Pre-Exposure Prophylaxis for HIV Prevention: Pills and Beyond

Raphael J. Landovitz, MD MSc
Professor of Medicine
David Geffen School of Medicine
University of California Los Angeles
Los Angeles, California

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Landovitz has served on scientific advisory boards for Gilead Sciences, Inc., and Merck & Co., Inc., and served as a consultant to Cepheid. (Updated 08/18/22)

Slide 2

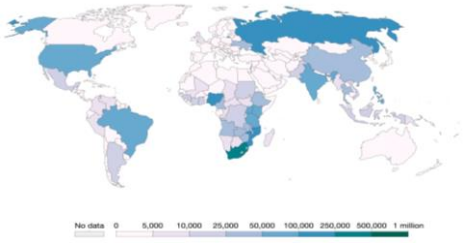
Learning Objectives

After attending this presentation, learners will be able to:

- Explain the origins of preexposure prophylaxis (PrEP)
- Identify the limitations of currently available PrEP agents and strategies
- Describe challenges and opportunities of long-acting injectable PrEP
- Summarize the current pipeline of PrEP agents

Slide 3

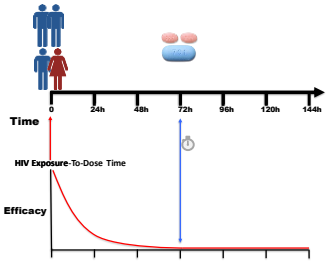
1.5 Million New Infections in 2019
4100 New Infections per Day



UNAIDS. GAP Report 2020.
OurWorldInData.org/hiv-aids

Slide 6

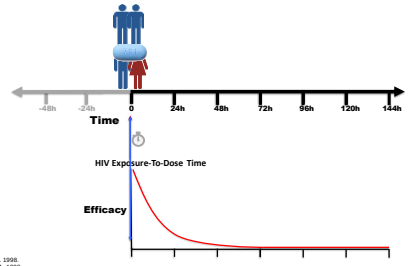
How Did We Get Here?



Tsai CC et al., J Virol. 1998.
Wade NA et al, NEJM. 1998.
Cohen RA et al, J Virol. 2000.

Slide 7

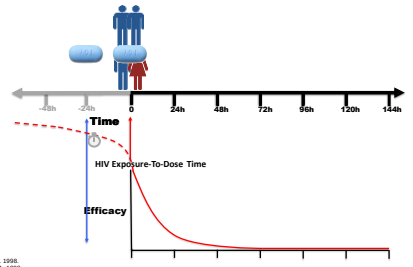
How Did We Get Here?



Tsai CC et al., J Virol. 1998.
Wade NA et al, NEJM. 1998.
Cohen RA et al, J Virol. 2000.

Slide 8

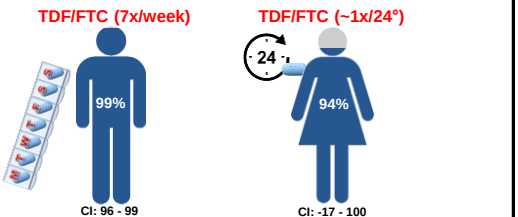
How Did We Get Here?



Tsai CC et al., J Virol. 1998.
Wiafe NA et al., NEJM. 1998.
Eilen RA et al. J Virol. 2000.

Slide 9

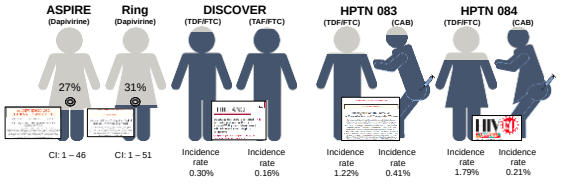
Maximizing the Potential Effectiveness



Anderson P et al, Sci Transl Med. 2012.
Donnell D et al, JAIDS. 2014.
Cottrell ML et al, JID. 2016.

