-Purpose Technologies (MPTs)*
  - *Broadly neutralizing antibodies (bnAbs)*

Discovery

- **Optimize integration of proven interventions to achieve high effectiveness and impact:**
  - *Biomedical*
  - *Socio-behavioral*
  - *Structural*

Impact

Clinical Research Sites

HPTN
HIV Prevention Trials Network

69
HPTN Sites

14
Countries

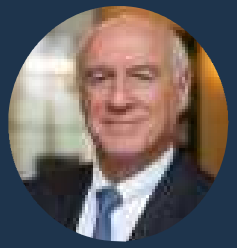
24
African Sites

4
Asian Sites

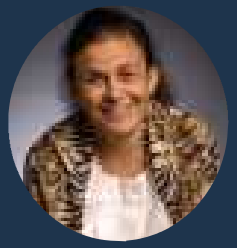
30
North American Sites

11
South American Sites

Network Structure – Leaders



Myron
S. Cohen



Wafaa
El-Sadr

Executive Committee (EC)

- Myron S. Cohen
- Wafaa El-Sadr
- Quarraisha Abdool Karim
- Chris Beyrer
- Sinead Delany-Moretlwe
- Deborah Donnell
- Susan Eshleman
- Sybil Hosek
- Raphael Landovitz
- Nyaradzo Mgodi
- David Serwadda
- Sten Vermund
- Nirupama Sista
- Melissa Turner
- Darrell Wheeler
- 2 NIH Representatives

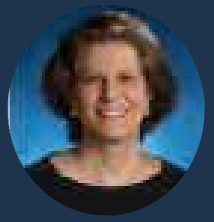
Leadership and Operations Center (LOC) FHI 360

Nirupama
Sista

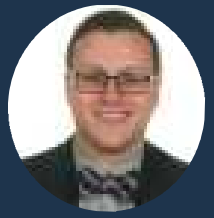
Statistical and Data Management Center (SDMC) SCHARP

Deborah
Donnell

Laboratory Center (LC) Johns Hopkins University



Susan
Eshleman



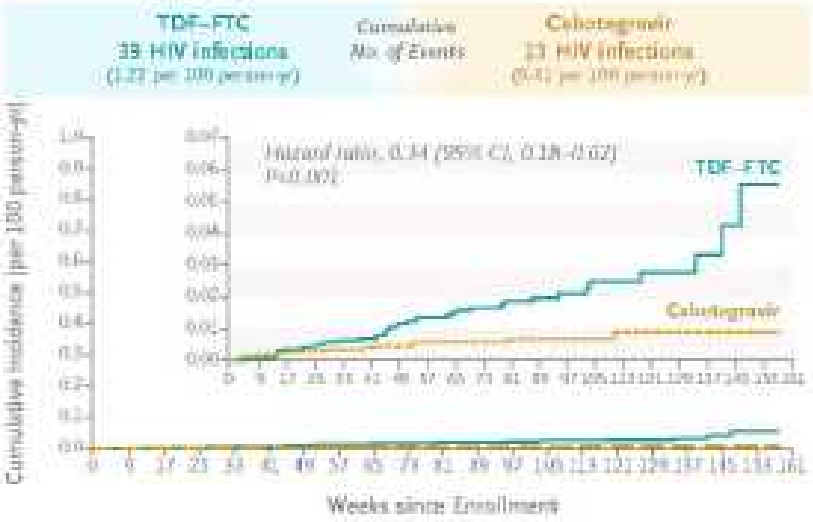
Mark
Marzinke

Working Group Leadership

Science Committees	Chair	Co-Chair
Adolescents at Risk	Audrey Pettifor	Linda-Gail Bekker
Sexual and Gender Minority	Kenneth Mayer	Nittaya Phanuphak
Substance Users	Steffanie Strathdee	Nabila El-Bassel
Women at Risk	Ada Adimora	Philippa Musoke
Working Groups	**Chair**	**Co-Chair**
Biomedical Sciences	Jeanne Marrazzo	Joseph Eron
Community	Melissa Turner	Ntando Yola
Ethics	Jeremy Sugarman	Jerome Singh
Socio-Behavioral Sciences	Ariane van der Straten	Julie Pulerwitz
Technical Liaisons		
Susan Buchbinder, Connie Celum, Sharon Hillier		

New ARVs for PrEP

Incident HIV Infection



Safety

Adverse Events	TDF–FTC (N=2282)	Cabotegravir (N=2280)
	no. (%)	no. (%)
Any adverse event of grade 2 or higher	2216 (92.7)	2196 (92.4)
Any adverse event of grade 3 or higher	767 (33.6)	727 (31.9)
Serious adverse event	121 (5.3)	130 (5.8)
Adverse events of special interest		
Seizure	5 (0.2)	2 (0.1)
Liver-related adverse event resulting in discontinuation of oral tablets or both oral tablets and injections	48 (2.1)	47 (2.1)

RESEARCH SUMMARY

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

Landovitz RJ et al. DOI: 10.1056/NEJMoa2101016

CLINICAL PROBLEM

More than 5000 new HIV infections occur each day worldwide, despite the availability of effective preventive strategies. Daily oral tenofovir disoproxil fumarate–emtricitabine (TDF–FTC) is one option for preexposure prophylaxis, but long-acting regimens could help increase adherence and, therefore, efficacy.

CLINICAL TRIAL

Design: An international phase 2b–3, randomized, double-blind, noninferiority trial was conducted to compare long-acting cabotegravir with daily TDF–FTC in adults at high risk for HIV infection.

Intervention: 4570 cisgender men and transgender women who have sex with men were assigned to receive long-acting intramuscular cabotegravir every 8 weeks plus oral placebo daily or placebo injections every 8 weeks plus oral TDF–FTC daily. The primary efficacy outcome was incident HIV infection.

RESULTS

Efficacy: During a median follow-up of 1.4 years, long-acting cabotegravir was superior to daily TDF–FTC in preventing incident HIV infection.

Safety: The occurrence of adverse events of grade 2 or higher — the primary safety outcome — did not differ substantially between the groups.

LIMITATIONS AND REMAINING QUESTIONS

- Integrase strand-transfer inhibitor resistance was detected in 4 participants in the cabotegravir group who acquired HIV infection; strategies are needed to prevent such resistance.
- The logistics of implementing cabotegravir-based prevention programs warrant further study.

Links: Full Article | NEJM Quick Take | Editorial

CONCLUSIONS

Injectable cabotegravir given every 8 weeks was superior to daily oral TDF–FTC for preventing HIV infection among high-risk cisgender men and transgender women who have sex with men.

