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

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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 sexually transmitted infections (STIs) on PrEP and PrEP on STIs
- Explain U=U

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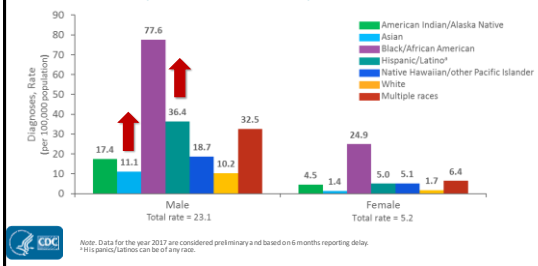
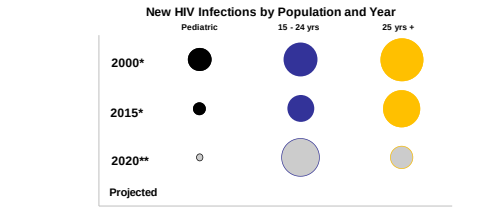
Rates of Diagnoses of HIV Infection among Adults and Adolescents by Sex and Race/Ethnicity, 2017—United States



Note. Data for the year 2017 are considered preliminary and based on 6 months reporting delay.
* Hispanics/Latinos can be of any race.

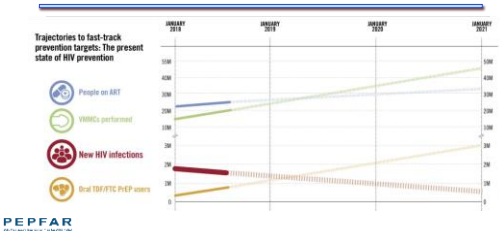
Epidemic Control by Age Group



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?"*

Epidemic HIV control requires implementing the tools we have at scale



PEPFAR

The need for primary HIV prevention

- Treatment as prevention is not enough to achieve epidemic control
  - Trials of TasP in Botswana, South Africa & Zambia achieved UNAIDS 90:90:90 targets had 30% reduction in population-level HIV incidence (not 60% as projected)
- HIV testing, linkages to care, viral suppression on ART *and* scale up primary prevention

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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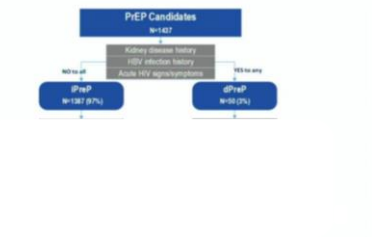
Results: iPrEP vs. dPrEP
NYC Sexual Health Clinics, Jan 2017-June 2018



Mikati, CROI 2019, Abstract 962

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Results: iPrEP vs. dPrEP
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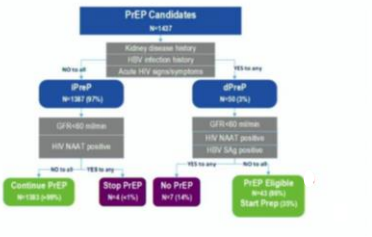

Mikati, CROI 2019, Abstract 962

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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, even though this is not FDA approved or endorsed by CDC

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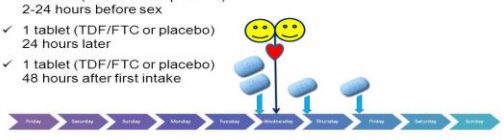
Ipergay : Event-Driven iPrEP

- ✓ 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



"2-1-1"

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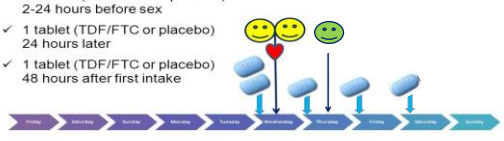

- ✓ Daily pills until 48 hour after last dose
- ✓ If last pill within 7 days, take single pill to start

"2-1-1-1-1…."

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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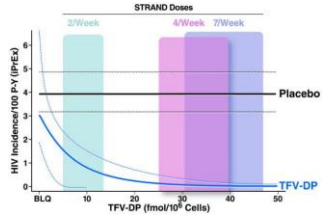
Molina et al, Lancet HIV 2017

4 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?

