Be Prepped for PrEP: Case-Based Discussion and PrEP in the Future

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Panelists

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Learning Objectives

After attending this presentation, learners will be able to:

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

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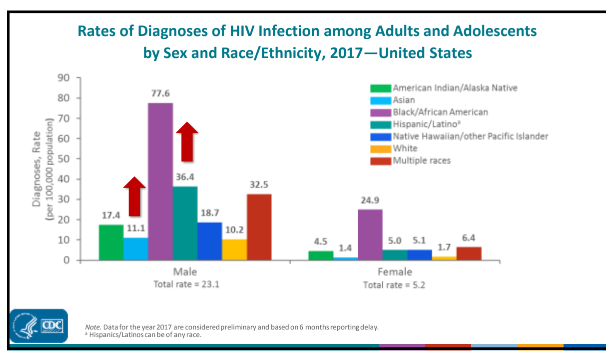
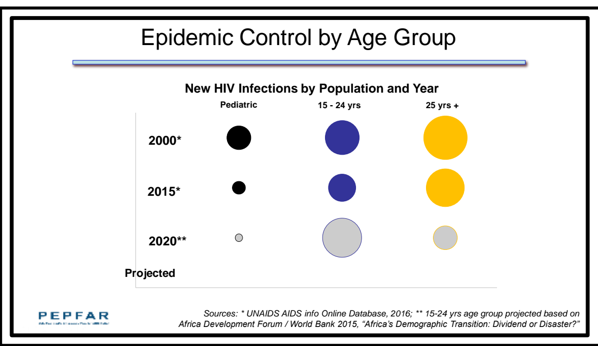
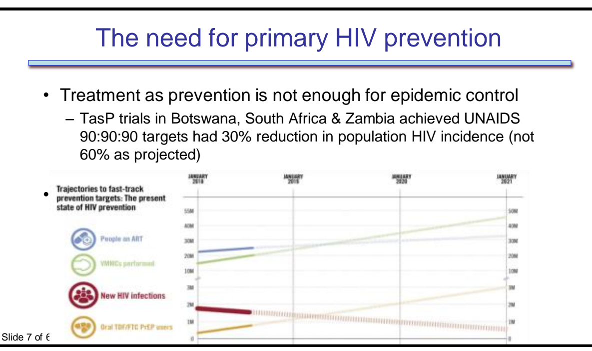

Rates of Diagnoses of HIV Infection among Adults and Adolescents
by Sex and Race/Ethnicity, 2017—United States
Diagnoses, Rate (per 100,000 population)
American Indian/Alaska Native
Asian
Black/African American
Hispanic/Latino[a]
Native Hawaiian/other Pacific Islander
White
Multiple races
17.4
11.1
77.6
36.4
18.7
10.2
32.5
4.5
1.4
24.9
5.0
5.1
1.7
6.4
Male
Total rate = 23.1
Female
Total rate = 5.2
Note. Data for the year 2017 are considered preliminary and based on 6 months reporting delay.
[a] Hispanics/Latinos can be of any race.


Epidemic Control by Age Group
New HIV Infections by Population and Year
Pediatric
15 - 24 yrs
25 yrs +
2000*
2015*
2020**
Projected
PEPFAR
Sources: * UNAIDS AIDS info Online Database, 2016; ** 15-24 yrs age group projected based on Africa Development Forum / World Bank 2015, "Africa's Demographic Transition: Dividend or Disaster?"


The need for primary HIV prevention
• Treatment as prevention is not enough for epidemic control
– TasP trials in Botswana, South Africa & Zambia achieved UNAIDS 90:90:90 targets had 30% reduction in population HIV incidence (not 60% as projected)
• Trajectories to fast-track prevention targets: The present state of HIV prevention
People on ART
VMMCs performed
New HIV infections
Oral TDF/FTC PrEP users
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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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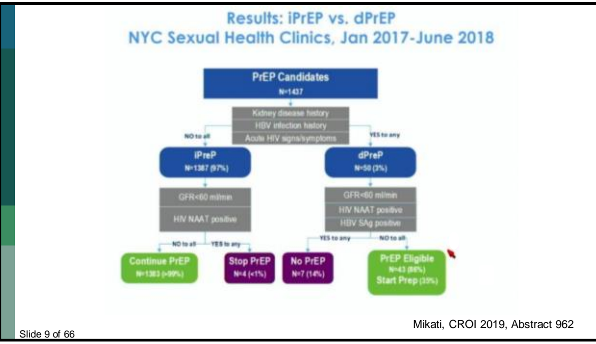