N Engl J Med. 2021 Aug 12;385(7):595-608

THE LANCET

Cabotegravir for prevention of HIV-1 in women: results from HPTN 084, a phase III, randomised controlled trial

Sinead Delany-Moretlwe, James P. Hughes, Peter Bock, Samuel Gurrion Ouma, Portia Hunidzarira, Dishiki Kalonji, Noel Kayange, Joseph Makhema, Patricia Mandima, Carrie Mathew, Elizabeth Spooner, Juliet Mpendo, Pamela Mukwekwerere, Nyaradzo Mgodi, Patricia Nahirya Ntege, Gonasagrie Nair, Clemensia Nakabiito, Harriet Nuwagaba-Biribonwoha, Ravindre Panchia, Nishanta Singh, Bekezela Siziba, Jennifer Farrior, Scott Rose, Peter L. Anderson, Susan H. Eshleman, Mark A. Marzinke, Craig W. Hendrix, Stephanie Beigel-Orme, Sybil Hosek, Elizabeth Tolley, Nirupama Sista, Adeola Adeyeye, James F. Rooney, Alex Rinehart, William R. Spreen, Kimberly Smith, Brett Hanscom, Myron S. Cohen, and Mina C. Hosseinipour on behalf of the HPTN 084 study group.
The Lancet, 2022-05-07, Volume 399, Issue 10337, Pages 1779-1789

ViiV CAB LA PrEP IS APPROVED in the US: What's Next?

- Open label extension (OLE) studies will estimate continued safety and protection, PK, resistance, etc., and include a pregnancy and adolescent substudies
- ViiV is working to gain approval for PrEP in all HPTN 083 and HPTN 084 in participating countries; affordable access where it is awaiting approval BEYOND the US
- Studies to explore different routes of administration (e.g., thigh). fewer injections/year and more
- Combine cabotegravir LA with contraceptives in future studies?

Pregnancy Sub-study in HPTN 084 OLE

- Estimate the incidence of pregnancy among participants during the OLE period
- Evaluate safety and infant outcomes among pregnant participants
- Evaluate the PK of CAB LA among pregnant participants, combining blinded, unblinded and OLE periods
- Evaluate concentration in breastmilk and infants among women who receive CAB LA injections during pregnancy and/or the early post-partum period.

HPTN-Gilead Collaboration

- **Long-acting injectable drug developed by Gilead – lenacapavir, a first-in-class selective HIV capsid inhibitor, with sub-cutaneous injections <u>every 6 months</u>**

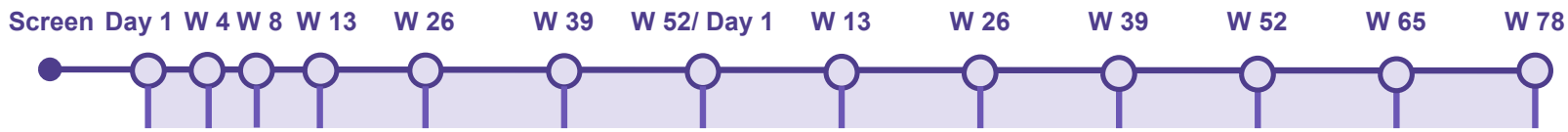
- **Gilead is pursuing simultaneous treatment and prevention studies, including two company sponsored efficacy studies for prevention**

- **HPTN and Gilead will develop two companion studies in collaboration:**

  - **HPTN 102/Purpose 3: A lenacapavir Phase 2 PK, safety, acceptability in cis-gender women in the US**
  - **HPTN 103/Purpose 4: A phase 2 PK, safety, acceptability of lenacapavir in people who inject drugs (PWID) in the US**

