What PAs Need to Know About HIV Prevention and Preexposure Prophylaxis (PrEP)

Jonathan Baker, PA-C Laser Surgery Care | NYC NYC District Director | NYSSPA Membership & Development | LBGT PA Caucus Speaker | LBGT PA Caucus Speakers Bureau Kerin R Berger, MHS, PA-C She/Her/Hers LA LGBT Center | Los Angeles, CA Sexual Health High Resolution Anoscopy Dermatology

1

Disclosure

- Jonathan Baker & Kerin Berger have no relevant financial, professional or personal relationships to disclose.
- We will discuss off-label use of medications and procedures:
 - Emtricitabine and tenofovir for Hepatitis B Virus treatment
 - Intermittent emtricitabine/tenofovir dosing for HIV pre-exposure prophylaxis

2

Objectives

At the end of this session, participants should be able to:

- Identify risk factors for HIV among patients
- Become familiar with HIV prevention methods, including PrEP, PEP, and treatment as prevention
- Reference current guidelines for the use of ARVs as prevention
- Discuss how HIV prevention can be tailored as part of patientcentered care

3

You're a PA in Internal Medicine...

A 54 year old black female patient presents for her annual exam

- PMHx: hypothyroid, post-menopausal
- Medications: levothyroxine, multivitamin
- NKDA, no significant family Hx, no surgical Hx
- Social Hx: Divorced from her husband 3 months prior

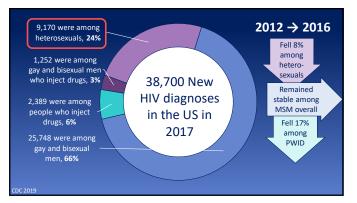
4

What STI Testing is Appropriate for this Pt?

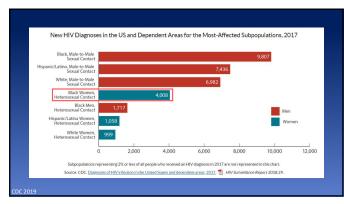
On sexual history the patient reports 2 male partners in the last 3 months. She does not use condoms because she is post-menopausal. She engages in oral-penile intercourse, oral-vaginal intercourse, penile-vaginal intercourse. She denies anal intercourse or anolingus.

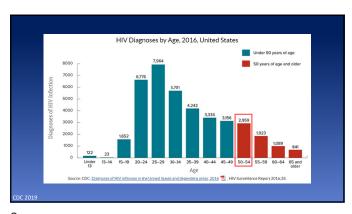
- HIV, urine gc/Ct, oral gc/Ct, syphilis
- She declines HIV testing stating that she is not at risk...
- What patient education is appropriate?

5

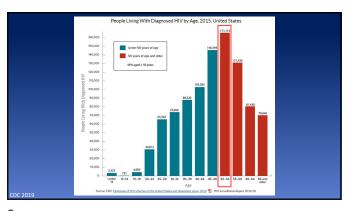


6



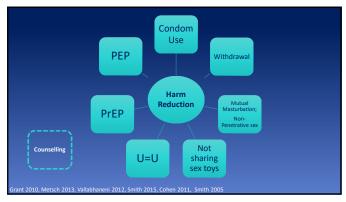


8



9

ab Results			
HIV Ag/Al	b NR	Syphilis	NR
Genital go	NR .	Genital Ct	NR
Oral gc		Oral Ct	NR
Now what	natient educati	on is appropriate	for this nationt?
ow what	рацепт еписан	on is appropriate	for this patients



11

CDC Recommendations for PrEP Heterosexual with opposite gender sexual partner in last 6 months • Infrequent condom use with 1+ partners with HIV risk factors OR • sexual relationship with HIV 624,000 individuals in the US meet this criteria

12

Preexposure Prophylaxis (PrEP) HIV-negative people at high risk of acquiring HIV employing antiretroviral medication to reduce risk of becoming infected with HIV as part of comprehensive HIV prevention services Daily oral tenofovir/emtricitabine is the only FDA approved PrEP

13

Pri	EP Randomized	Controlled Clini	cal Tr	ials
Study	Location	Population	Drug	Prevention
iPrEX	International & Domestic	2,499 MSM	F/TDF	44%
Partners PrEP	Africa (Kenya, Uganda)	4,758 heterosexual Serodiscordant couples	TDF F/TDF	62% 73%
TDF2	Botswana	1,219 heterosexuals (♂&೪)	F/TDF	63%
Bangkok Tenofovir	Bangkok	2413 IVDU (&&)	TDF	48.9%
iPergay	France & Canada	414 MSM (2-1-1 dosing)	F/TDF	86%
Discover	International & Domestic		F/TAF	TAF noninferior*
FEM-PrEP	Africa	1,951 heterosexual women	F/TDF	Unable to
VOICE	Africa	5,029 heterosexual women	F/TDF	Evaluate

14

Prep Real World Efficacy Estimated >450,000 individuals on Prep with ~6 cases of failure • No HIV diagnoses among 657 individuals in the Kaiser system • No HIV diagnoses among 972 individuals in the Northern CA Kaiser • PROUD Study- 544 patients randomized to delayed or immediate Prep • 3 infections in "immediate" arm

