Common Preexposure Prophylaxis Questions: An Interactive Case-Based Presentation

Susan P. Buchbinder, MD
Clinical Professor, Medicine and Epidemiology
University of California San Francisco
San Francisco, California

Learning Objectives

After attending this presentation, learners will be able to:

- Discuss the benefits of same-day PrEP starts
- Describe the 2-1-1 PrEP regimen and the populations for whom it is best suited
- Identify the relative advantages and disadvantages of TDF/FTC vs. TAF/FTC PrEP

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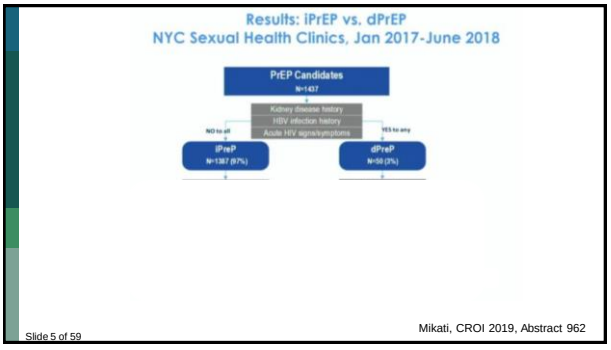
ARS Question 1: An initial question

Do you start PrEP on the same day, or wait for test results before prescribing PrEP?

1. Same day
2. Wait for lab results
3. I haven't prescribed PrEP
4. Something else



Mikati, CROI 2019, Abstract 962

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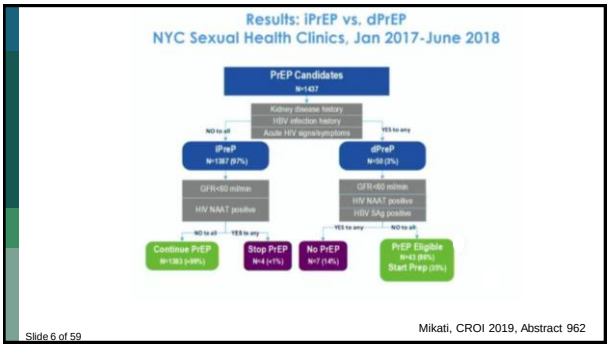

Mikati, CROI 2019, Abstract 962

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ARS Question 2: How are you handling PrEP prescriptions now?

Given challenges with having patients come to the clinic, how are you now prescribing PrEP?

1. Requiring 3-monthly clinic visits and 3-month refills
2. Providing extra refills without additional HIV testing
3. Doing home HIV testing without any STI testing, then refills
4. Doing home HIV and STI testing, then refills
5. Not prescribing PrEP
6. Something else

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ARS Question 3: Case 1

A 22 year old man who has sex with men comes to your office seeking PrEP. He has multiple partners, never uses condoms, and his most recent receptive anal sexual encounter was 48 hours ago. He is asymptomatic. What would you recommend?

1. Send an HIV test to the lab, and start PrEP if the test comes back negative.
2. Start PrEP today
3. Start PEP today

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Post-exposure prophylaxis

- Must be started within 72 hours of a high-risk exposure; as early as possible is best.
- Order an HIV Ag/Ab test, GC/CT/syphilis/HBV/HCV, renal function, LFTs, pregnancy test (when appropriate)
- Start 28-day, 3-drug regimen immediately, usually with an INSTI and 2 NRTIs
- Can transition to PEP after 28 days if HIV Ag/Ab test negative

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ARS Question 4: Case 2

A 21 year old woman asks you to prescribe PrEP. She states that she always uses condoms with her multiple sexual partners but would like to stop using them. What do you recommend?

1. You don't offer PrEP because condoms have worked well for her up to this point, and you don't want to risk STIs
2. You don't offer PrEP because it doesn't work well in women
3. You offer PrEP but tell her it works less well if she has bacterial vaginosis or STIs
4. You offer PrEP and counsel that only condoms will prevent STIs, but let her make the condom decision

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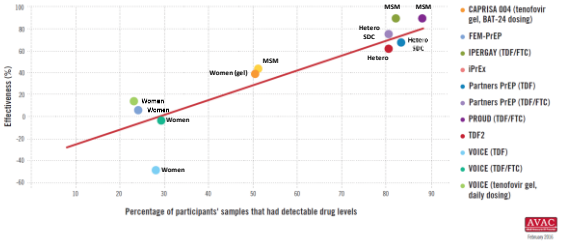
PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention



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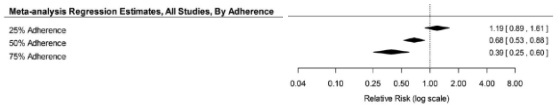
Does PrEP work for cis women?