HPTN 102 &103- Gilead Purpose 3 & 4

Visit Schedule



ARM A

Oral LEN on Days 1 and 2 + SC LEN every 26 weeks

Daily oral F/TDF

ARM B

Daily oral F/TDF

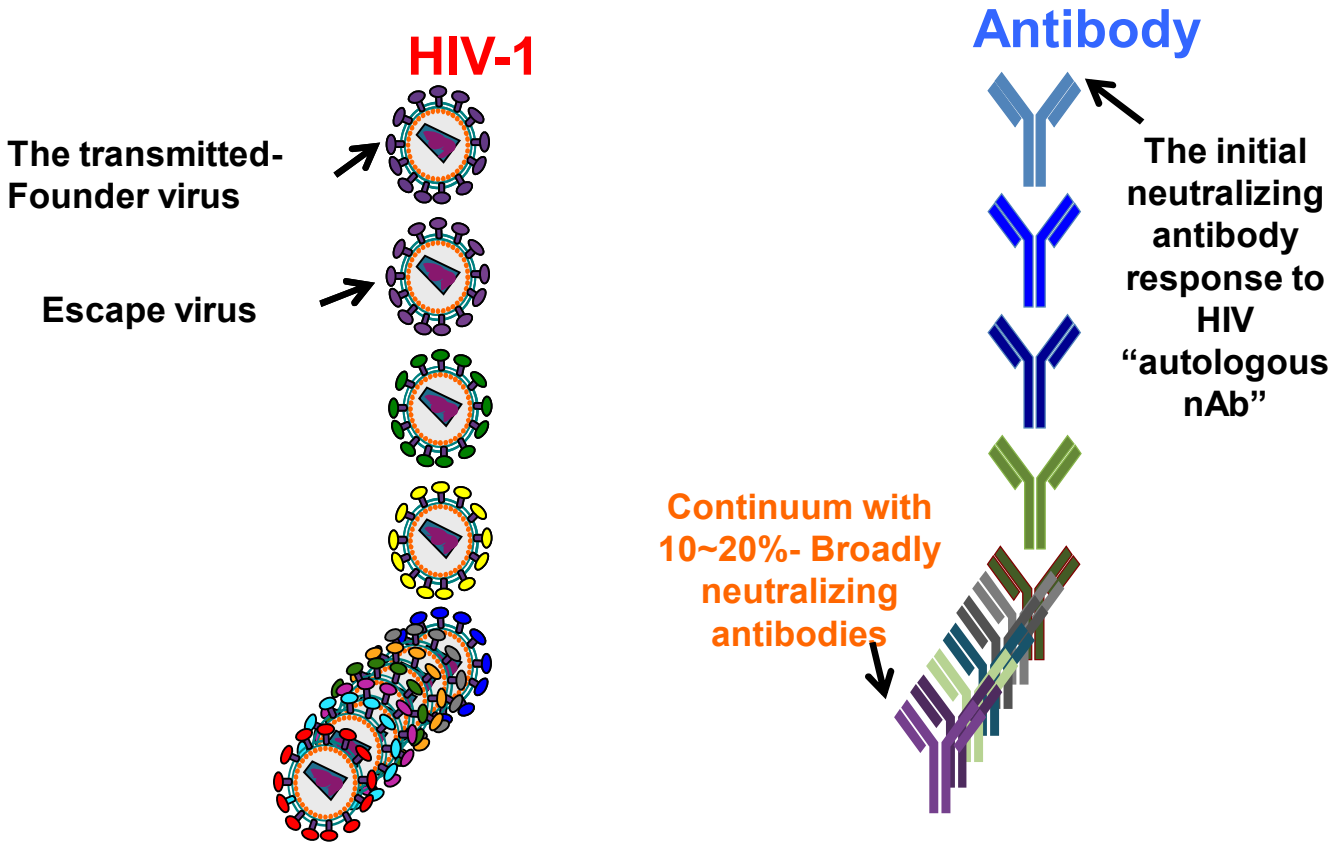
Daily oral F/TDF

Approximately 1 year of randomized open-label study duration

Approximately 1.5 years of PK tail coverage for Arm A after completion of or early transition from 52 weeks of randomized open-label phase; continued access for Arm B

Broadly neutralizing antibodies for Prevention

Broadly Neutralizing Antibodies



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

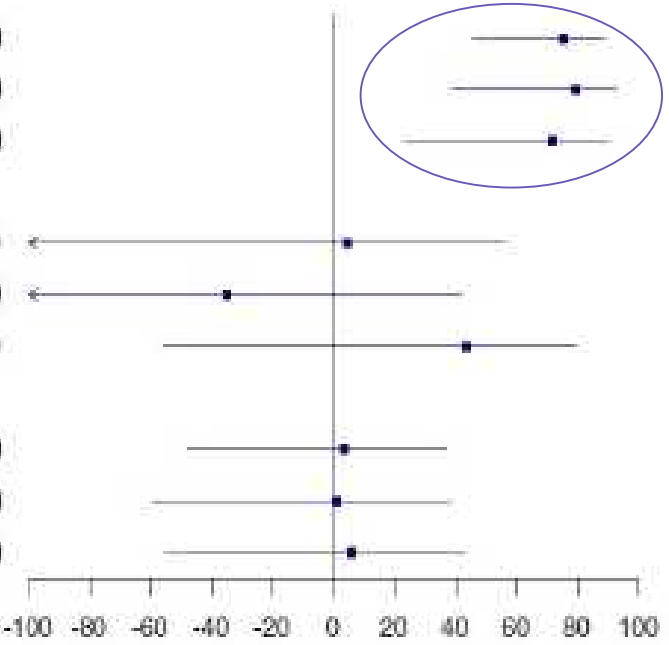
Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

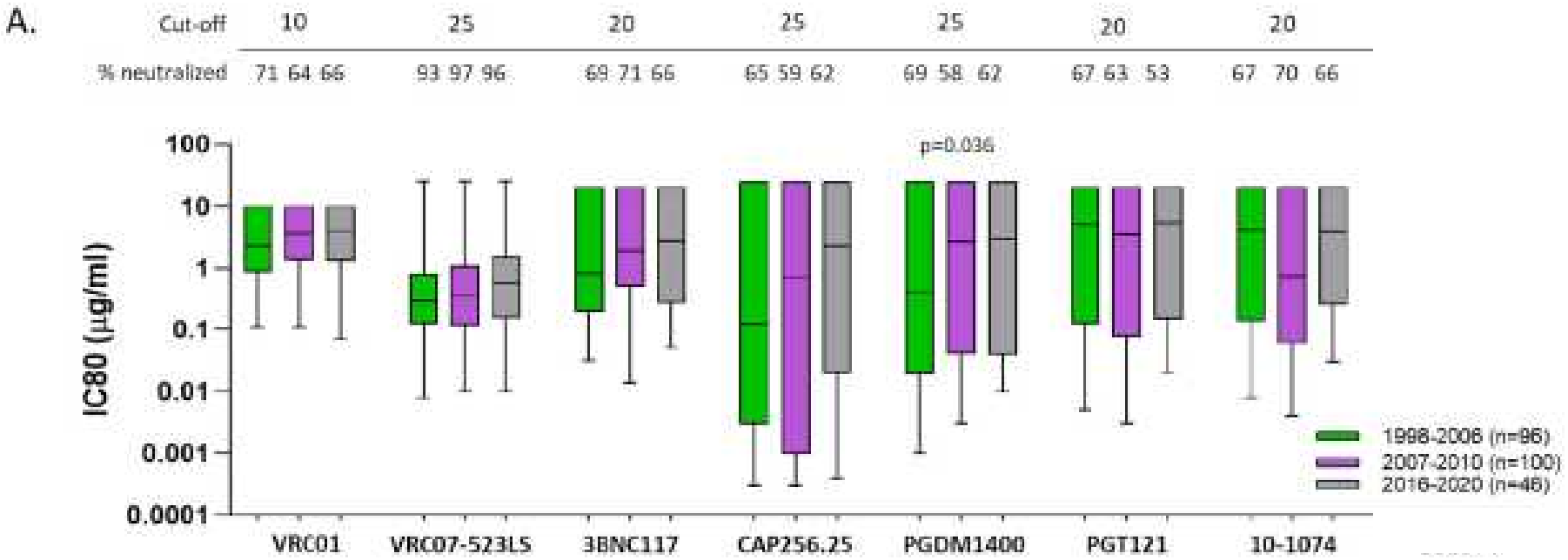
N Engl J Med. 2021 Mar 18;384(11):1003-1014

Prevention Efficacy Declines with Resistance

Neutralization Resistance Level	Treatment arm	No. of HIV-1 Infections	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)
<1 µg/ml	Control	19	2203	0.86	
	VRC01 Pooled	9	4427	0.20	75.4 (45.5, 88.9)
	VRC01 10 mg/kg	4	2210	0.18	79.2 (39.1, 92.9)
	VRC01 30 mg/kg	5	2217	0.23	71.5 (23.3, 89.4)
1-3 µg/ml	Control	10	2203	0.45	
	VRC01 Pooled	19	4427	0.43	4.2 (−108.7, 56.0)
	VRC01 10 mg/kg	13	2210	0.59	−35.2 (−214.3, 41.8)
	VRC01 30 mg/kg	6	2217	0.27	43.5 (−55.8, 79.5)
>3 µg/ml	Control	35	2203	1.59	
	VRC01 Pooled	70	4427	1.58	3.3 (−48.0, 36.8)
	VRC01 10 mg/kg	37	2210	1.67	0.9 (−59.7, 38.5)
	VRC01 30 mg/kg	33	2217	1.49	5.8 (−55.1, 42.7)