Slide 10

"PrEP 3.0": Trials of Novel PrEP Agents



Slide 11

The Power of Targeted PrEP Implementation

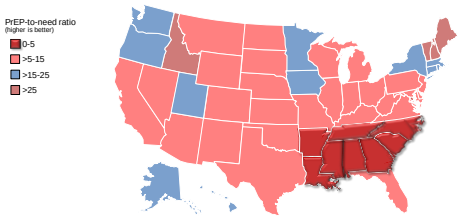
Reduction in HIV Incidence Attributed to Scaling Up PrEP Access

Rural Kenya/ Uganda	San Francisco	Seattle	London	Sydney
74% Reduction (2016-2020)	58% Reduction (2012-2018)	50% Reduction (2014-2020)	54% Reduction (2015-2020)	32% Reduction (2016-2017)

Kosa C, et al. *PLoS Med.* 2021;18(2):e1003492.
Buchbinder SP, et al. *J Acquir Immune Defic Syndr.* 2019;82(suppl 3):S176-S182.
Seattle & King County and the Infectious Disease Assessment Unit. HIV/AIDS Epidemiology Report:2021; Volume 90.
UK Health Security Agency. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1037215/hiv-2021-report.pdf. 12/2021.
Gnatch A, et al. *LancetHIV.* 2018;5:e629-e637.

Slide 12

PrEP-to-Need Ratio (2021)

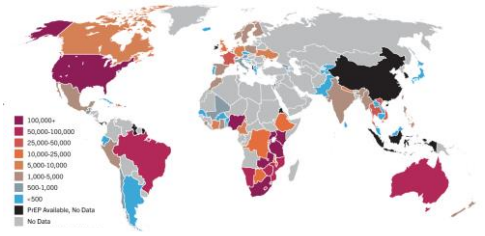


PrEP-to-need ratio: the number of PrEP users to the number of people newly diagnosed with HIV.

Adapted from AIDSVu. https://map.aidsvu.org/map.

Slide 13

PrEP Initiations by Country, July 2022



AVAC Global PrEP Tracker, Q2 2022, https://www.avac.org/infographic/prep-initiations-country-worldwide

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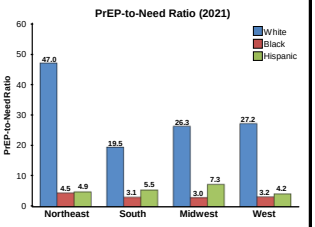
Trends in PrEP Use in the United States (2012-2021)

- PrEP-to-need ratio
  - Number of PrEP users divided by the number of new HIV diagnoses in that group in the same year
  - Equity metric, no "target" level
- US prevention programs in all regions have demonstrated larger gaps in PrEP-to-need ratios by race/ethnicity
  - Southern states lagged all other regions
- Better programs are needed to provide PrEP to communities and people at greatest risk for HIV infection



Sullivan P, et al. *J Int AIDS Soc*. 2022;25(suppl 3):227. Abstract OALB0106.

Slide 15

CDC 2021 PrEP Update: Identifying Persons at Substantial Risk of Acquiring HIV Infection

- Sexually active adults and adolescents who had anal or vaginal sex in the past 6 months **AND** any of the following
  - HIV-positive sexually active partner (especially if partner has an unknown or detectable viral load)
  - Bacterial STI in past 6 months
  - History of inconsistent or no condom use with sexual partner(s)
- PWID
  - HIV-positive partner **OR** sharing injection equipment

Previous 2017 Guidance on Substantial Risk of Acquiring HIV Infection

- MSM
  - HIV-positive sexual partner
  - Recent bacterial STI
  - High number of sexual partners
  - History of inconsistent or no condom use
  - Commercial sex work
- Heterosexual women and men
  - Same as MSM plus in a high HIV prevalence area/network
- PWID
  - HIV-positive injecting partner
  - Sharing injection equipment

CDC. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021.

