

Common PrEP Questions: A Case-Based Discussion

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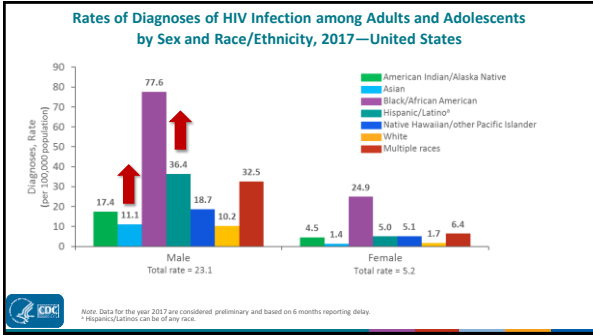
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Learning Objectives

After attending this presentation, learners will be able to:

- Identify US populations at highest risk of HIV infection
- Counsel patients about how to take different preexposure prophylaxis (PrEP) regimens
- Describe the impact of STIs on PrEP and PrEP on STIs
- Explain U=U

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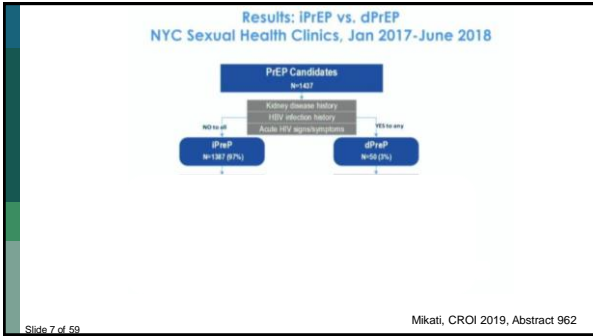


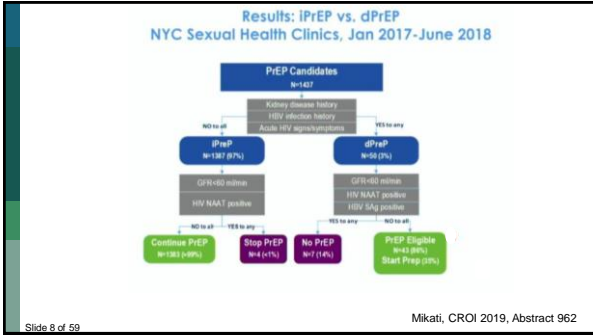
ARS Question 1

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. Something else

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ARS Question 2

When you prescribe PrEP, how do you most commonly prescribe it?

1. 1 month of PrEP, require patient to return before giving refills
2. 3 months of PrEP, require patient to return before giving refills
3. 3 months of PrEP, with refills
4. 12 months of PrEP
5. Something else

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PrEP prescribing: The Goldilocks problem

- Want to give enough PrEP to ensure coverage of risk, but not so much that PrEP users don't come in for q 3 month HIV/STI testing
- Analysis of data from San Francisco primary care clinics found that prescriptions of ≤ 30 days were associated with higher rate of PrEP discontinuation (OR 1.5, 95% CI 1.1-2.2)
- However, only 2/3 of PrEP intervals had HIV/STI testing done, even when allowing for intervals of 4 months
- Panel management associated with better adherence to follow-up HIV/STI testing

Slide 10 of 59 Spinelli, CROI 2018 #1028
Spinelli et al, OFID 2018

ARS Question 3: Case 1

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?

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ARS Question 3: Case 1

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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Does PrEP work for cis women?

Yes, if they take it regularly

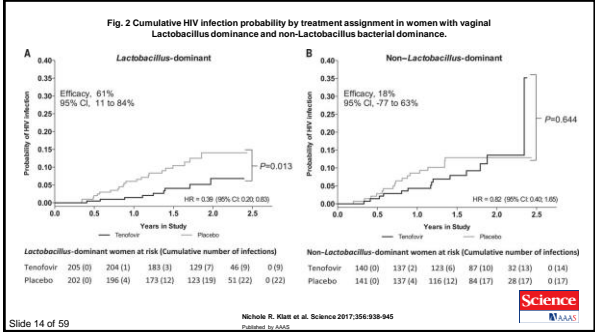
Meta-analysis Regression Estimates, All Studies, By Adherence