Viruses are not getting significantly more resistant over time to most bnAbs



Mkhizhe, Morris, Moore, Beaume et al

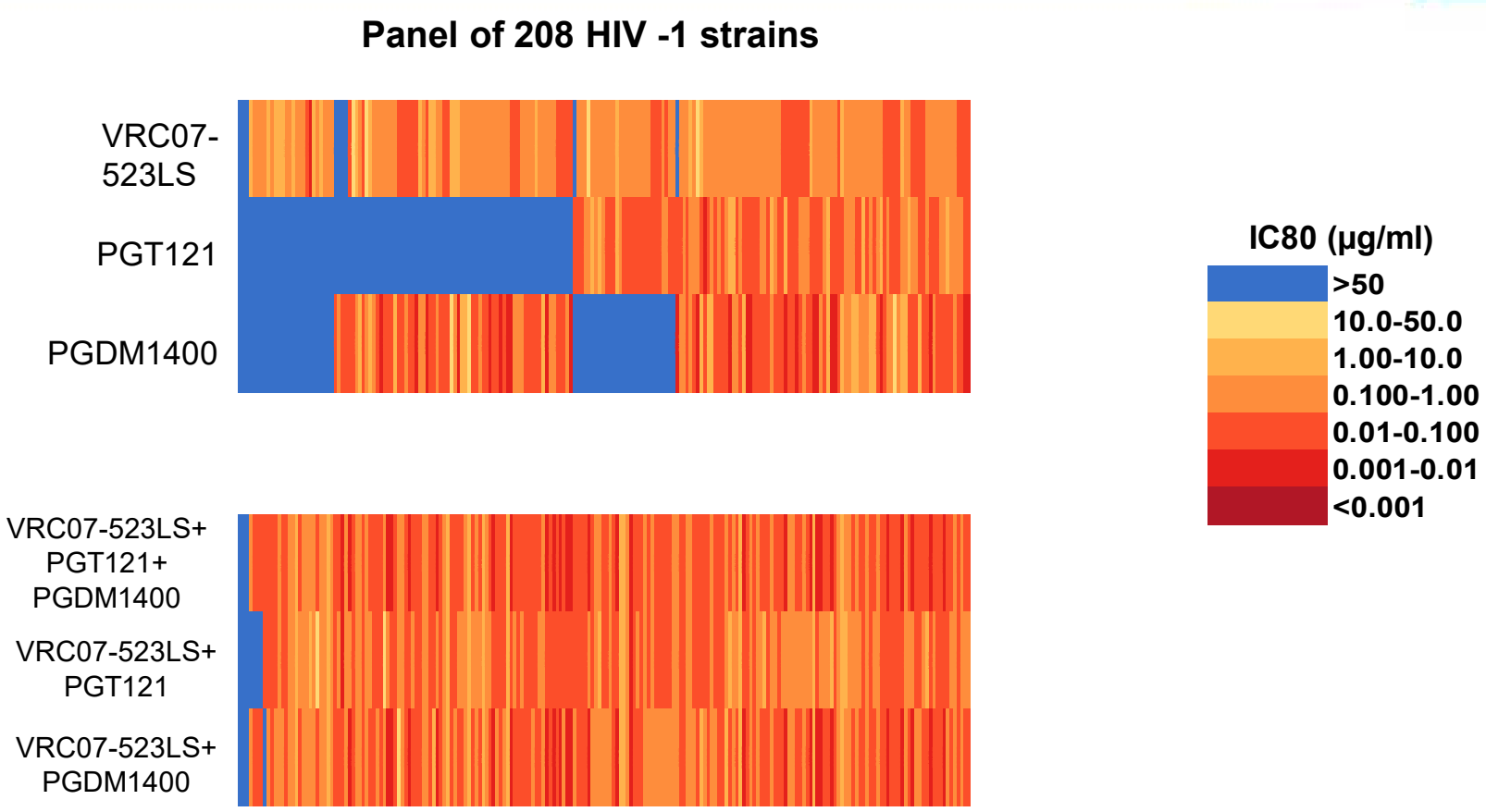
Differences of neutralization sensitivity between viruses over calendar time were evaluated using the Jonckheere-Terpstra test for trend.

Criteria for a bNab PrEP Product

- Breadth (90% coverage)?
- Potency (SubQ administration????)
- Durability (6 months)?
- All mAbs combinations provide similar duration of coverage
- Safety comparable to small molecule antiretroviral PrEP agents

bnAB PrEP MIGHT provide another tool, avoid ART resistance, and serve as very long-acting HIV prevention

Antibody Combination for PrEP?



bNab PrEP Products

Study	Product (s)	Routes	Long-acting	Combination	Status
HVTN 703/HPTN 081 HVTN 704/HPTN 085	VRC01	IV			Completed
HVTN 127/HPTN 087	VRC07-523LS	IV, SC, IM	√		Manuscript in progress
HVTN 130/HPTN 089	PGT121 PGDM1400 10-1074 VRC07-523LS	IV	√	√	Manuscript in progress
HVTN 136/HPTN 092	PGT121.414.LS VRC07-523LS	IV, SC	√	√	Enrollment complete
HVTN 140/HPTN 101	**PGDM1400LS VRC07-523LS PGT121.414.LS**	**IV, SC (?)**	√	√	Currently enrolling
HVTN 141/HPTN 105	**VRC01.23LS ePGDM1400v9-LS ePGT121v1-LS**	**IV, SC (?)**	√	√	Protocol in development

Concept sheet

A Phase I, Open-Label Study of the Safety, Antiviral & Immunomodulatory Activity of Broadly Neutralizing Antibodies 3BNC117-LS-J and 10-1074-LS-J in Combination in ART-treated Adults in sub-Saharan Africa Living with HIV During a Monitored Analytical Treatment Interruption

Submitted by: 3BNC117-LS-J + 10-1074-LS-J ATI Concept Team April 20, 2022

Background and rationale:

As the global community works to extricate itself from the COVID pandemic, the HIV pandemic enters its 40th year. In the last 40 years, great strides have been made in HIV prevention, treatment and cure. Yet, considerable gaps remain in each of these realms—and have widened during the COVID pandemic—as evidenced by ongoing HIV incidence in the face of persistent challenges with ART initiation and adherence (1-3) and limited success with curative strategies, thus far (4-6). Broadly neutralizing antibodies (bnAbs) have the potential to fill gaps in all of these areas, and analytical treatment interruption trial designs facilitate simultaneous exploration of bnAbs' potential for prevention, treatment and cure.