PrEP prescribing

- 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
- San Francisco primary care clinics: prescriptions of $\leq$30 days associated with 1.5 fold higher rate of PrEP discontinuation
  - Only 2/3 of PrEP intervals had HIV/STI testing done, even when allowing for intervals of 4 months
- Need differentiated PrEP delivery to simplify access
  - Drop-in visits, reminders, peer navigators, pharmacy delivery

Spinelli, CROI 2018 #1028
Spinelli et al, OFID 2018

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ARS Question 2: Case 1

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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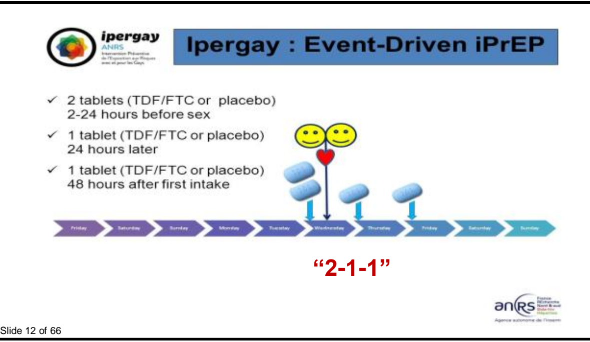

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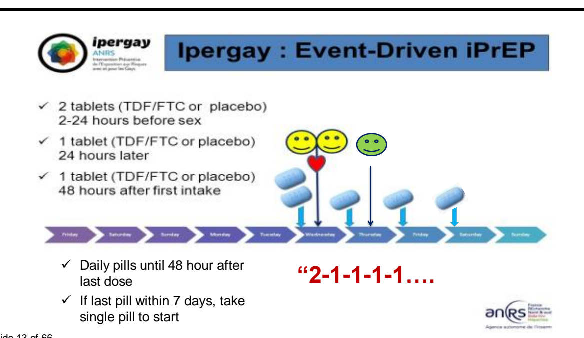

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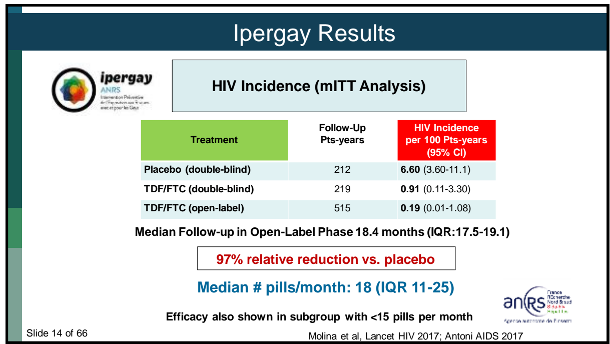

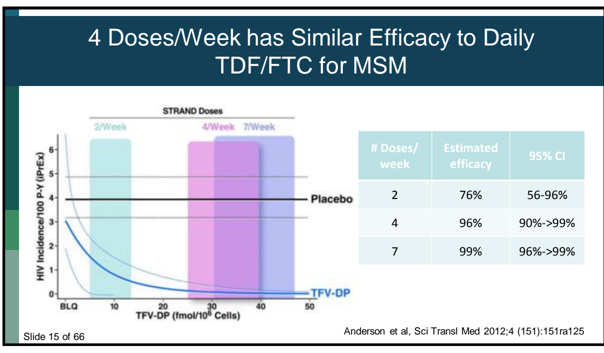

Considerations about 2-1-1 vs Daily PrEP

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

	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 3: Case 2

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

MSM or TGW participants

Randomized 1:1

Double-blinded

Active controlled

F/TAF QD n=2694

96 weeks

F/TDF QD n=2693

At entry and Q12W:
Adherence counseling
Prevention services
- Risk reduction counseling
- Condoms/lubricant

Primary analysis:
HIV incidence/100 PY
when 100% complete W48 & 50% complete W96

Open-label switch for 48 weeks

Eligibility required high sexual risk of HIV
- 2+ episodes condomless anal sex in past 12W **or** rectal gonorrhea/ chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR ≥60 mL/min
- Prior use of PrEP allowed

Study conducted in NA, EU in cities/sites with high HIV incidence
- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%

Primary efficacy endpoint: HIV incidence
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