• 20 infections in "deferral" arm (12 month deferral)

No HIV diagnoses among 3700 MSM New South Whales (ongoing)
 35% statewide reduction in HIV diagnosis among MSM

2015, Chan 2016, Marcus 2016, McCormack 2016, Grulich 2018

ik 2015, Chan 2016, Marcus 2016, Miccormack

15

Reduc	ction in HIV Diagn	osis	
	*0.9		
	5% Increased in states with low PrEP uptake	23% Decrease in with high PrEP u	
*EADC of	f states in the top quintile and k	*-4.7	untaka
Sullivan 2018	2012-2016	owest quintile of PTEP	иртаке

You're a PA in Primary Care...

A 25 year old Latino, male patient presents to establish care

- No PMHx, medications, drug allergies, family Hx, surgical Hx
- Social Hx: Admits social etoh, denies drug use
- Sexual Hx: He asks "this is confidential right? Will my parents find out my answers?" He reports only ever having 1 partner and always using condoms.

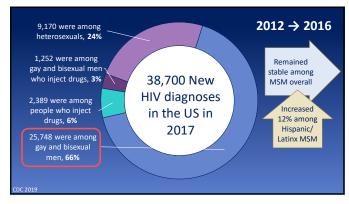
17

You're a PA in Primary Care...

You assure your visibly nervous pt of confidentiality & standard Qs

- Your culturally sensitive sexual history identifies:
 - M, AMAB (assigned male at birth), He Pronouns, who reports having only male sexual partners x 4 years. No primary partner. Engages in anal intercourse, oral-penile sex. Denies oral-anal sex. He sometimes meets his partners on a social app on his phone.
- No longer visibly nervous, he admits to 4 partners in the last 6 months & intermittent condom use

18

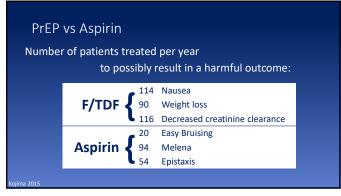


...However... 38,700 is still too many! HIV infections among MSM remain about 26,000/year 35% increase among MSM 25-34 yo 20% increase among latinx MSM 50% of new HIV infections occur in southern states which represent 37% of the US populations

20

You're a PA in Primary Care... You've never prescribed PrEP, but you recently learned about it You feel ready to write (electronically submit) your first Rx The patient asks: Is it safe?

21



You're a PA in Primary Care...

Phew! Good thing you watched this presentation!

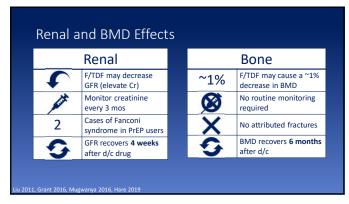
The patient asks:

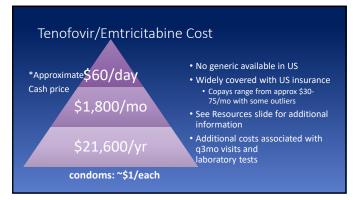
- What are the side effects?
- Will my insurance cover it?
- When will I need to come back?

23

Common	Uncommon	Serious
Diarrhea (2%)	Vomiting	↓ Bone mineral density
Dizziness (2%)	Abdominal pain	Kidney failure
Gas	Decreased appetite	Lactic acidosis
Nausea	Weight loss	Liver disease
Headache	Malaise	Muscle weakness
Rash	Muscle pain/cramp	Pancreatic disease
Skin discoloration	Dysphagia	
	Shallow breathing	
	Sleepiness	

24





26

Baseline Labs • HIV Ag/Ab • RPR • Hep A total ab (MSM) • Hep B surface ab/ag • Hep C ab • GC/CT (genital, pharyngeal, rectal) • Creatinine • Urine HCG

27

Q	3 Month Follow Up Labs
	HIV Ag/Ab Creatinine
	oatient's risk (q3-6months): • RPR, three site GC/CT
CDC 2018	

Lab Results:		• CMP:	
• HIV Ag/Ab	NR	• Glucose	121
<u>o.</u>	NR	Sodium	142
• Syphilis		 Potassium 	4.3
 Genital gc/Ct 	NR	 Chloride 	108
 Oral gc/Ct 	NR	Urea Nitrogen	20
Rectal gc/Ct	NR	Creatinine	1.15
• HBsAb/HBsAg	Reactive/NR	• AST • AIT	26 22
• HAV Ab, HCV Ab	NR	• Alk Phos	88
[HCG test in FCBP	1		

29

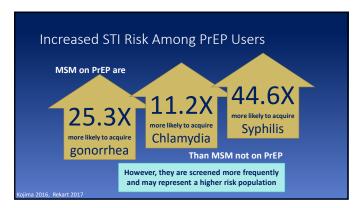
3 month Lab Resu	lts:	• CMP:		
HIV Ag/Ab	NR	 Glucose 	121	
• Syphilis	NR	Sodium	142	
•		 Potassium 	4.3	
Genital gc/Ct	NR	 Chloride 	108	
• Oral gc/Ct	Gc+/Ct-	 Urea Nitrogen 	20	
• Rectal gc/Ct	NR	 Creatinine 	1.15	
~ ·		• AST	26	
· HBsAb/HBsAg	Reactive/NR	• ALT	22	
• HAV Ab, HCV Ab	NR	 Alk Phos 	88	

30

Will PrEP Increase Risky Behaviors?