Analysis of 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

	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**

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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 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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Experiences with event-driven PrEP

- Event-driven PrEP chosen by:
  - 55% of MSM in France
  - 43% of MSM initiating PrEP in Belgium roll-out
  - 27% of MSM in Amsterdam cohort
  - Switching between daily and event-driven PrEP in 15% of MSM in France
- Comparable coverage of sex acts with daily & event-driven PrEP among MSM in Bangkok
  - Lower coverage with event-driven PrEP than daily PrEP among MSM in Harlem & young women in Cape Town

Molina, AIDS 2018
Vuylsteke Sexual Health 2018
Hoornenborg, JIAS 2018
Grant Clin Infect Dis 2018
Bekker Lancet HIV 2018

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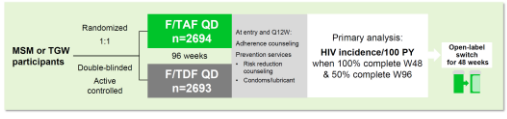
DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



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%

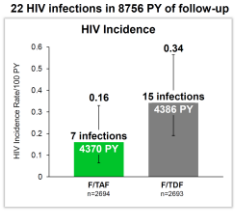
Primary efficacy endpoint: HIV incidence
- Evaluated by rate ratio with noninferiority (NI) margin <1.62
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

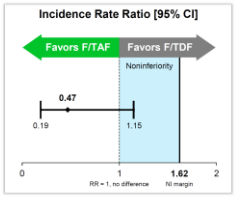
F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

Hare, CROI 2019, Abstract 104LB

DISCOVER Primary Endpoint Analysis: HIV Incidence

22 HIV infections in 8756 PY of follow-up





F/TAF is noninferior to F/TDF for HIV prevention

CI, confidence interval; RR, rate ratio.

Hare, CROI 2019, Abstract 104LB

Which medication should I prescribe for daily PrEP?

ARS Question 4: Case 3

A 29 yo HIV-negative male patient with multiple partners asks you about the recent news about injectable PrEP. He wants to know if it is better than oral PrEP.

What do you say?

1) Tell him that injectable cabotegravir is superior to oral PrEP
2) Tell him that it is non-inferior to oral PrEP
3) Tell him that you don't know, as only the press release is available and will get back to him after the results are published

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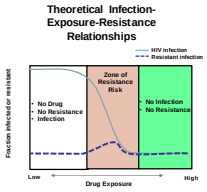
Long-acting agents: benefits, challenges & unknowns

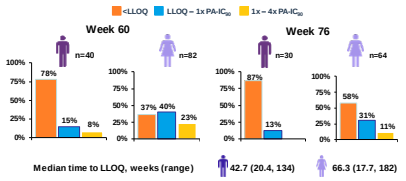
- Adherence advantages: dosing every 2-3 months
- Opportunity for integration with injectable hormonal contraception
- Long $t_{1/2}$ in non-removable method may require oral lead-in to assess toxicity before administering LA formulation
- May have prolonged sub-therapeutic tail; great concern for poorly adherent



Markowitz et al. Lancet HIV 2017;4:e33:1-40

Graphic courtesy of John Mellors

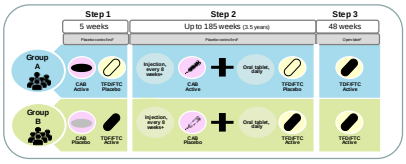
Cabotegravir LA Pharmacokinetic Tail



Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.

HPTN 083 and 084: Phase 3 CAB LA PrEP trials

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender African women (084)



HPTN 083 Study Population

- 4,565 cisgender MSM and TGW who have sex with men included in the analysis; average age of 28 years
- May 14, 2020: DSMB met for planned interim analysis & stopped blinded phase of the study because met non-inferiority endpoint
- Overall incidence 0.79% (95% CI 0.59-1.05%)
- Fewer infections in CAB than TDF/FTC (12 vs. 38)
- Injection site reactions higher in CAB arm (80% vs. 30%) with 49 (2%) discontinuing

ARS Question 5: Case 4

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

– 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 that 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 either 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)

Adapted from Celum, THSY0805, AIDS 2016

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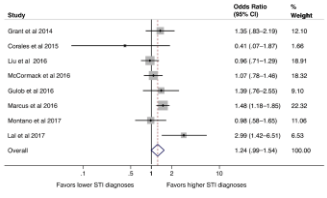
Effect of PrEP on STI incidence

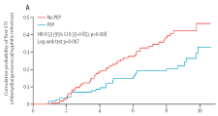
- Rates of bacterial STIs increasing over time; however, rises pre-date PrEP use
- High rates of STIs in many studies of PrEP users
- Mixed results about whether PrEP increases rate of STIs; and interpretation complicated by association of PrEP use with high-risk sexual practices
- PrEP users should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



Traeger et al, CID 2018

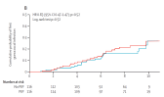
What about doxycyline PEP to reduce STIs?