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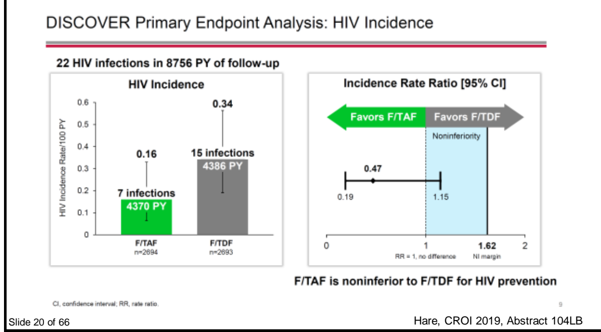
Hare, CROI 2019, Abstract 104LB



F-TAF for PrEP

- F-TAF is noninferior (but not superior) to TDF for MSM
  - Median age of 34; 74 transgender women
  - Evidence based on 22 infections, 5 of which occurred at enrollment
  - No data in cis-gender women
- Well tolerated, less effect on bone density & renal markers
- Limitations of counterfactual HIV incidence
  - Estimated 4.4% HIV incidence, without accounting for racial distribution
- High incidence of STIs: 45% GC, 42% CT, and 10% syphilis
- Submitted for FDA review

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Hare, CROI 2019, abstract 104LB

ARS Question 4: Case 3

Your 29 yo HIV-negative male patient was diagnosed with secondary syphilis (macular rash, myalgias, RPR 1:64).

- He is interested in starting PrEP. He also asks about whether PrEP will work for him given his syphilis diagnosis.

What do you do?

1. Wait for his syphilis titers to drop 4-fold
2. Tell him that PrEP is not as effective if someone has syphilis
3. Tell him that PrEP works in presence of STIs, prescribe PrEP same day and call back with labs
4. Wait for HIV RNA
5. Something else

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Do STIs reduce the efficacy of PrEP?

- No evidence STIs lower PrEP efficacy in RCTs
  - iPrEX: Syphilis incidence of 7.3/100 p-yr; 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)

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

Study	Odds Ratio (95% CI)	% Weight
Grant et al 2014	1.35 (.83–2.19)	12.10
Corales et al 2015	0.41 (.07–1.87)	1.66
Liu et al 2016	0.96 (.71–1.29)	18.91
McCormack et al 2016	1.07 (.78–1.46)	18.32
Gulob et al 2016	1.39 (.76–2.55)	9.10
Marcus et al 2016	1.48 (1.18–1.85)	22.32
Montano et al 2017	0.98 (.58–1.65)	11.06
Lal et al 2017	2.99 (1.42–6.51)	6.53
Overall	1.24 (.99–1.54)	100.00

.1 .5 1 2 10

Favors lower STI diagnoses — Favors higher STI diagnoses

Traeger et al, CID 2018

What about Doxycyline PEP to reduce STIs?

Molina Lancet ID 2018

- Substudy in IPERGAY tested efficacy of doxycycline as STI PEP in MSM
- 1:1 randomization to doxy vs. no pill
- Told to take 200 mg within 24 hours & within 72 hours after sex
- Tested every 2 months for syphilis, GC, chlamydia

Primary outcome:
47% decrease in syphilis, CT and GC

Limitations of IPERGAY doxy PEP study

- Relatively small numbers of participants & short follow-up time
- Homogeneous (white, older, educated) participants
- Doxy PEP used in context of intermittent PrEP
  - Not known about episodic doxy dosing by daily PrEP users
- Only HIV-uninfected MSM
- No transgender women
- Studied in Europe, with higher TCN resistance in GC than in US

- *Stay tuned: additional studies of doxy PEP efficacy are starting in both HIV- MSM/TGW on PrEP and HIV+ MSM/TGW*

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ARS Question 5: 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

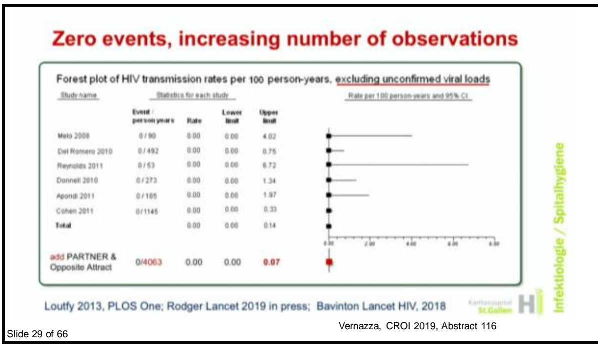
Healthcare workers who experience sharps/mucosal injuries

Undetectable VL in this context:	<200 c/mL

VL, viral load

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)

Slide 28 of 66 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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Partner 2 study: No transmissions from MSM on ART with VL <200