Slide 16

Oral PrEP Options

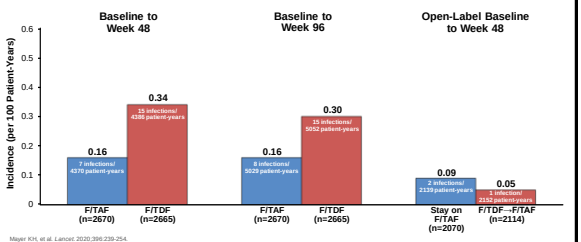
	Daily F/TDF	Daily F/TAF	Non-Daily F/TDF
FDA-approved	Yes	Yes	No
Persons at substantial risk for acquiring HIV infection	MSM/TGW Heterosexual cisgender women/cisgender men Adolescents (weight ≥35 kg)	MSM/TGW Non-vaginal exposure Adolescents (weight ≥35 kg)	MSM
Dose	200/300 mg qd (creatinine clearance >60 mL/min)	200/25 mg qd (creatinine clearance ≥30 mL/min)	2:1:1* 2 pills: 2 to 24 hours before sex 1 pill: 24 hours after initial 2-pill dose 1 pill: 48 hours after initial 2-pill dose
Key supporting studies	IPrEx/OLE, PROUD/OLE, Kaiser Permanente study, Demo project Partners PrEP, Botswana TDF2, VOICE, FEM-PrEP Bangkok tenofovir study/OLE ATN113	DISCOVER	IPERGAY/OLE Prévenir

OLE: open-label extension.
*Subsequent sexual events:
If sex occurs on consecutive day after completing the 2-1-1 doses, take 1 pill/day until 48 hours after the last sexual event.
If a gap of <7 days occurs between the last pill and the next sexual event, resume 1 pill daily.
If a gap of ≥7 days occurs between the last pill and next sexual event, start again with 2 pills.

CDC. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021.

Slide 17

DISCOVER Trial: HIV Incidence



Mayer KH, et al. *Lancet*. 2020;396:239-254.
Ogbuagu O, et al. *Lancet HIV*. 2021;8:e397-e407.
Spinner C, et al. *J Int AIDS Soc*. 2021;24(suppl 4):29. Abstract OALC0501.

Slide 18

ANRS Prévenir Study:
Daily Versus On-Demand PrEP in High-Risk MSM

Ongoing, open-label, prospective study (Paris region)

- HIV-negative, high-risk adults
- Inconsistent condom use
- Creatinine clearance (≥50 mL/min)
- HBsAg negative (on-demand arm)

Participants may choose either daily or on-demand PrEP and could switch regimens during trial

Daily PrEP (n=1544)

On-Demand PrEP (n=1515)

- **Primary endpoint: demonstrate ≥15% reduction of new HIV diagnoses in the Paris region**
- **Baseline demographics (similar between daily and on-demand arms)**
  - Median age: 36 years
  - White: 86%
  - MSM: 99%
  - No regular sex partner: 55%
  - History of PrEP use: 56%
  - Use of Chemsex: 14%
- **Number of condomless sex acts in prior four weeks: 2**
- **Number of sexual partners in prior three months: 10**

Molina J-M, et al. *Lancet HIV* 2022;9:e554-e562.

Slide 19

ANRS Prévenir Study:
Daily Versus On-Demand PrEP in High-Risk MSM

- HIV infections (n=6; 3 in each group) over a mean follow-up of 22.1 months
- Overall HIV incidence: 1.1 per 1000 patient years (95% CI: 0.4-2.3)
  - An estimated 361 infections were averted*
- Both groups had high rates of retention and correct PrEP use
- Number of sex acts (17,882 among 3049 persons)
- Daily PrEP users had more partners and more frequent sex versus on-demand PrEP (*P*<0.0001)
- High incidence of bacterial and viral STIs
- Safety
  - Discontinuations due to adverse events (n=4, 2 in each group)

	Daily PrEP (n=1540)	On-Demand PrEP (n=1509)
Follow-up (patient-years)	2713	2723
HIV incidence per 1000 patient-years (95% CI)	1.1 (0.2-3.2)	1.1 (0.2-3.2)
At last sexual intercourse (%) Correct PrEP use	98	98
Creatinine clearance <50 mL/min per 1000 patient-years (95% CI)	2.5 (1.4-4.2)	2.2 (0.8-4.8)

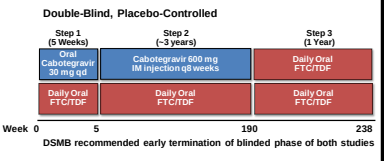
*Assumes an HIV incidence of 6.6/100 patient-years observed in placebo group of Ipergay study.