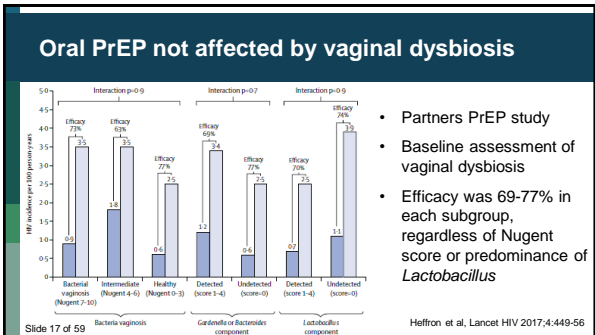


BUT:

- 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**

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ARS Question 4: Case 2

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?

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ARS Question 4: Case 2

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?

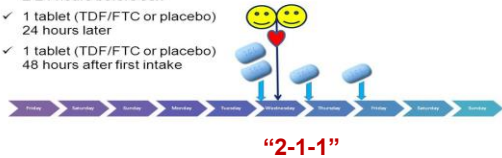
1. Encourage him to use condoms
2. His exposure is relatively low, so don't worry about PrEP
3. Encourage him to take daily PrEP
4. Have him start PrEP 7 days before sexual episodes
5. Prescribe "on-demand" or "2-1-1" PrEP, even though this is not FDA approved or endorsed by CDC

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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

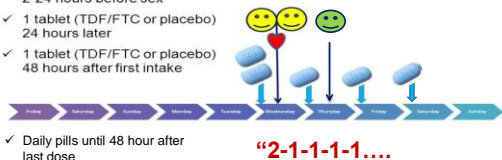


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Ipergay Results




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)

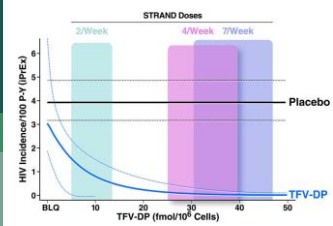
97% relative reduction vs. placebo

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



Slide 20 of 59 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%

Slide 21 of 59 Anderson et al. Sci Transl Med 2012;4 (151):151ra125

What about less frequent sex?

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

	IPERGAY RCT	2017 Sub-analysis
Median # sex acts/month	10	5
Median # pills taken/month	15	9.5

	Person years	# HIV infections	HIV incidence rate/100 py (95% CI)	P
Placebo	64.8	6	9.3 (3.4-20.1)	
TDF/FTC	68.9	0	0.0 (0.0-5.4)	0.013

Slide 22 of 59 Antoni et al. AIDS 2017

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 PrEP as alternative to daily PrEP for MSM
 - Use if can plan ahead for pre-dose, can take post-doses, use with all partners
- 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 flare	Can be safely 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 5: Case 3

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?

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ARS Question 5: Case 3

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

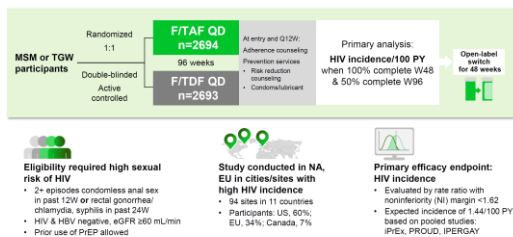
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Modest renal effects in older persons and those with low baseline GFR

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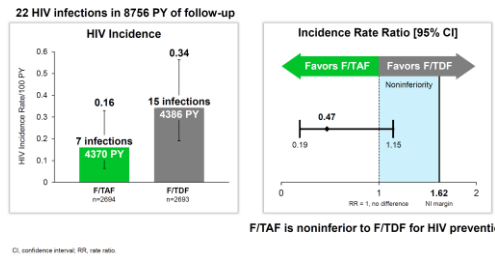
DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



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Hare, CROI 2019, Abstract 104LB

DISCOVER Primary Endpoint Analysis: HIV Incidence



Slide 29 of 59 Hare, CROI 2019, Abstract 104LB

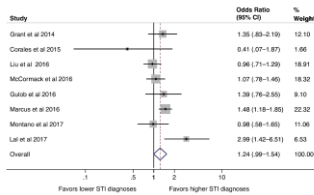
Do STIs reduce the efficacy of PrEP?