	Number of linked transmissions	Upper 95% CI limit*	Couple-years of follow-up	Number of condomless sex acts	HIV-negative men reporting sex act, n/N (%)†
Condomless anal sex	0	0·23	1593	76 088	778/779 (99·9%)
Insertive condomless anal sex	0	0·27	1343	52 087	709/777 (91·2%)
Receptive condomless anal sex with ejaculation	0	0·57	650	20 487	436/776 (56·2%)
Receptive condomless anal sex without ejaculation	0	0·43	865	22 995	577/773 (74·6%)
Any condomless sex with an STI†	0	3·17	116	6090	NA

Rate of within-couple HIV transmission (per 100 couple-years of follow-up)

- 782 MSM couples followed for 1600 couple-years with 76000 reports of condomless sex
- Upper limit of risk from condomless anal sex is 0.23 per 100 couple-yrs of follow-up
  - 3.17 in HIV- MSM with an STI
- 15 HIV- MSM became HIV+, all from outside partners, based on viral sequencing

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Rodger A et al Lancet 2019

ARS Question 6: Case 5

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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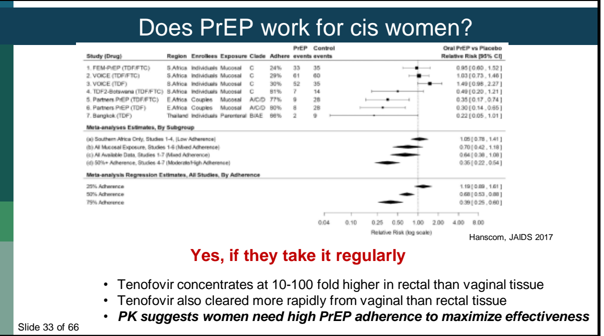
Does PrEP work for cis women?



Hanscom, JAIDS 2017

Yes, if they take it regularly

- 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 high PrEP adherence to maximize effectiveness***

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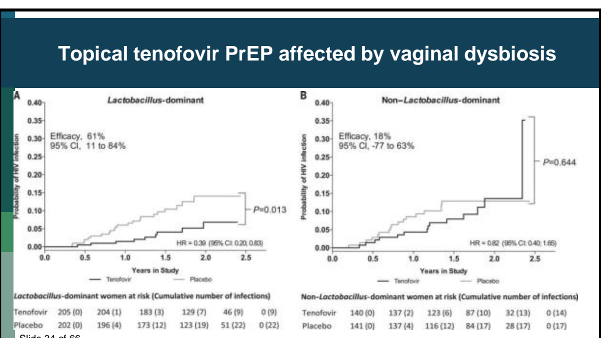
Topical tenofovir PrEP affected by vaginal dysbiosis



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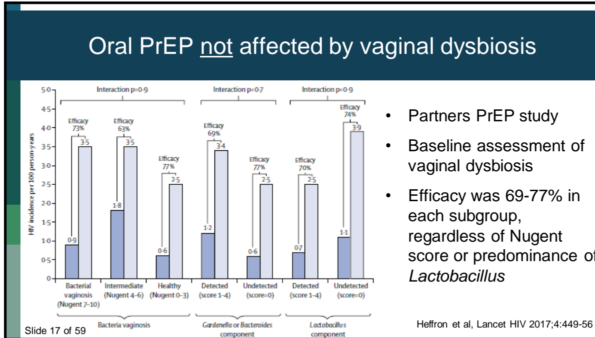
Nichole R. Klatt et al. Science 2017;356:938-945

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 7: Case 6

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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How to manage ambiguous HIV test results

Quarterly PrEP Screening

Ambiguous or Discrepant HIV Tests
1. Confirm the presence or absence of infection
   - Repeat serologic or RNA tests (DNA tests not validated)
   - Use a test from another manufacture
2. Manage antiretroviral drugs

Continue PrEP if adherent	Stop PrEP reassess HIV Status	Start ART if not adherent to PrEP
Maintains Protection **Risk of Resistance**	Facilitate Diagnosis **Risk of Infection**	Drug Related AEs **Confirm Diagnosis**

PrEPline: 855-448-7737 (11am- 6pm PST)

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

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ARS Question 8: Case 7

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

Calculated using a reference case of a 25-year old woman not pregnant, not using PrEP, with a partner with viral load of 10,000 copies/ml

Thomson KA et al. JID 2018

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PrEP safety in pregnancy

- Study of 30 women who became pregnant while on PrEP
  - No difference in rates of miscarriage, congenital anomalies, or growth through 1 year of infancy
- Systematic review of 26 articles about TFV exposure in HIV+ pregnant women and 7 in HIV- pregnant women
  - No significant differences in adverse pregnancy outcomes or infant outcomes
- WHO recommends PrEP in pregnancy for women at risk