Multi-Purpose Technologies

Source: Adapted from Initiative for Multipurpose Prevention Technologies

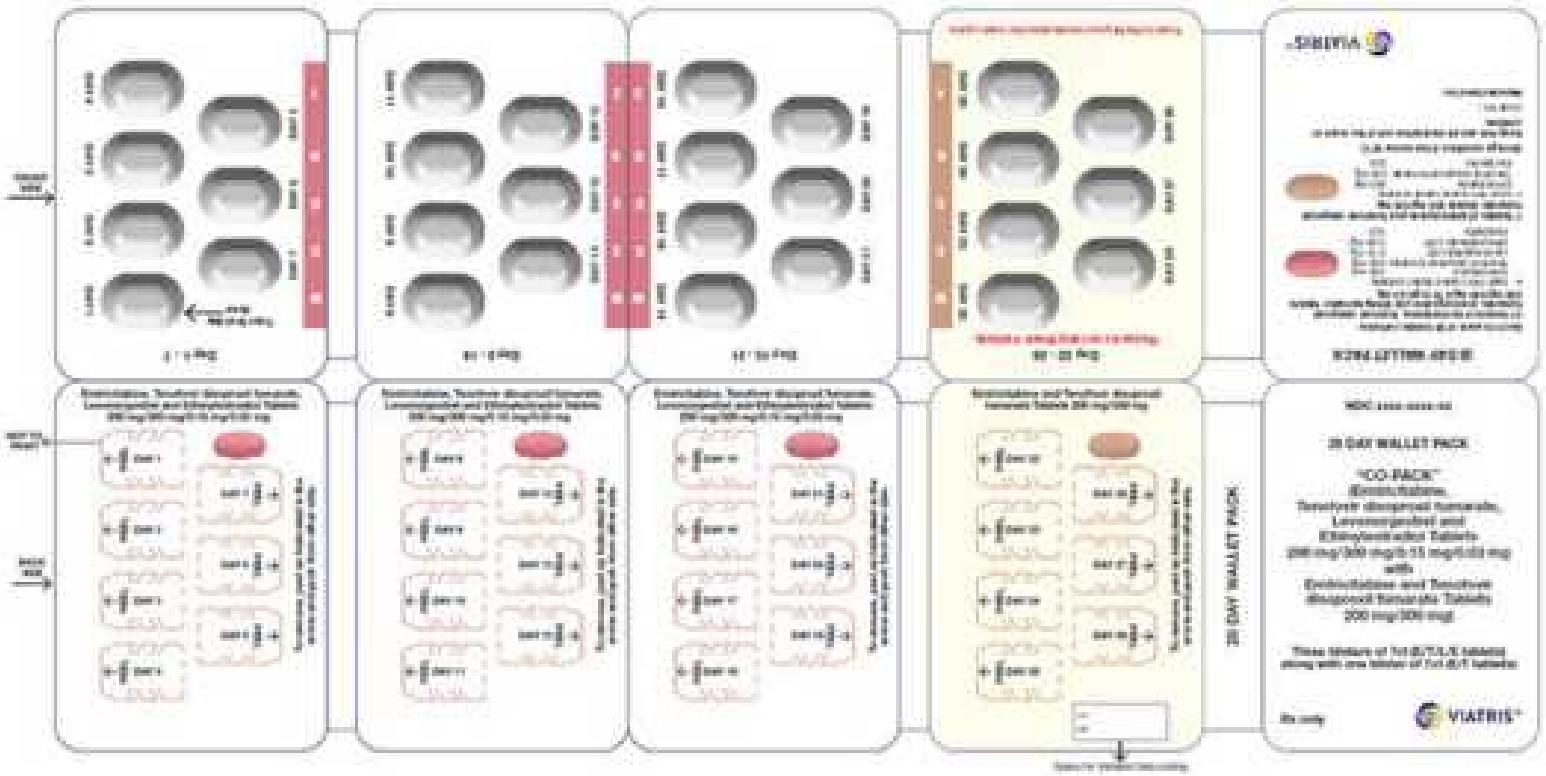
Women want MPTs

83%

of women prefer HIV/STI prevention products with contraception vs. HIV/STI prevention alone

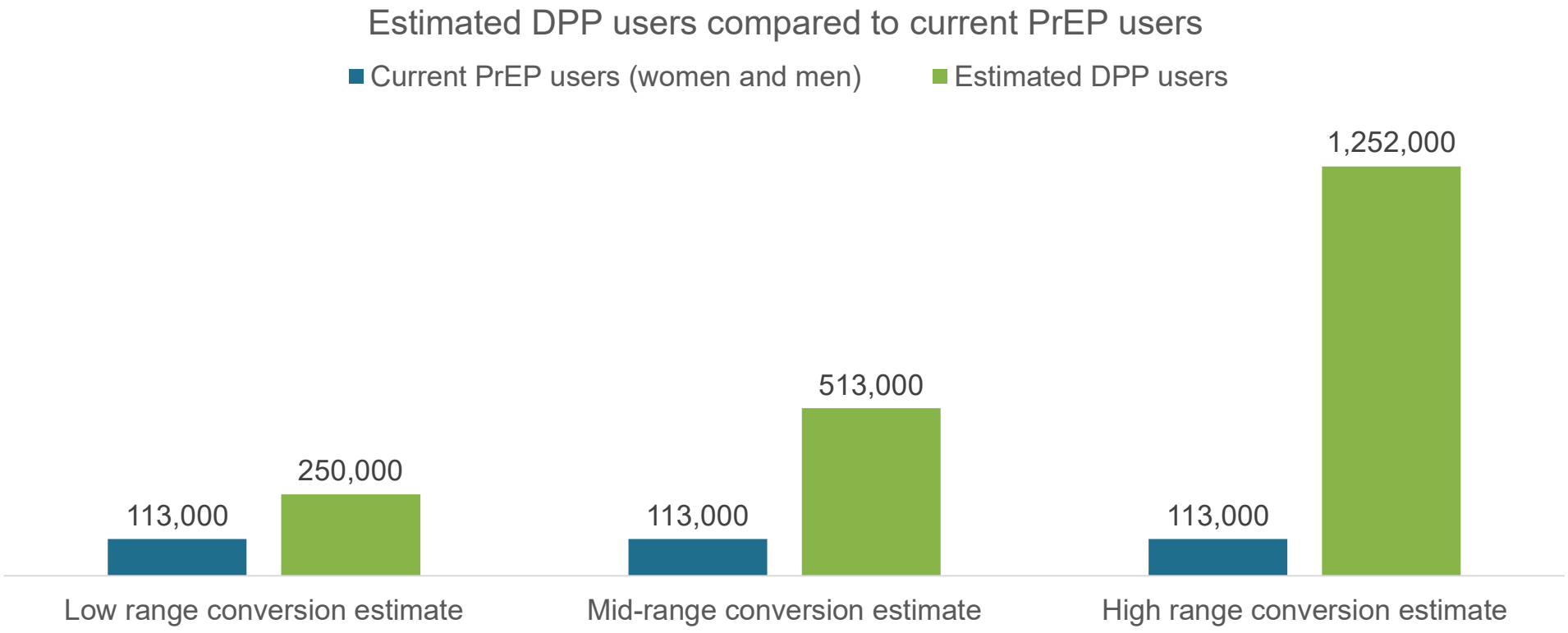
Source: Plagianos et al. (2018) Abstract PO.93, HIV R4P Conference, Madrid, Spain, 21–25 October