Yes, if they take it regularly



Hanscom, JAIDS 2016; 73:606-608

BUT:

- Tenofovir concentrates at 10-100 fold higher in rectal than vaginal tissue
- Tenofovir also cleared more rapidly from vaginal than rectal tissue

- ***PK suggests women need to take daily TDF/FTC 6-7 days/week to maximize effectiveness, although demonstration data suggest may be effective even if less frequent dosing***

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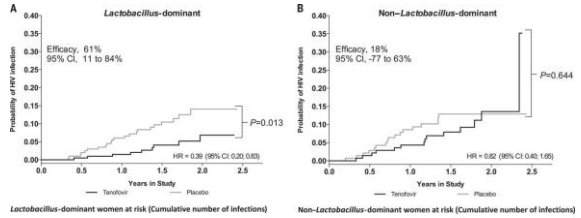
Fig. 2 Cumulative HIV infection probability by treatment assignment in women with vaginal Lactobacillus dominance and non-Lactobacillus bacterial dominance.



Nichole R. Klatt et al. Science 2017;356:938-945

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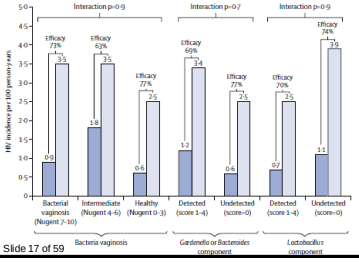
Oral PrEP not affected by vaginal dysbiosis



- Partners PrEP study
- Baseline assessment of vaginal dysbiosis
- Efficacy was 69-77% in each subgroup, regardless of Nugent score or predominance of *Lactobacillus*

Heffron et al, Lancet HIV 2017;4:449-56

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ARS Question 5: Case 3

A 34 year-old MSM has sex with new partners approximately twice per month. He doesn't want to take a daily pill because his sexual exposures are relatively infrequent, but he doesn't always use condoms. What would you do?

1. Encourage him to use condoms
2. His exposure is relatively low, so don't worry about PrEP
3. Encourage him to take daily PrEP
4. Have him start PrEP 7 days before sexual episodes
5. Prescribe "on-demand" or "2-1-1" PrEP

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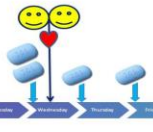
Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



"2-1-1"

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Ipergay : Event-Driven iPrEP

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- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake

- ✓ Daily pills until 48 hour after last dose
- ✓ If last pill within 7 days, take single pill to start

"2-1-1-1-1-1…."

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Ipergay Results

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
Placebo (double-blind)	212	**6.60** (3.60-11.1)
TDF/FTC (double-blind)	219	**0.91** (0.11-3.30)
TDF/FTC (open-label)	515	**0.19** (0.01-1.08)

Median Follow-up in Open-Label Phase 18.4 months (IQR:17.5-19.1)

97% relative reduction vs. placebo

Median # pills/month: 18 (IQR 11-25)

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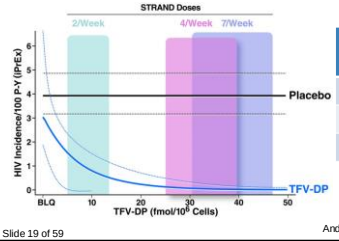
Molina et al, Lancet HIV 2017;4:e402-10

4 Doses/Week has Similar Efficacy to Daily TDF/FTC for MSM



# Doses/ week	Estimated efficacy	95% CI
2	76%	56-96%
4	96%	90%->99%
7	99%	96%->99%

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Anderson et al, Sci Transl Med 2012;4 (151):151ra125

What about less frequent sex?