Molina J-M, et al. *Lancet HIV* 2022;9:e554-e562.

Slide 20

HPTN 083 and 084: Long-Acting Injectable Cabotegravir for PrEP

- Phase 3 studies
- Double-blind, placebo-controlled persons at high-risk for HIV infection in general good health
- No IDU, HCV, HBV, seizure disorder, CVD, abnormal liver function
- HPTN 083: MSM/transgender women
- HPTN 084: cisgender women



Matching oral and IM placebos included in the oral and injection phase double-blind arms.
HPTN 083 was conducted in US, Brazil, Peru, Argentina, South Africa, Vietnam, and Thailand.
HPTN 084 was conducted in Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, and Zimbabwe.

Landovitz RJ, *et al. N Engl J Med.* 2021;385:595-608.
Delany-Moretlwe S, *et al. Lancet.* 2022;399:1779-1789.
Delany-Moretlwe S, *et al. J Int AIDS Soc.* 2022;25(suppl 3):227-228. Abstract OALBX0107.

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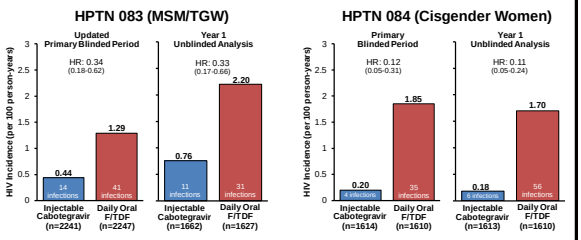
HPTN 083 and 084: HIV Incidence



Landovitz RJ, *et al. N Engl J Med.* 2021;385:595-608.
Delany-Moretlwe S, *et al. Lancet.* 2022;399:1779-1789.
Delany-Moretlwe S, *et al. J Int AIDS Soc.* 2022;25(suppl 3):227-228. Abstract OALBX0107.

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Assessments for Injectable Cabotegravir PrEP Follow-Up Care

1 Month After 1st Injection	Every 2 Months Beginning With 3rd Injection	Every 4 Months Beginning With 3rd Injection	Every 6 Months Beginning With 5th Injection	At Least Every 12 Months
• HIV Ag/Ab test • HIV-1 RNA assay	• HIV Ag/Ab test • HIV-1 RNA assay	• Bacterial STI screening for MSM and TGW who have sex with men – Gonorrhea/ chlamydia (oral, rectal, urine) – Syphilis (blood)	• Bacterial STI screening for all heterosexually-active cisgender women and cisgender men – Gonorrhea/ chlamydia (oral, rectal, urine) – Syphilis (blood)	• Assess desire to continue injections for PrEP • Chlamydia screening – Heterosexually active cisgender women and cisgender men (vaginal, urine)

- When discontinuing cabotegravir injection
  - Re-educate patients about the "tail" and risks during declining cabotegravir levels
  - Assess ongoing HIV risk and prevention plans
  - If PrEP is indicated, prescribe daily oral F/TDF or F/TAF beginning within 8 weeks after last injection
  - Continue follow-up visits with HIV testing (including RNA testing) quarterly for 12 months

PWID: although controversial, some may consider assessing access to clean needles/syringes and drug treatment services every 2 months beginning with 3rd injection.

CDC. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Published December 2021.