- 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, & CT

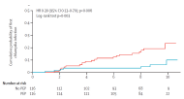


Primary outcome: 47% decrease in syphilis, CT and GC

Molina Lancet ID 2018



No reduction in GC



70% decrease in CT

73% decrease in syphilis

Limitations of IPERGAY doxy PEP study

- Relatively small numbers of participants
- Relatively short follow-up time
- Relatively homogeneous (white, older, educated) participants
- Given in context of intermittent PrEP
- In Europe, with different antibiotic resistance than in US
- Only HIV-uninfected MSM
- No transgender women

- *Stay tuned: efficacy trial in SF and Seattle with HIV+ MSM and HIV- MSM on PrEP with evaluation of AMR, starting 2019*

ARS Question 6: Case 5

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**

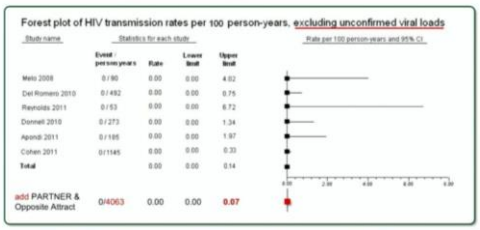
1. Prevention Access Campaign Consensus Statement. Available from: https://www.preventionaccess.org/consensus (Accessed: October 2019). 2. CATIE Fact Sheet. Available from: https://www.catie.ca/en/fact-sheets/transmission/hiv-viral-load-hiv-treatment-and-sexual-hiv-transmission (Accessed October 2019)

VL, viral load

Nwokolo, CROI 2019, Abstract 117

Zero events, increasing number of observations

Forest plot of HIV transmission rates per 100 person-years, excluding unconfirmed viral loads



Loutfy 2013, PLOS One; Rodger Lancet 2019 in press; Bavinton Lancet HIV, 2018

Infektiologie / Spitalhygiene

Vernazza, CROI 2019, Abstract 116

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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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

ARS Question 7: Case 6

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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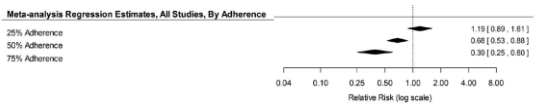
Does PrEP work for cis women?

Yes, if they take it well but does not have to be perfect



Hanscom, JAIDS 2016; 73:606-608

Notes:

- From PK studies: tenofovir concentrates at 10-100 fold higher in rectal than vaginal tissue and is cleared more rapidly from vaginal than rectal tissue
  - Suggest women need to take TDF/FTC 6-7 days/week to maximize effectiveness
- **However, several PrEP demonstration projects in African young women (HPTN 082, 3Ps) with HIV incidence of 0-1% with average of 4 doses taken per week**

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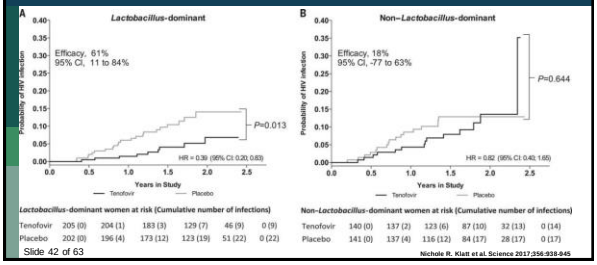
Topical tenofovir PrEP affected by vaginal dysbiosis



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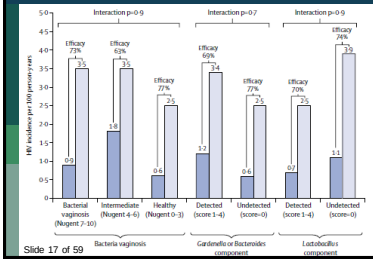
Nichole R. Klatt et al. Science 2017;356:938-945

However, 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*

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

ARS Question 8: 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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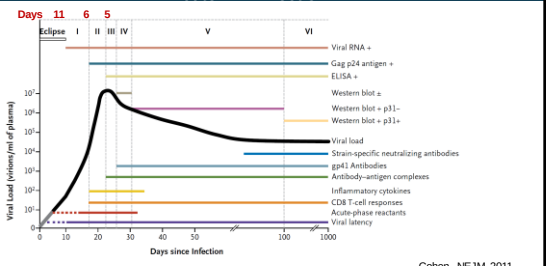
Sequential Appearance of Viral Markers and Antibodies during Acute HIV Infection