- 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 (Mumane, 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-yr 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



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ARS Question 6: Case 4

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?

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ARS Question 6: Case 4

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**

VL: viral load

Nwokolo, CROI 2019, Abstract 117

1. Prevention Research Campaign Community Statement. Available from: <https://www.preventionresearch.org/community> (revised October 2018). 2. CATIE Fact Sheet. Available from: <https://www.catie.ca/en/fact-sheets/transmission-by-oral-load-the-treatment-and-undetectable-viral-load> (revised October 2018).

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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Underutilization of PrEP in Partners of HIV positive MSM

918 HIV positive MSM with 1,912 HIV negative partners

10% of MSM HIV patients with HIV-negative partners reported having a partner taking PrEP



Among all reported HIV-negative partners...

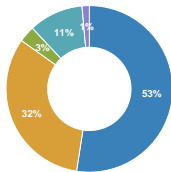


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Beer et al, CROI 2018, #1052

Viral load in 284 MSM self-reported to be undetectable

■ Undetectable ■ <832 ■ 833-999 ■ 1,000-9,999 ■ >10,000



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Teran, CROI 2018, #997

ARS Question 7: Case 5

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?

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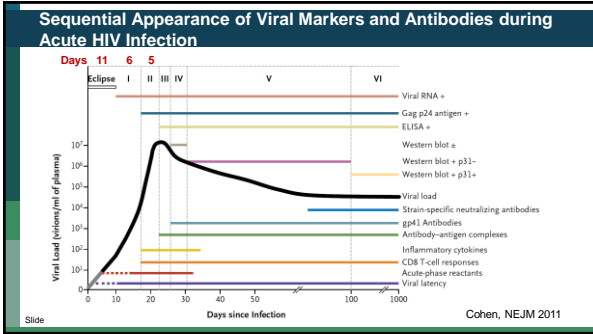
ARS Question 7: Case 5

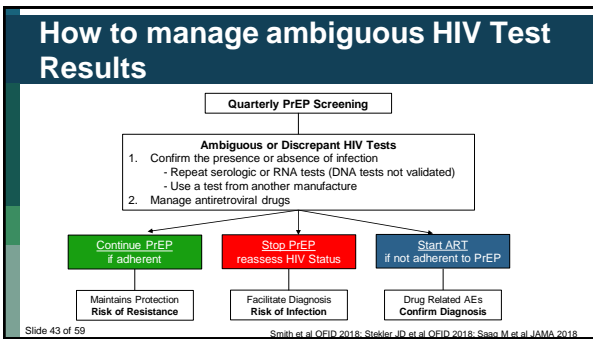
Your 31 year old patient on PrEP comes in for his routine quarterly lab tests. His 4th generation antibody test comes back positive, but the confirmatory test and viral load come back negative.

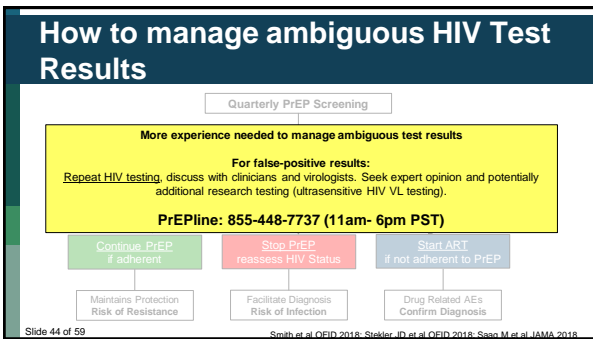
What do you do?

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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ARS Question 8: Case 6

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?

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ARS Question 8: Case 6

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.

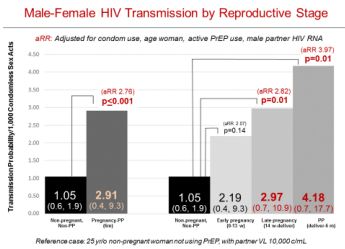
What do you recommend?

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



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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

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ARS Question 9: Case 7

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?