HPTN 105 - A Dual Prevention Pill for HIV and Pregnancy



The study product for the co-formulated MPT tablet will be provided in blister packs containing 21 tabs of emtricitabine, tenofovir disoproxil fumarate, levonorgestrel, and ethinyl estradiol (200 mg/300mg/0.15 mg/0.03 mg) + 7 tabs of emtricitabine, tenofovir disoproxil fumarate (200 mg/300mg).

Potentially a 2- to 10-fold increase in PrEP usage



Begg, L. et al. (2020) "Estimating the market size for a dual prevention pill: adding contraception to pre-exposure prophylaxis (PrEP) to increase uptake," *BMJ Sex Reprod Health*. OAP. doi:10.1136/bmjsrh-2020-200662

Achieving Population Impact

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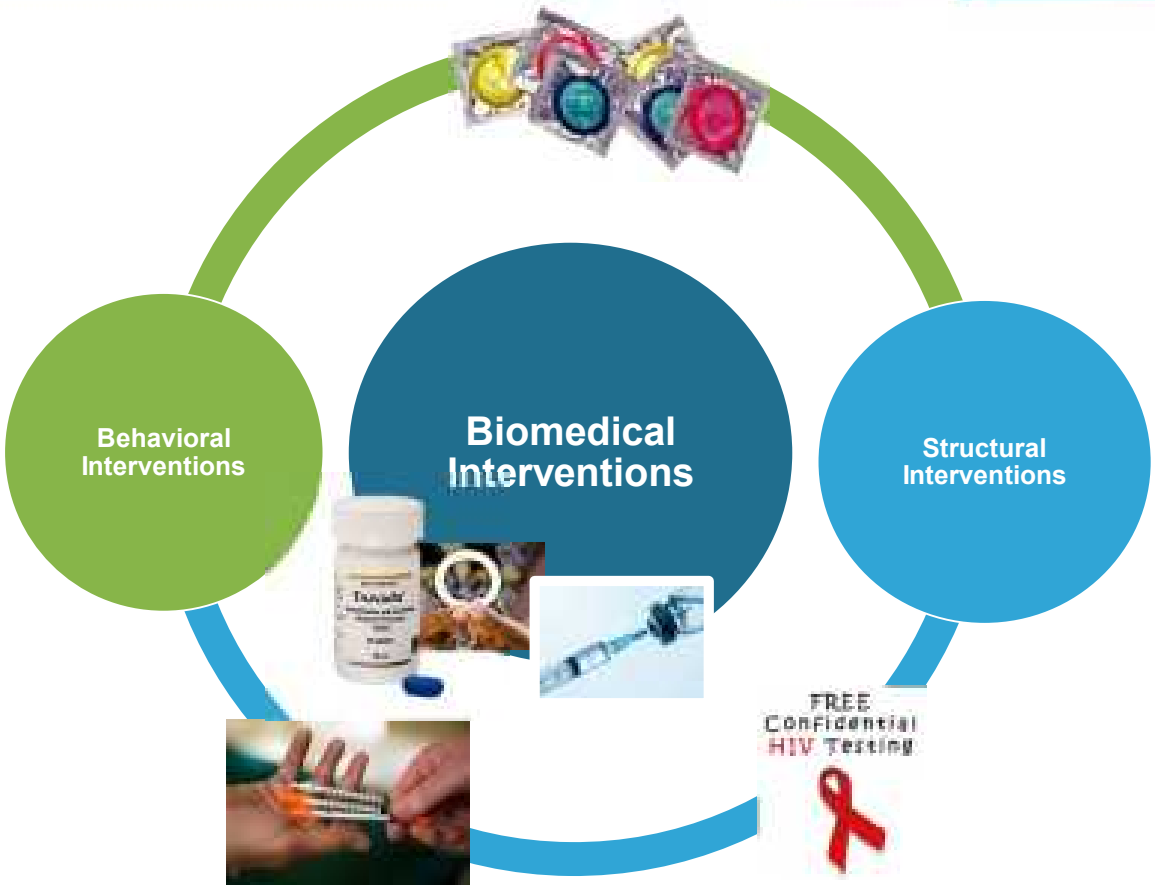
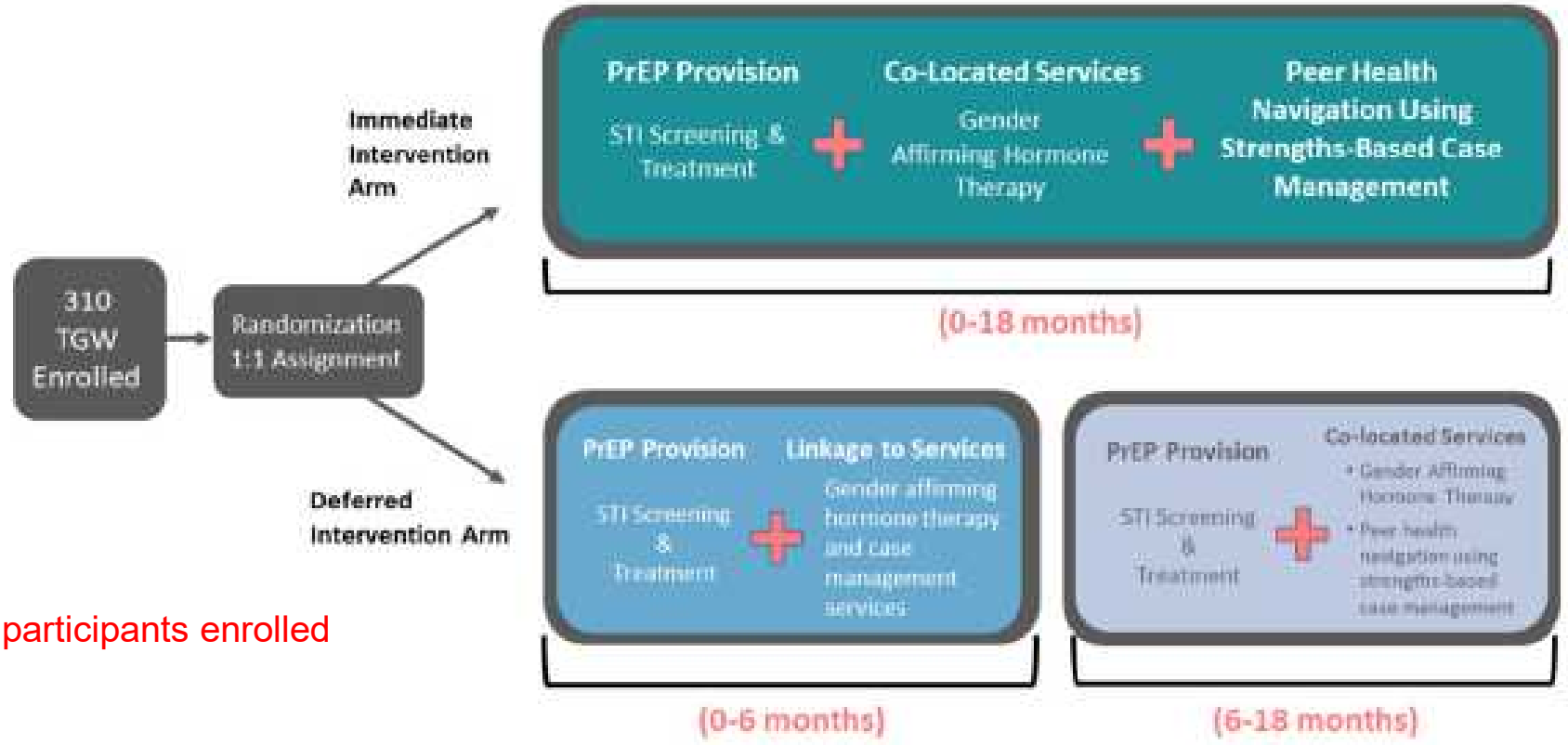
Integrated Strategies