An analysis of the IPERGAY study evaluating 269 patients (134 person-yrs) who took on-demand PrEP less frequently **(≤15 pills/month)** AND reported using PrEP systematically or often during sexual intercourse

	Person years	# HIV infections	HIV incidence rate/100 py (95% CI)	P
Placebo	64.8	6	9.2 (3.4- 20.1)	
TDF/FTC	68.9	0	0.0 (0.0-5.4)	0.013

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Antoni et al, Lancet HIV 2020

Recommendations for 2-1-1 PrEP

- **CDC continues to recommend daily PrEP only**
  - **only licensed indication by FDA**
- **IAS-USA guidelines recommend 2-1-1 TDF/FTC PrEP as alternative to daily PrEP for MSM; WHO has endorsed 2-1-1 PrEP**
  - **Use if can plan ahead for pre-dose, can take post-doses, use with all partners**
  - **Only F/TDF used; don't use with F/TAF**
- **Daily PrEP is the only recommended option for cis- and transgender women and PWID**

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Considerations of 2-1-1 vs Daily PrEP

	2-1-1 PrEP	Daily PrEP
Who can use it?	Only studied in MSM	Anyone
Chronic HBV	Can trigger a flair	Can be safety used
Planning	Need to plan sex at least 2 hrs in advance	No planning needed
"Forgiveness"	Not forgiving of missed doses	Forgiving of missed doses during the week

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ARS Question 6: Case 4

A 48 year-old MSM with hypertension comes in requesting PrEP. He has multiple partners, frequent sex, and frequent STIs. His creatinine is 1.7, creatinine clearance is 61 ml/min. What would you do?

1. Prescribe daily TDF/FTC
2. Prescribe daily TAF/FTC
3. Prescribe every other day TDF/FTC
4. Prescribe 2-1-1 PrEP
5. Tell him he should use condoms. PrEP won't work well because of multiple STIs, and you're concerned more PrEP will lead to more STIs

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Modest renal effects in older persons and those with low baseline GFR

- **In iPrEx OLE and SF Kaiser** (Marcus JAIDS 2016), **risk of eGFR<70 if:**
  - **Baseline eGFR<90**
  - **>40-50 years old**
- **In Partners PrEP and Partners Demo** (Mugwanya, JAIDS 2016)
  - **Same as above or weight < 55kg**
  - **>75% of creatinine increases unconfirmed on repeat test**
  - **No difference in picking up true renal effects if q 3 vs 6 month testing**
- **In Thai IDU study (**Martin, CID 2014)
  - **No effect of recent IDU on creatinine**
  - **More likely to have renal effects with increased age**
- **All studies**
  - **Creatinine reverts to near baseline after trial**
  - **Re-challenge has been used successfully**

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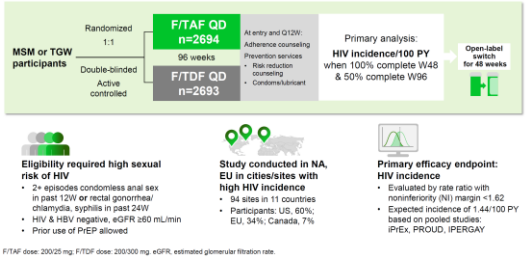
DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



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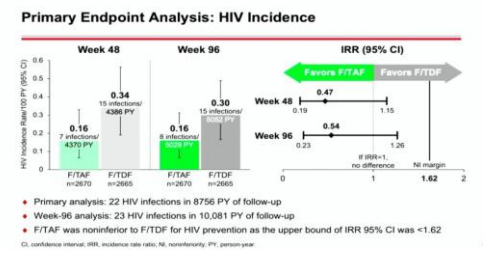
Hare, CROI 2019, Abstract 104LB

DISCOVER Trial: HIV incidence



Ogbuagu, Abstract 92, CROI 2020

DISCOVER: Differences in safety at 96 weeks

Favors F/TAF

- **Bone mineral density**: 1-2% difference in BMD at spine and hip; no difference in fractures
- **Renal function**: 4 ml/min difference in eGFR at 96 weeks

Favors F/TDF

- **Lipids**: 11 mg/dl lower total cholesterol; no difference in TC: HDL
- **Body weight**: 1 kg difference in body weight

Ogbuagu, Abstract 92, CROI 2020

Which medication should I prescribe for daily PrEP?