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ARS Question 9: Case 7

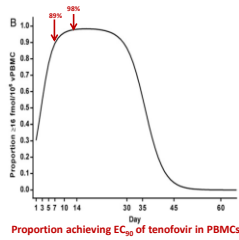
A 29 year old woman in a serodifferent relationship would like to stop using condoms. Her partner is not virally suppressed. She wants to know how long she has to take daily PrEP before she is protected.

What do you tell her?

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

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How long do you need to take PrEP before protected?



In blood (PBMCs)

- 89% achieve EC_{50} after 7 doses
- 98% by 13th dose

Recommended for MSM:

- Start TDF/FTC PrEP 7 days before
- Continue 28 days after (based on animal data)

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

ARS Question 10: Case 8

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?

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ARS Question 10: Case 8

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

- Several studies suggest small reductions in TDF levels

Bottom line: limited data, TDF/FTC likely works in trans women but more data needed

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

Pharmokinetic study of men and trans women

- Design: Open label, one way (estrogen on TFV/FTC) study
- Subjects: 8 cis men, 8 trans women (HIV-Neg; 18-65 years)
- Inclusion: Screening estradiol > 100 pg/mL (TGW only)
- Creatinine Clearance (CrCl) \geq 70 mL/min
- No contraindication to TDF/FTC

Findings: Lower intracellular TFV-DP and FTC-TP among TGW, but NS

	TFV-DP			FTC-TP		
	PBMC C _{24h}	PBMC AUC	Colon Cell C _{24h}	PBMC C _{24h}	PBMC AUC	Colon Cell C _{24h}
% Reduction (TGW/CGM)	16%	24%	36%	-1%	12%	44%
p value	0.30	0.12	0.44	0.98	0.28	0.38

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Shieh et al HIVR4P 2018

ARS Question 11: Case 9

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 antiretroviral resistance, and he's pretty sure his partner mentioned M184V. He doesn't like using condoms.

What do you recommend?

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ARS Question 11: Case 9

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 antiretroviral resistance, and he's pretty sure his partner mentioned M184V. He doesn't like using 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
Hoorneborg 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 12

What is most exciting to you in the future of PrEP?

1. Long-acting injectable cabotegravir
2. Long-acting injectable rilpivirine
3. Oral EfdA (MK-8591)
4. Broadly neutralizing antibodies
5. Vaginal rings
6. Maraviroc

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What's happening with topical PrEP?

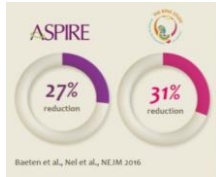
Dapivirine ring studies

- Early efficacy: ~30%
- Open label extension: 54%
- Undergoing regulatory review

Multipurpose technology

- Possibility of combining with contraception or anti-STD interventions

Rectal douches also under development



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Systemic approaches

- Long-acting ARVs
 - ❖ Cabotegravir (INSTI) being evaluated
 - ❖ Challenges: oral lead-in, long pharmacologic tail needs coverage
 - ❖ Other agents, other methods of delivery (e.g., implants)
- Active vaccination
 - ❖ 2 efficacy trials in sub-Saharan Africa; 1 planned in the Americas/Europe
 - ❖ Use viral vectors with protein sub-unit boost
- Passive vaccination
 - ❖ 1 efficacy trial in SSA, 1 in North/South America
 - ❖ Use broadly neutralizing antibody infused or injected

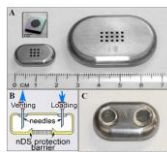
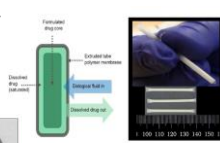
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Implantable devices



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

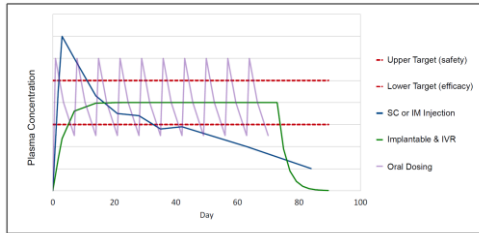
- E.g., Nexplanon .06mg/day



Chiu, CROI 2017
Durham, CROI 2018
Hendrix, MTN 2017

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Formulation PK profiles compared



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Question-and-Answer

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