HPTN 091: Study Design



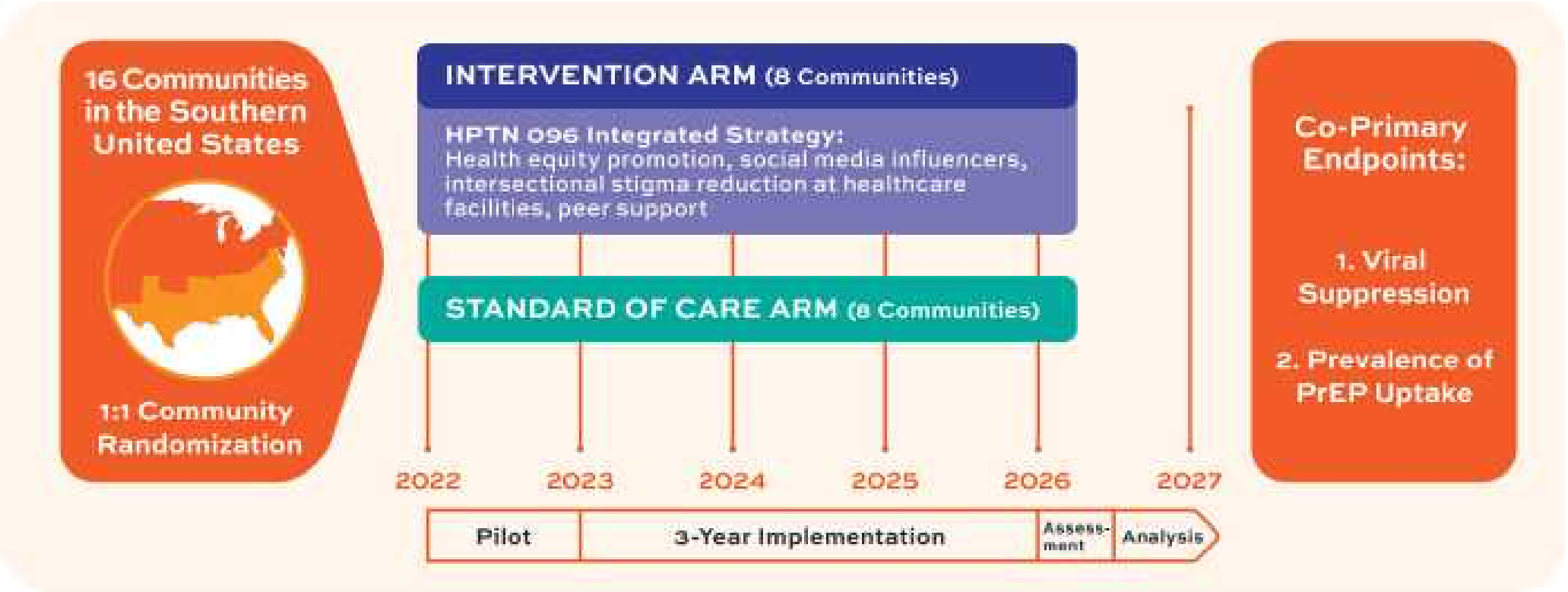
169 participants enrolled

Integrated Strategies – HPTN 094

Comparing the efficacy of “one stop” integrated health services prevention in a mobile unit (Intervention): medication for opioid use disorder (MOUD), ART or PrEP, STI test and treat, harm reduction supplies – including naloxone kits plus peer navigation to an active control arm that receives peer navigation to integrated health services in the community for people who inject opioids living with HIV or at risk

174 participants enrolled

Getting to Zero in Black MSM in the American South (HPTN 096)



Pilot communities activated !

How Does The Integrated Strategy Work?