Do STIs reduce the efficacy of PrEP?

- No evidence STIs lower PrEP efficacy in RCTs
  - iPrEX: Syphilis incidence of 7.3/100 py; no interaction with PrEP efficacy (Solomon, CID 2014)
  - Partners PrEP: No difference in PrEP efficacy among those with STIs (Murnane, AIDS 2013)
- No evidence in open label studies
  - PROUD in UK: 73% with baseline STI & 86% effectiveness of PrEP (McCormack, Lancet 2015)
  - US MSM PrEP Demo study: 90/100 p-yr STI incidence & 0.43/100 p-yrs HIV incidence (Liu, JAMA Int Med 2015)

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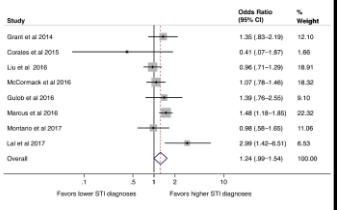
Effect of PrEP on STIs

- Rates of bacterial STIs increasing over time; however, rises pre-date PrEP use
- High rates of STIs in many studies of PrEP users
- Mixed results about whether PrEP increases rate of STIs; and interpretation complicated by association of PrEP use with high-risk sexual practices
- PrEP users should be screened every 3 months for STIs



Traeger et al, CID 2018

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ARS Question 7: Case 5

Your 26-year old cis-gender female patient says she just heard about a new long-acting injectable PrEP agent, and she'd like to learn more about it. What do you tell her?

1. Long-acting cabotegravir is given as two injections every 12 weeks for PrEP
2. Long-acting cabotegravir was shown to provide a higher level of protection than TDF/FTC, but only for MSM
3. Long-acting cabotegravir must be given with a 1-month oral lead in and a prolonged oral phase when discontinued
4. Long-acting cabotegravir should be combined with long-acting rilpivirine when used as PrEP

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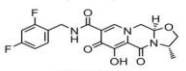
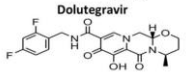
Cabotegravir Long Acting Injectable (CAB LA)

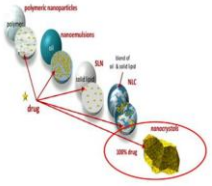
GSK1265744
(GSK744)



Dolutegravir



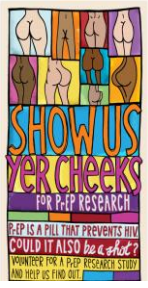
- Cabotegravir is an analog of dolutegravir, differing by one carbon atom
- Oral $t_{1/2}$: 40 hours
- CAB-LA: milled nanocrystals
- Injectable $t_{1/2}$: 21-50 days
- Rifampin reduces plasma concentrations by 60%



Muller et al. European Journal of Pharmaceutics and Biopharmaceutics 2011
Spreen 7th IAS 2013; Min ICAAC 2009
Taoda International Congress on Drug Therapy in HIV Infection 2012
McPherson et al, Expert Opin on Investig Drugs 2018

Two Efficacy Trials of CAB-LA

- **HPTN 083 for MSM/TGW globally**
- **HPTN 084 for women in sub-Saharan Africa**
- **Both have 3 steps:**
  1. **Oral lead-in**
  2. **Loading at 0 and 4 weeks, q 8 week injections**
  3. **Oral to cover the PK tail for 1 year**
- **Both trials are using F/TDF as comparator**
- **Bridging studies to adolescent MSM/TGW and cis-women**



Preliminary Results: HPTN 083 (Cabotegravir-LA)

- May 14, 2020: DSMB met for planned interim analysis
- Stopped blinded phase of the study because met the pre-specified non-inferiority early stopping boundary
- Overall incidence 0.79% (95% CI 0.59-1.05%)
- CAB was superior to F/TDF (OR 0.34, 95% CI 0.18-0.62); appeared to provide protection in all subgroups (age, race/ethnicity, gender)
- Injection site reactions higher in CAB arm (80% vs. 30%) with 49 (2%) discontinuing

As yet unanswered questions for CAB-LA

- Does it work in cis-gender women? (HPTN 084 is nearly fully enrolled)
- What was adherence like in each of the arms?
- Why/when breakthrough infections in each of the arms?
  - Oral vs. injectable phases?
  - Due to adherence?
  - Due to transmitted resistance?
- Did resistance develop after infection in each of the arms?