Heffron AIDS 2018
Mofenson AIDS 2017
WHO policy brief 2017

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ARS Question 9: 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 gender-affirming hormones
- In iPrEX, women on hormones less likely to take PrEP

PK of TDF/FTC in TGW on hormones
- Small non-significant reductions in tenofovir levels in blood or rectal tissue

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

Deutsch et al, Lancet HIV 2015
Anderson et al, JAIDS 2016
Shiedh HIVR4P 2018

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What does future PrEP look like?
New potential agents & formulations for PrEP

- Dapivirine ring
- Cabotegravir LA
- Different formulations
  - Long-acting: Injectable & implants
  - Topical: vaginal rings, rectal douche, inserts
- Broadly neutralizing antibodies
- Multipurpose prevention technologies

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Dapivirine ring & HIV protection

- 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
- Open-label studies show greater use and suggest ~50% risk reduction
- Under regulatory review by EMA

ASPIRE

27% reduction

31% reduction

Subgroup analyses: 60% reduction in HIV among women >25 years of age

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

Injectable cabotegravir Benefits, challenges & unknowns

- Adherence advantages: dosing every 2 months
- Opportunity for integration with injectable hormonal contraception
- Prolonged sub-therapeutic tail concern for poorly adherent
  - 43 wks in men & 66 wks in women
- Efficacy being studied in HPTN 083 (MSM in the Americas) and HPTN 084 (African young women) compared to oral Truvada

Theoretical Infection-Exposure-Resistance Relationships

HIV infection
Resistant infection
Fraction infected or resistant
No Drug
No Resistance
Infection
Zone of Resistance Risk
No Infection
No Resistance
Low
High
Drug Exposure

Markowitz, Lancet HIV 2017
Landovitz HIV R4P 2018, abstract OA 15.06LB
Graphic courtesy of John Mellors

Implantable Devices

- **Reversible with removal**
- **Long-acting (months to years)**
- **Potential for Multi-purpose**
- **Current development**
  - **TAF, CAB, EFdA**
  - **Others**

Schlesinger, et al, Pharm Res 2016
Gunawardana, et al., AAC 2015

Broadly neutralizing antibodies (bNAbs) for prevention

- 5-10% of HIV+ individuals develop broadly neutralizing serum antibodies after 2-3 years
- So far, this has not been reproduced with vaccines
- Goal is to provide HIV protection by administering bNAbs that target HIV-1 envelope and/or CD4 binding site
- First efficacy trial (AMP) is completely enrolled; IV infusions of single bNAb (VRC01)
- Next step: combination bNAbs administered SQ

AMP

REGIMEN	MSM & TG in the Americas	Women in SSA	TOTAL	
VRC01 10 mg/kg	900	500	1300	10 infusions total & Infusions every 8 weeks
VRC01 30 mg/kg	900	500	1300	
Control	900	500	1300	
Total	2700	1500	4200	Study duration: ~22 months

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'Behaviorally congruent' on-demand topical PrEP

- Integrate HIV prevention products with sexual practices
  - Tenofovir rectal douches
- Fast-dissolving inserts or films
  - TAF/elvitegravir
  - Griffithsin

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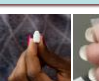
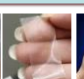
PrEP can not be one size fits all

Pill

Vaginal ring

Injectable


Vagina/rectal tablets


Vaginal/rectal film

Implants

Tenofovir-containing pills are not feasible for everyone. There is a pipeline of new PrEP prevention products that could deliver additional options.

No single formulation will work or be workable for every person.

Choice will be important to meet diverse needs.

Efficacy, choice & coverage are all critical.

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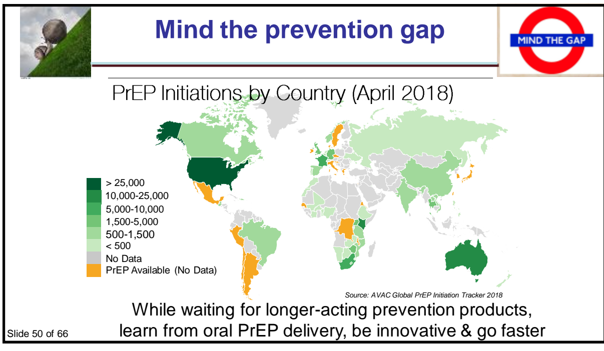

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HPTN 082 HERS

3P

POWER

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