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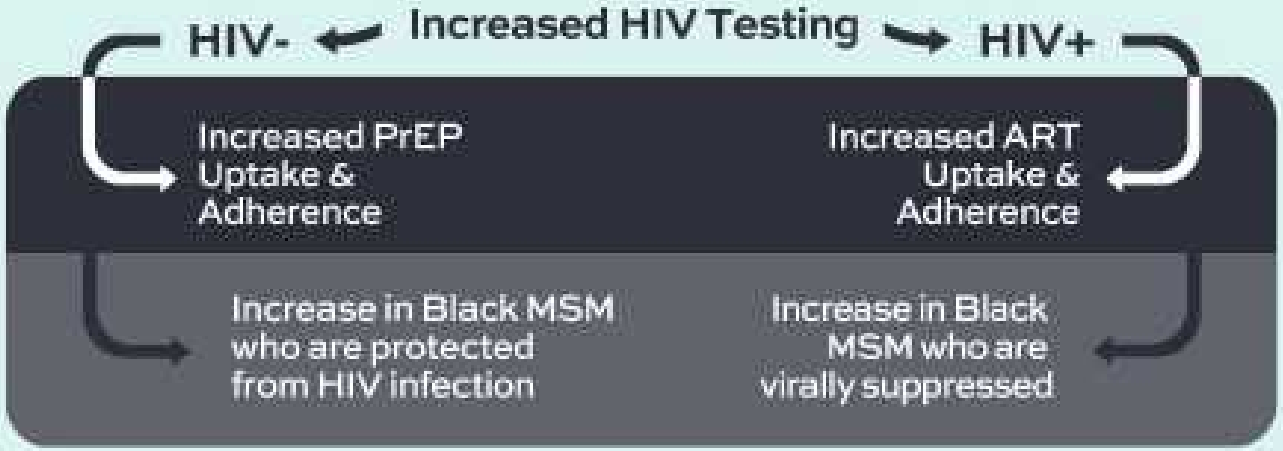
Community-Level Integrated Strategy



Community-Level Outcomes

Community Engagement

<u>Community Engagement is pivotal part of all HPTN studies.</u>

Examples:

- Advocacy for affordable post-trial access to CAB LA in low- and middle-income countries where HPTN 083 and HPTN 084 being conducted
- Active in the development of forthcoming research initiatives (HPTN 102, 103, 104, and 106)
- Convened civil society consultation in preparation for implementation for HPTN 084 OLE
- Community led study branding for HPTN 096

HPTN Scholars Program

HPTN
HIV Prevention Trials Network
SCHOLARS PROGRAM

- Domestic Program established in 2010
  - 48 Scholars to date
- International Program established in 2015
  - 15 Scholars to date
- 60+ Scholars since 2010 (some were in multiple cohorts)
  - 34% men; 66% women
  - 20 datasets: HPTN 037-HPTN 082
  - 50+ mentors
- HPTN involvement
  - Protocol Team Members (HPTN 073, 078, 094, 096)
  - Protocol Team Leadership (HPTN 091, HPTN 096)
  - Memberships/Observerships: Black Caucus, Scientific Committees, and Working Groups

Meet the 2022-2023 HPTN Scholars

Dr. Tina Herrera

Dr. David Zelaya

Dr. Donte Boyd

Dr. Waru Gichane

Dr. Sophia Zamudio-Haas

Dr. Victoria Ndyanabangi

Kudzai Hlahla

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Trials Network

HPTN

Ethics Guidance for Research

Revised February 2020; Updated
December 2021

EDITORIAL

Myron S. Cohen & Lawrence Corey

Combination prevention for COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has produced the fear and disorder inevitably provoked by emerging pathogens. As such, it should also inspire consideration of our experience with HIV over the past 40 years. As with HIV, the mad to reducing infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19), and attendant morbidity and mortality, requires medical and nonmedical strategies. The most important lesson learned from tackling HIV is to use a combination of prevention strategies.

The first step to stopping the spread of SARS-CoV-2 has already been taken—behavioral changes. This reflects a rapid but imperfect understanding of the transmission of this virus. At the beginning of the AIDS epidemic, changes in sexual behavior, condom promotion, and government interventions (closing "hotspots" of HIV transmission such as bathhouses) made a difference. For SARS-CoV-2, masks and gloves, hand hygiene, and "shelter in place" mandates have already demonstrated benefits. More efficient behavioral intervention requires better understanding of the rules governing SARS-CoV-2 transmission. What are the risks from exposure to respiratory droplets, airborne virus, and surface contamination? What concentration of SARS-CoV-2 is required for transmission? Evidence suggests that SARS-CoV-2 transmission is greatest very early in infection prior to development of symptoms—the same lesson learned from HIV. Given this rule [illegible] that will require large trials with [illegible] participants [illegible] is moving more in ear[illegible]

> **"HIV has taught us that multiple concomitant prevention strategies are essential."**

trviral agents reduce the HIV viral load to a point where infected people no longer transmit. This approach, which uses combinations of powerful antiretroviral agents, is now the mainstay of HIV prevention worldwide.

For SARS-CoV-2, we have leapt into a cacophony of clinical trials of drug candidates with differing degrees of plausibility. Preliminary results from a large randomized controlled trial show that the antiviral drug remdesivir substantially reduced the duration of hospitalization for COVID-19. To date, COVID-19 testing results have been used primarily for patient isolation, contact tracing, and quarantine. But effective therapies will lend great urgency for the universal availability of rapid and reliable testing for SARS-CoV-2 infection, so that treatment can be provided when indicated.

Long-acting antiviral agents and monoclonal antibodies that neutralize SARS-CoV-2 may become important nonvaccine pharmacologic tools for prevention. Antiviral agents that prevent replication of SARS-CoV-2 could be used as pre-, peri-, or postexposure prophylaxis. Several different potent monoclonal antibody combinations designed to treat and prevent SARS-CoV-2 will enter clinical trials in June 2020.

Ultimately, a safe and effective vaccine is crucial for preventing COVID-19. Vaccine efforts started immediately after the discovery of SARS-CoV-2. Numerous vaccine candidates have been identified, and early-phase vaccine studies of several are underway. Proof of vaccine efficacy [illegible]

. Science. 2020 May 8;368(6491):551.

Beyond the Magic Bullet: What Will It Take to End the AIDS Epidemic?

Wafaa M. El-Sadr, MD, MPH, MPA

ABOUT THE AUTHOR

Wafaa M. El-Sadr is Global Director of ICAP at Columbia University, Mailman School of Public Health, Columbia University, New York, NY.

prevented the sexual transmission of HIV among heterosexual serodiscordant couples. Evidence soon followed of similar efficacy among gay men in serodiscordant partnerships.[4] The recognition that treatment not only provides individual benefit but also prevents

FIGURE 1— Integrated Strategies for HIV Prevention

Despite these advances, the successful prevention of HIV transmission

in this region, misperceptions regarding personal risk, competing life priorities, and difficulties in negotiating safer sex

El-Sadr. AJPH, July 2021

Thank you very much to all study participants, investigators and site staff, community groups, collaborators and funders

Overall support for the HIV Prevention Trials Network (HPTN) is provided by:

- National Institute of Allergy and Infectious Diseases (NIAID)
- Office of the Director (OD), National Institutes of Health (NIH)
- National Institute on Drug Abuse (NIDA)
- National Institute of Mental Health (NIMH)
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- ViiV Healthcare, Gilead Sciences, The Bill and Melinda Gates Foundation, and Viatris
- Collaborations with HVTN, ACTG, IAVI, AVAC and Rockefeller University

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