CAB LA pharmacokinetic Tail – Weeks 60 and 76

Landovitz, R et al. PLOS Med 2020

ARS Question 8: Case 6

A 29 year old MSM in a serodifferent relationship with an HIV positive partner comes in requesting PrEP. When you ask him, he explains that his partner is fully virally suppressed and has been for over a year, but he would feel more comfortable being on PrEP. What do you do?

1. Prescribe PrEP
2. Prescribe PrEP for now, with the hope of eliminating PrEP in the future if his partner remains suppressed
3. Tell the patient that he doesn't need PrEP because U=U
4. What's U=U??

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Undetectable = Untransmittable

U=U refers to the concept that an individual with an undetectable HIV VL is **incapable** of transmitting their HIV infection to **sexual partners**[1]

Sexual partners

Reduced VL also significantly **reduces risk of transmission**[2] via other routes:

Unborn babies

Healthcare workers who experience sharps/mucosal injuries

Undetectable VL in this context: **<200 c/mL**

1. Prevention Access Campaign Consensus Statement. Available from: https://www.preventionaccess.org/consensus (Accessed October 2018); 2. CATIE Fact Sheet. Available from: https://www.catie.ca/en/fact-sheets/transmission/hiv-viral-load-hiv-treatment-and-sexual-hiv-transmission (Accessed October 2018)

VL, viral load

Nwokolo, CROI 2019, Abstract 117

Policy statements on U=U

On September 27, 2017, the US CDC sent out a "Dear Colleague" letter stating:

"…. people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner."

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Condom Effectiveness

Heterosexuals (Giannou et al, Expert Rev Pharmacoecon Outcomes Res 2016)

- Meta-analysis of 25 studies, >10,000 couples
- **Overall effectiveness: 71-77%**

MSM (Smith et al, JAIDS 2015;68:337-344)

- Data from 2 large cohorts
- **70% effective**

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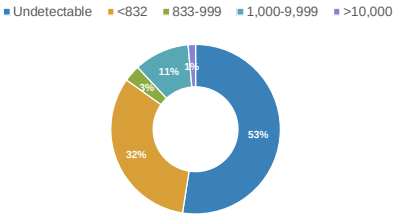
Viral load in 284 MSM self-reported to be undetectable



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Teran, CROI 2018, #997

ARS Question 9: Case 7

Your 31 year-old patient on PrEP comes in for his routine quarterly lab tests. His 4th generation antibody test comes back positive, but the confirmatory test and viral load come back negative. What do you do?

1. Repeat the tests but continue PrEP, as you assume the 4th gen test is a false positive
2. Repeat the tests and stop PrEP, but start ART for acute HIV infection
3. Repeat the tests and stop PrEP until you can determine what the infection status is
4. Something else

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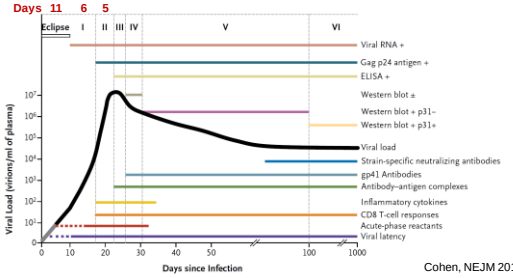
Sequential Appearance of Viral Markers and Antibodies during Acute HIV Infection



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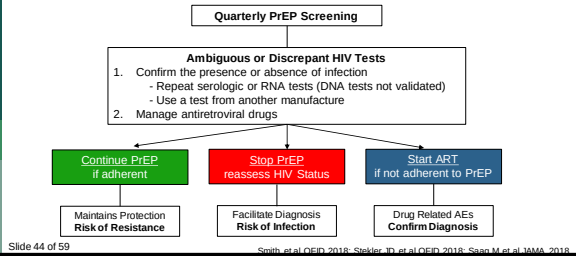
Cohen, NEJM 2011