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Comparison of acute HIV infection (AHI) to infections that occur in the setting of long-acting early viral inhibition (LEVI)

	AHI	LEVI
Cause	Phase of natural HIV infection	Long-acting anti-viral PrEP agent (prototype: CAB-LA)
Onset	New infection	Infection during PrEP Initiation of PrEP agent during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Protean, often no symptoms reported
Detection	Ag/Ab assay, RNA assays (including less sensitive POC and pooled tests), DNA assays, total nucleic acid assays	Ultrasensitive RNA assay (often low or undetectable RNA, low/undetectable DNA, diminished/delayed Ab production)
Duration	1-2 weeks (until Ab detection)	Months (until viral breakthrough, cessation of anti-viral exposure or ART start)
Persistence	Rare*	Weeks-months after anti-viral agent is discontinued
Transmission	Very likely	Unlikely (except possibly through blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when viral load is low)

...ceval 24

CAB PrEP Implementation (similar issues for CAB/RPV for ART, redux)

Insurance variability
- Coverage
- Residence in pharmacy vs. medical benefit
  - Share-of-cost implications thereof
- Requirement for Buy-and-Bill vs. Specialty Pharmacy
- Unclear reimbursement by CMS until J-code July 1, 2022

Institutional Requirements
- Institutional support for Buy-and-Bill
- Institutional allowance of Brown/White/Clear Bagging

US CDC. DHHS. PrEP for the prevention of HIV infections in the United States – 2021 Update

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CAB PrEP Implementation (similar issues for CAB/RPV for ART, redux)

Clinic Requirements
- Operations/Work flow for administration
- Patient Tracking
- Bridging with missed doses (inconsistency between RCTs and PI)
- Reloading (inconsistency between RCTs and PI)

Provider Hesitancy
- Which to recommend?
- How to counsel re: Onset? Durability?
- Resistance and options for ART choice in breakthrough
- Complexity (and anguish!) of discordant results

US CDC. DHHS. PrEP for the prevention of HIV infections in the United States – 2021 Update

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Making Good Decisions Absent Limited/No Data

What to start?
- Whatever the patient will adhere/persist with best
- There is no ethical/moral "obligation" to use CAB

Onset of protection?
- PK suggests time from first injection (irrespective of OLI) to 8x PA-IC90 is median 2 days, 95% by 7 days
- Durability – incredibly interpatient variability (077 data), likely varies by sex (maybe BMI), wouldn't assume more than 9-10 weeks for males, 12? for females

Breakthroughs (nee: failures)
- Poorly understood to date
- Salvage with DOR or r/PI if infection likely to have occurred within 1 year, DTG/BIC-based ART >1 year?

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What's Next?

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Monthly Dapivirine Ring

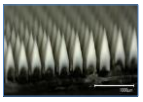
- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
  - Discreet
- Slowly releases ARV dapivirine
- Reduced women's HIV-1 risk by ~30% in two Phase III trials
- Interim data from open-label studies show greater use and suggest ~50% risk reduction
  - New interim data presented at R4P
- EMA regulatory approval!
- WITHDRAWN FROM US REGULATORY REVIEW

Nel A et al. NEJM 2016
Baeten J et al. NEJM 2016
Baeten J et al. CROI 2018, #143LB
Nel A et al. CROI 2018, #144LB

Slide 29

What's Next for CAB?

- Microarray Patch (MAP) for Long-Acting HIV PrEP



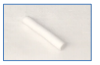
Light microscopic image (x25) of MAP

PATH · USAID · PEPFAR

- CAB LA Reformulation: double-strength concentration (400mg/mL)

- ViiV/GSK internal program
- ClinicalTrials.gov NCT04484337

- CAB Implant: non-biodegradable, retrievable



- ViiV/GSK internal & external collaboration (Northwestern Univ. SLAP-HIV UM1 NIH grant)

Rein-Weston, ID Week Oct 2019
https://doi.org/10.1093/ofid/ofz415.2491

Hope, et al. HIV R4P Jan 2021 Virtual Slide 30

Islatravir (MK-8591): First-in-Class HIV Nucleoside RT Translocation Inhibitor (NRTTI)

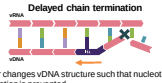
- ISL is the first nucleoside reverse transcriptase translocation inhibitor (NRTTI) in development for the treatment and prevention of HIV-1 infection[1]
- ISL is rapidly converted to its active TP form within target cells,[1] which inhibits reverse transcriptase by multiple mechanisms of action to suppress HIV-1 replication

