Preexposure Prophylaxis for HIV Prevention: What Clinicians Need To Know Raphael J. Landovitz, MD, MSc Professor of Medicine University of California Los Angeles

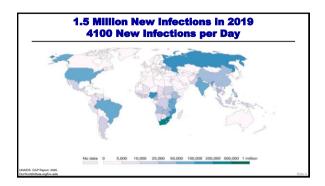
Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

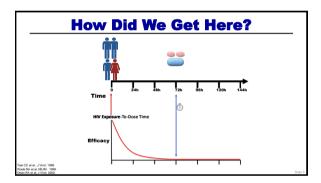
Dr Landovitz has served on Scientific Advisory Boards for Merck & Co, Inc, and served as a consultant to Cepheid. (Updated 09/28/22)

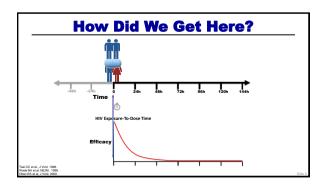
Learning Objectives

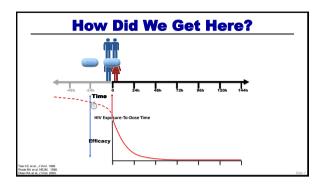
After attending this presentation, learners will be able to:

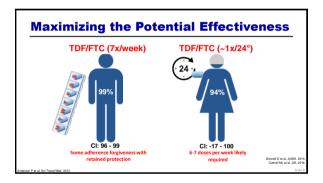
- Explain the origins of preexposure prophylaxis (PrEP)
- Identify the limitations of currently available PrEP agents and strategies
- Describe challenges and opportunities of long-acting injectable PrEP
- Summarize the current pipeline of PrEP agents

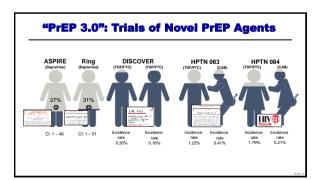




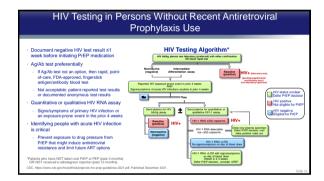


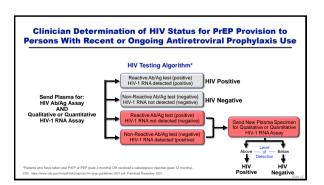


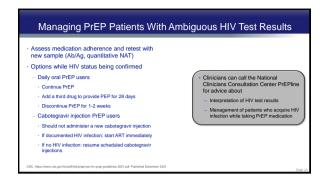




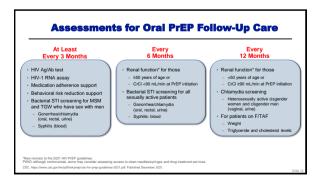
CDC 2021 PrEP Update: Identifying Persons at Substantial Risk of Acquiring HIV Infection - Sexually active adults and adolescents who had anal or vaginal sex in the past 6 months AND any of the following - HIV-positive sexually active partner (especially if partner has an unknown or detectable viral 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



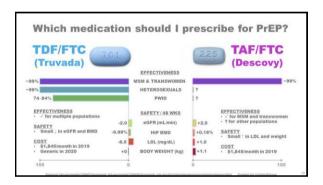


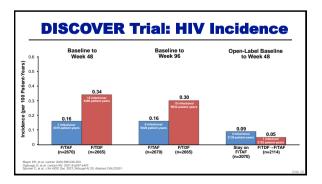


	Daily F/TDF	Daily F/TAF	Non-Daily F/TDF
FDA-approved	Yes	Yes	No
Persons at substantial risk for acquiring HIV infection	MSM/TGW Heterosexual cisgender women/cisgender men Adolescents (weight ≥35 kg)	MSM/TGW Non-vaginal exposure Adolescents (weight ≥35 kg)	MSM
Dose	200/300 mg qd (creatinine clearance >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









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

Daily PrEP (n=1544)

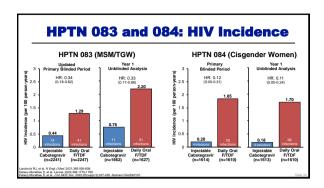
- Primary endpoint: demonstrate ≥15% reduction of new HIV diagnoses in the Paris region
- Baseline demographics (similar between daily and on-demand arms)

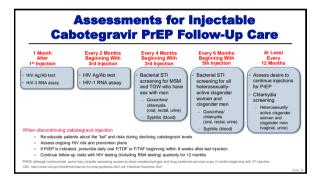
Median age: 36 years White: 86% MSM: 99%

- 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

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 HIV incidence per 1000 patient-years (95% CI) 1.1 (0.2-3.2) Number of sex acts (17,882 among 3049 At last sexual intercourse (%) Correct PrEP use Daily PrEP users had more partners and more frequent sex versus on-demand PrEP (P<0.0001) 98 98 2.5 (1.4-4.2) 2.2 (0.8-4.8) High incidence of bacterial and viral STIs Discontinuations due to adverse events (n=4, 2 in each group)

HPTN 083 and 084: **Long-Acting Injectable Cabotegravir for PrEP** Phase 3 studies Double-Blind, Placebo-Controlled 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 Step 3 (1 Year) HPTN 083: MSM/transgender HPTN 084: cisaender 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 nA4 was conducted in Botswana, Kernya, Malawi, South Africa, Swaziland, Uganda, and Zim





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 PEP agent (prototype: CAB-LA) infection during PEP (Pagent during acute/early infection Infection during PEP) infection Symptoms Pever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands Ag/Ab assays, finctuloring less sensitive PCC and pooled tests), DNA assays, (including less sensitive PCC and

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

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

- 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

Making Good Decisions Absent Limited/No Data

- 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?



Monthly Dapivirine Ring

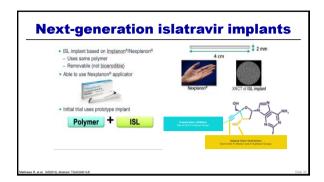


A et al. NEJM 2016 fen J et al. NEJM 2016 fen J et al. CROI 2018, #143LB ^ --- al. CROI 2018, #144LB

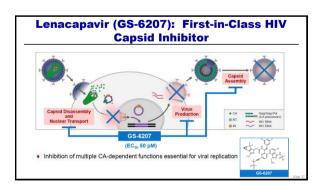
- Flexible silicone vaginal ring developed by IPM
 Woman-initiated
 Self-inserted monthly
 Discree
 Silowly releases ARV dapivirine
 Reduced women's HIV-1 risk by
 -30% in two Phase III trials
 Interim data from open-best studies
 show greater use and suggest -50% risk reduction
 New interim data presented at Ref
 Ref
 EMA regulatory approve*

 EMA regulatory approve*
- EMA regulatory approval! WITHDRAWN FROM US REGULATORY REVIEW

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-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







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 - HYTN 704/HPTN 085 (n=2699): MSM/transgender persons - HYTN 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

Thank you!

Questions? rlandovitz@mednet.ucla.edu