How to manage ambiguous HIV Test Results



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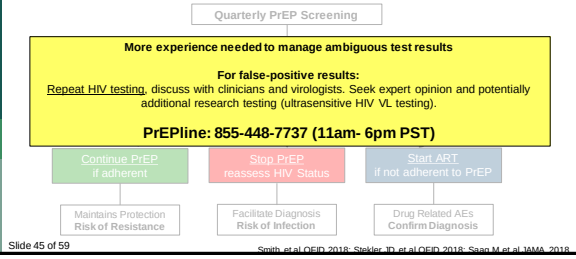
Smith, et al OFID 2018; Stekler JD, et al OFID 2018; Saag M et al. JAMA. 2018

How to manage ambiguous HIV Test Results



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Smith, et al OFID 2018; Stekler JD, et al OFID 2018; Saag M et al. JAMA. 2018

ARS Question 10: Case 8

A 28 year-old HIV negative woman is in a serodifferent relationship with an HIV positive man. He is newly diagnosed, and not yet stably virally suppressed. The couple wants to have a baby. What do you recommend?

1. Wait for the male partner to become fully virally suppressed for at least 6 months before attempting pregnancy
2. Use PrEP – it's safe peri-conception and in pregnancy
3. Don't use PrEP – its safety is unknown. Use sperm washing instead
4. Something else

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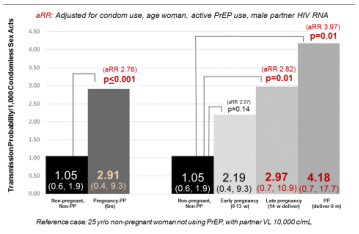
HIV risk increases during pregnancy

- 2,751 HIV-uninfected females in African HIV serodiscordant couples followed for ≤48 mos in 2 HIV prevention studies between 2004-2012
- Frequent HIV and pregnancy testing
- Genetic linking of HIV infections

Male-Female HIV Transmission by Reproductive Stage



Thomson KA et al. JID 2018

PrEP safety in pregnancy

- Study of 30 women who became pregnant while on PrEP
  - No difference in miscarriage, congenital anomalies, or growth through 1 year of infancy
- Systematic review of TFV exposure in pregnancy (26 in HIV positive women, 7 in HIV negative women)
  - No significant difference in adverse pregnancy or infant outcomes

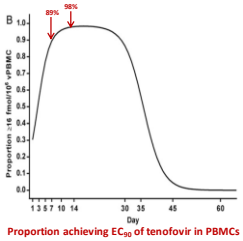
Heffron, AIDS 2018
Mofenson, AIDS 2017

ARS Question 11: Case 9

A 29 year old woman in a serodifferent relationship would like to stop using condoms. Her partner is not virally suppressed. She wants to know how long she has to take daily PrEP before she is protected. What do you tell her?

1. 3 days
2. 7 days
3. 20 days
4. 28 days
5. I have no idea

How long do you need to take PrEP before protected?



Proportion achieving EC_{90} of tenofovir in PBMCs

Cottrell et al, CID 2015;60:804-810

In blood (PMBCs)
- 89% achieve EC_{90} after 7 doses
- 98% by 13th dose

Recommend for MSM:
- 7 days before, or double dose start
- 2 days after last sexual act to stop based on 2-1-1

Recommend for Women
- CDC recommends 20 days before, but growing consensus that 7 days may be adequate
- Women need 6-7 doses/week while men only need 4-7 doses for maximal protection

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ARS Question 12: Case 10

A 35 year-old transgender woman reports that she has infrequent condomless sex and is reluctant to start PrEP because she believes PrEP will interfere with her gender-affirming hormones. How do you counsel her?

1. You tell her we have data that PrEP does not affect hormone levels and encourage PrEP use
2. You tell her we don't know if PrEP affects hormone levels but encourage PrEP use
3. You tell her we don't know if PrEP affects hormone levels, nor do we know if it works for trans women and encourage condoms
4. You recommend 2-1-1 PrEP so that she has less PrEP exposure

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Does PrEP work for trans women?