ISL-TP has high antiviral potency against HIV-1 and drug-resistant variants,[1,2] and a half-life in PBMCs of approximately 190 hours after oral administration in adults without HIV[3]

Translocation inhibition

- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed chain termination



- Islatravir changes vDNA structure such that nucleotide incorporation is prevented
- Islatravir is not in the RT active site and is not susceptible to RT-associated resistance mutations
- **Viral replication is inhibited**

ISL, islatravir; PBMCs, peripheral blood mononuclear cell; RT, reverse transcriptase; TP, triphosphate; vDNA, viral DNA; vRNA, viral RNA.
1. Markowitz M, Grobler JA. *Curr Opin HIV AIDS* 2020;15:27–32; 2. Grobler JA et al. HIV Glasgow 2018 poster #O343; 3. Ankrom W Islatravir Intracellular Triphosphate T1/2 Supports Extended Dose Intervals. CROI 2021. #2101.

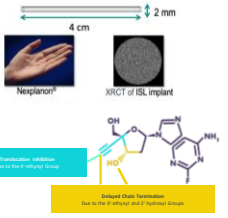
Hillier S, et al. HIV R4P Abstract OA04.05 Slide 31

Next-generation islatravir implants

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator

- Initial trial uses prototype implant

Polymer + ISL



Matthews R, et al. IAS2019 Abstract TUAC0401LB Slide 32

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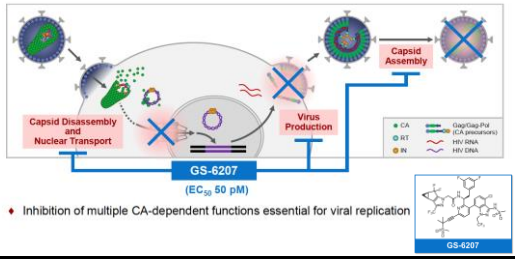
Lenacapavir (GS-6207): First-in-Class HIV Capsid Inhibitor



- Inhibition of multiple CA-dependent functions essential for viral replication

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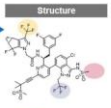
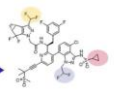
Lenacapavir (GS-6207) and LEN Analog (GS-CA1)

	Structure	Status	PBMC EC_{50} (nM)
LEN[1] (GS-6207) Gilead Long-acting Capsid Inhibitors		• Favorable safety & tolerability profile in clinical trials* • 2.3-log_{10} HIV-1 RNA decline after 9 days of monotherapy* • Q6M formulation in Phase 2/3 trials in PLWH	HIV† 0.050 SHIV‡ 0.569
GS-CA1[2] (LEN analog)		• Preclinical efficacy in hu-mice • Tool compound for preclinical research studies	HIV† 0.130 SHIV‡ 0.748

- Multi-stage capsid-specific MOA
- High metabolic stability, low clearance & low solubility

*GS-US-200-4538; GS-US-200-4071; GS-US-200-4072, †Tested in human PBMC, ‡Tested in rhesus macaque PBMC

Bekerman E, et al. CROI 2021, Abstract #717

Slide 35

Antibody Mediated Prevention Trials:

Broadly Neutralizing Monoclonal Antibodies for HIV Prevention

Phase 2b, proof-of-concept studies in persons at high-risk for HIV infection

- HVTN 704/HPTN 085 (n=2699): MSM/transgender persons
- HVTN 703/HPTN 081 (n=1924): women at high risk for HIV infection

Randomized groups

- VRC01 low/high IV dose (10/30 mg/kg) or placebo q8 weeks

VRC01 did not prevent overall HIV acquisition more effectively than placebo

	HIV Incidence (per 100 person-years)	VRC01 Prevention Efficacy (%)
HVTN 704/HPTN 085		
Pooled VRC01	2.35	27
Placebo	2.98	
HVTN 703/HPTN 081		
Pooled VRC01	2.49	9
Placebo	3.10	
Persons with VRC01-sensitive isolates		
Pooled VRC01	0.20	75
Placebo	0.86	

Corey L, et al. NEJM. 2021

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Question-and-Answer Session