Cohen, NEJM 2011

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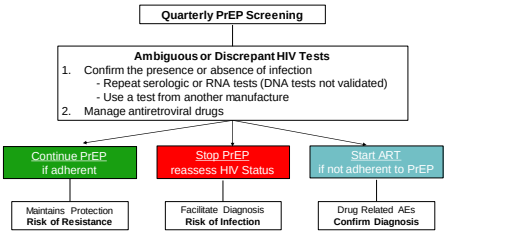
How to manage ambiguous HIV test results



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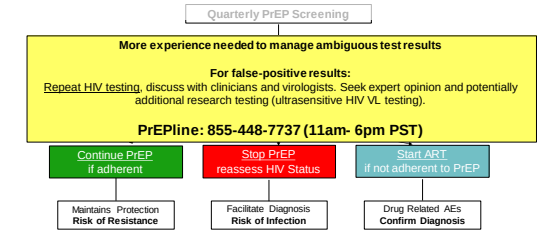
Smith et al OFID 2018; Stekler JD et al OFID 2018; Saag M et al JAMA 2018

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 9: 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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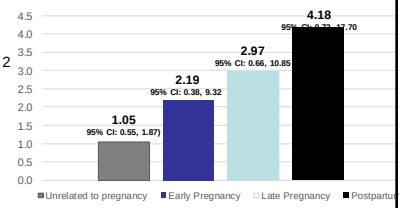
HIV risk increases during pregnancy

- 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



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 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 adverse infant outcomes

Heffron AIDS 2018; Mofenson AIDS 2017

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ARS Question 10: Case 9

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 but TDF/FTC likely works in trans women and more data are needed

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

Pharmokenetic study of men and trans women

- Design: Open label, one way (estrogen on TDF/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) ≥ 70 mL/min
- No contraindication to TDF/FTC

Findings: Lower (but nonsignificant) intracellular TFV-DP & FTC-TP among TGW

	TFV-DP			FTC-TP		
	PBMC C_{tau}	PBMC AUC	Colon Cell C_{tau}	PBMC C_{tau}	PBMC AUC	Colon Cell C_{tau}
% 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

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

- Dapivirine ring
- Cabotegravir LA
- Different formulations
  - Topical delivery (rings, rectal douche, inserts)
  - Injectable
  - Implants
- Broadly neutralizing antibodies
- Multipurpose prevention technologies

PrEP can not be one size fits all

Pill | Vaginal ring | Injectable | Vaginal/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.

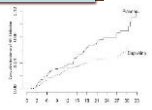
Efficacy, choice & coverage are all critical.

Acknowledgments

- Susan Buchbinder
- Jared Baeten
- Jean-Michel Molina
- Funders: NIH, BMGF, USAID

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



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

'Behaviorally congruent' on-demand PrEP

- Integrate HIV prevention products with other parts of sexual practices
  - Tenofovir rectal douches
- Fast-dissolving inserts or films
  - TAF/elvitegarvir
  - Griffithsin

Implantable Devices

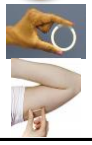
- **Reversible with removal**
- **Long-acting (months to years)**
- **Potential for Multi-purpose**
- **Current development**
  - **TAF, CAB, EFdA**
  - **Others**

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

Multipurpose Prevention Technologies

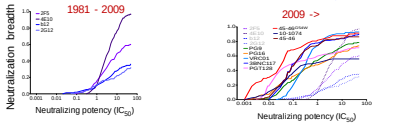
Tackling at least 2 of the 3

- Tenofovir/Levonorgesterol segmented ring
  - Phase I complete
  - CONRAD
- Dapivirine/Levonorgesterol matrix ring
  - Phase I enrolling
  - IPM
- Contraceptive & HIV prevention implant?



Identification of new generation bNAbs: greater *breadth and potency*

Wardemann, Science 2003; Scheid, Nature 2009



- bnAbs are active against a wide range of HIV-1 subtypes
- Potent & protect *in vitro* and in animal studies *in vivo*

Broadly neutralizing antibody for prevention: the AMP study

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

- Can a single bnAb (CD4bs bnAb -- VRC01) prevent infection?
  - At which dose? In both MSM/TGW and cis-women?
  - AMP is fully enrolled; results anticipated in 2021
- Combination bNAbs may be needed
  - Safety & efficacy with greater neutralization breadth

Question-and-Answer