In iPrEx, 339 participants were identified as trans women
- No infections in women with detectable tenofovir in blood, but only 18% had detectable levels

Trans women express concern about interaction of TDF/FTC with hormones
- In iPrEX, women on hormones less likely to take PrEP

Studies planned or underway to evaluate interaction of TDF/FTC on hormones
- Some but not all studies suggest small reductions in TDF levels
- No apparent effect seen on female and male hormone levels

Bottom line: limited data, TDF/FTC appears to work in trans women but more data needed to understand PK

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Deutsch et al, Lancet HIV 2015; Anderson et al, JAIDS 2016

ARS Question 13: Case 11

A 35 year-old MSM in a serodifferent relationship comes in seeking PrEP. He states that his partner has been unsuppressed, and is just starting a new treatment regimen. The partner had to change his regimen because of ARV resistance, and (since the partner is also your patient), you know he has an M184V. Neither uses condoms.

What do you recommend?

1. They should continue to use condoms until the partner has been fully virally suppressed for at least 6 months.
2. You prescribe TDF/FTC or TAF/FTC
3. You prescribe three-drug PEP
4. Something else

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Breakthrough infections

- PrEP Breakthrough infections despite documented high adherence

	Location	Duration on PrEP before HIV diagnosis	Resistance Mutations	Adherence Measure
Cohen et al	US	13 months	**M184V**, L74V	DBS, Hair
Knox et al	Canada	24 months	M41L, D67G, T69D, K70R, **M184V**, Y215E	DBS
Markowitz et al	US	5 months	K65R, **M184V**	DBS, Hair
Hoornenborg et al	Amsterdam	8 months	No major resistance	DBS
Thaden et al	US	14 months	**M184V**, K70T, K65R	Hair
Colby et al	Thailand	8 weeks	**M184V**	Hair

DBS=Dried Blood Spot

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Cohen et al Lancet HIV 2018

ARS Question 14: Last ARS question

What is most exciting to you in the next phase of HIV prevention?

1. Islatravir (EfdA or MK-8591)
2. Broadly neutralizing antibodies
3. Vaccines
4. Vaginal rings

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Islatravir is a unique, highly potent, long-acting antiretroviral

Novel multi-MOA: NRTTI

ISL has the properties that enable daily, weekly and monthly low-dose oral and yearly implantable regimens for HIV treatment and prophylaxis

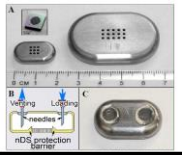
Markowitz, Abstract 89LB, CROI 2020

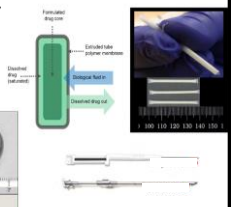
Markowitz M, et al. Curr Opin HIV AIDS 2020 Jan; 15(1):7-12.

Implantable devices

Drug must be extremely potent, as total mass dose to be loaded is small

- E.g., Nexplanon .06mg/day





Chua, CROI 2017
Durham, CROI 2018
Hendrix, MTN 2017

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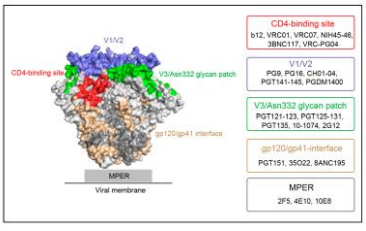
Broadly Neutralizing Antibody Targets



Zhang, Int J Molecular Sciences, 2016

Imbokodo and Mosaico: Efficacy trials

- **Imbokodo**: 2600 women in sub-Saharan Africa
  - Fully enrolled, in follow-up
- **Mosaico**: 3800 men and transgender women/men who have sex with men in Americas and Europe
  - Just beginning enrollment
- Both studies include:
  - Months 0, 3: Ad26 mosaic
  - Months 6,12: Ad26 mosaic with clade C gp140
    - Mosaico also adds mosaic gp140
- PrEP is available to all study participants

IMBOKODO

MOSAICO

HVTN 706/HPX3002

What's happening with topical PrEP?

Dapivirine ring studies
- Early efficacy: ~30%
- Open label extension: ~40-60%
- Undergoing regulatory review

Multipurpose technology
- Possibility of combining with contraception or anti-STD interventions

Rectal douches also under development

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Question-and-Answer Session