

Preexposure Prophylaxis for HIV Prevention: What Clinicians Need To Know

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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 Merck & Co, Inc, and served as a consultant to Cepheid. (Updated 09/28/22)

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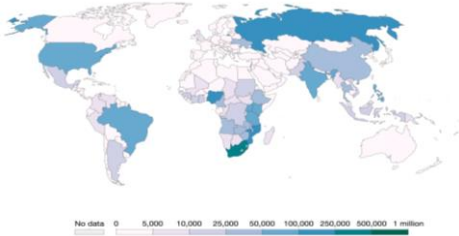
Learning Objectives

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

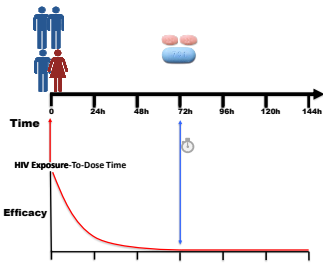
1.5 Million New Infections in 2019 4100 New Infections per Day



UNAIDS, GAP Report, 2020.
OurWorldData.org/htw-2019

SS14-4

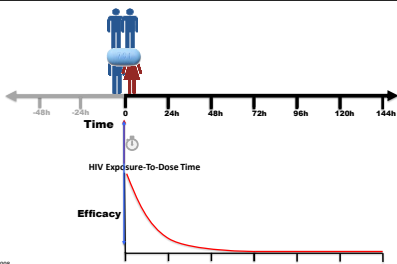
How Did We Get Here?



Tsai CC et al. J Virol. 1998.
Wainwright NA et al. NEJM. 1998.
Chen RA et al. J Virol. 2000.

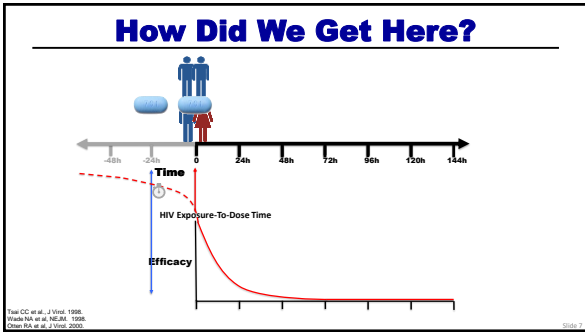
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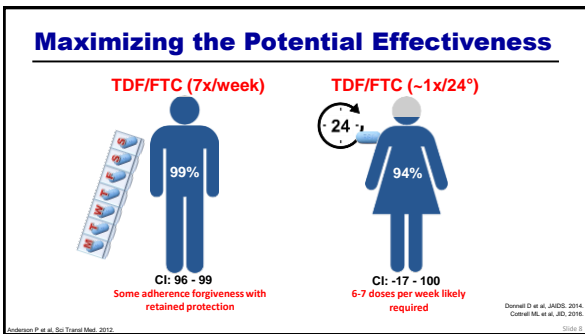
How Did We Get Here?

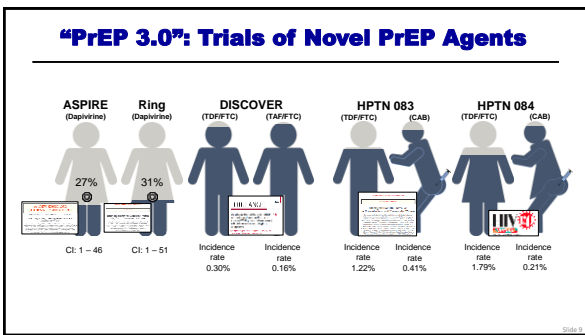


Tsai CC et al. J Virol. 1998.
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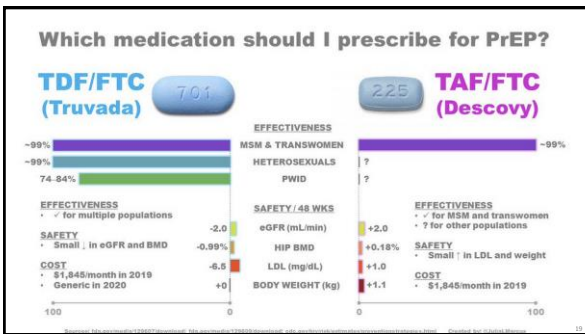
SS14-6

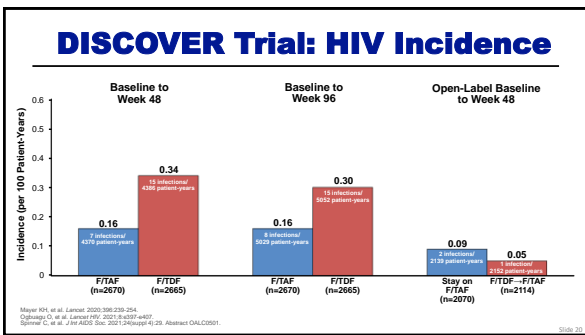












CAB PrEP Implementation (similar issues for CAB/RPV for ART, redux)

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

© 2022 CDC. DASH 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

© 2022 CDC. DASH 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?

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

NMI A.M. NEJM 2016
 NMI A.M. NEJM 2016
 Berman J. et al. CROI 2016 #1463B
 NMI A.M. CROI 2016 #144LB

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 infection¹
- 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 HIV³

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

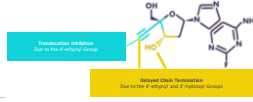
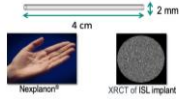
ISL, Islatravir; PBMCs, peripheral blood mononuclear cells; RT, reverse transcriptase; TP, triphosphate; vDNA, viral DNA; vRNA, viral RNA.
 1. Markovits M, Gostler JK. Curr Opin HIV AIDS 2020;15:27-32. 2. Gostler JA et al. HIV Glasgow 2018 poster P0343. 3. Ankrum W. Islatravir Intracellular Triphosphate T12 Supports Extended Dose Intervals. CROI 2021 #1210.

Next-generation islatravir implants

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

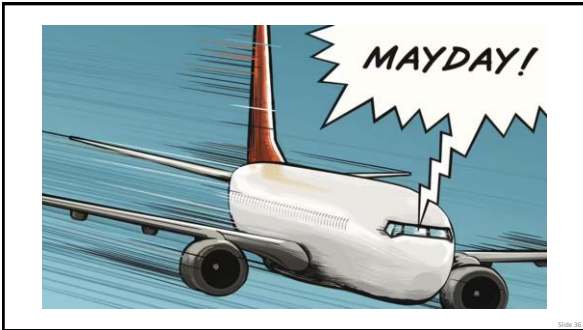
- Initial trial uses prototype implant

Polymer + ISL



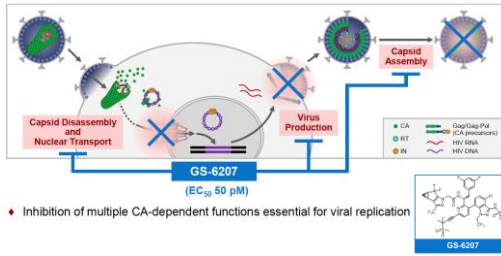
Matthew B. et al. (2018) Abstract TUA040118

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



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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	

www.niaid.nih.gov

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Thank you!

Questions?
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Q and A Session