Risk homeostasis\risk compensation posits an individual will maintain an average level of risk they find acceptable.

31



32

STI Ris	sk in PrEP Users		
275 M	SM at risk of HIV	1922	2 MSM in 5 cities*
ex	oosure in DC:	29%	who were using PrEP were:
41%	who were using PrEP were:	2X	as likely to be tested in the past year
3X	more likely to self report an STI in the past year	1 /=	Slightly more likely to have gc/Ct detected at any site (15% vs 12%)
=	Just as likely to have a current STI	1 /=	↑ risk of rectal Ct otherwise similar
s 2019, Chapin-Ba	rdales 2019	*(SF, DC, NY,	, MIA, Houston)

33

physic	cal, mental and social well-being
	in relation to sexuality."
	-World Health Organization

Hepatitis C Transmission Among PrEP Users

- Sexual transmission of HCV among MSM living with HIV is well documented; few cases among HIV-negative MSM
- 2 cases of sexual HCV acquisitions among 485 MSM in Kaiser San Francisco

Volk 2015, CDC 201

35

You're a PA in Primary Care...

6 months later your patient returns:

 \bullet Does my body get resistant to it if I take it every day?

36

PrEP and	d HIV Viral	l Resistance
----------	-------------	--------------

Inadequate ARV therapy is known to result in resistance; individuals who become infected with HIV should discontinue PrEP immediately to prevent development of resistance

37

You're a PA in Primary Care...

NR

NR

NR

6 month Lab Results:

- HIV Ag/Ab
- Syphilis
- Genital gc/Ct
- Oral gc/Ct
- Rectal gc/Ct
- HBsAb/HBsAg Reactive/NR
- HAV Ab, HCV Ab NR

- CMP:
 - Glucose
 - Sodium
 - Potassium

142

- Chloride
- Urea Nitrogen

38

You're a PA in Emergency Medicine...

A 30 year old MSM presents citing exposure to HIV 6 hours prior

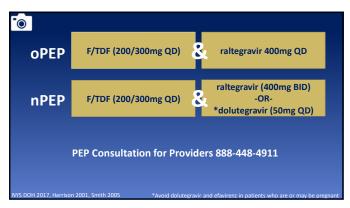
- Sexual Hx: He engaged in condomless oral and insertive anal intercourse with a partner of unknown HIV status
- Medications: tenofovir/emtricitabine, citalopram
- No drug allergies, family Hx, surgical Hx
- Social Hx: Admits social etoh, denies drug use

39

Post Exposure Prophylaxis (PEP)

- Expert consultation is recommended in all cases, but do not delay PEP initiation
- Begin PEP within 72 hours of exposure; preferably within 2 hours
- Baseline Labs: HIV, CBC, CMP
- Repeat HIV Ab at 6 wks, 2 mos, 6 mos
- Occupational PEP HCW exposure to HIV+ or unknown status source
- Non-occupational (nPEP) Sexual or IVDU exposure

40



41

You're a PA in Emergency Medicine...

The patient is already on F/TDF PrEP, does he need PEP?

- Additional ARVs for PEP are not recommended when a patient is already on PrEP
- PEP has limited evidence
- What if the patient wasn't on PrEP?

42

PEP to	PrEP 1	Transitior
--------	--------	------------

What is the indication for a patient utilizing PEP to initiate PrEP?

43

You're a PA in Gynecology...

A 45 yo female presents for annual pap and exam

- Medications: OCP
- No drug allergies, family Hx, surgical Hx
- Sexual Hx: Monogamous with a male partner for 3 years
 Engages in oral, receptive vaginal, and receptive anal intercourse
 Partner is living with HIV
- Social Hx: Admits social etoh, denies drug use

She read about an HIV-prevention drug... Can she start it?

44

Treatment as Prevention



Undetectable = Untransmittable

odger 2016, Donnell 2010, Cohen 201

45

Patient Awareness of PrEP

- Disparities by race
 - Non-Hispanic black MSM significantly less likely to be aware of PrEP compared to Non-Hispanic white MSM
- - College educated MSM were significantly more aware of PrEP than MSM with education levels up to the $8^{\rm th}\,\rm grade$
- Having an HIV test or a +STI test **did not** increase awareness of PrEP
- Increased awareness if patients were out to their PCP

46

500 wo	men seeking care	W	omen Suggested
at 4 F	P clinics in ATL:		Advertising: brochures,
18%	Knew about PrEP		posters, phone calls, etc.
10/0	before the study	a	Conversations: with staff
28%	had ≥1 risk consistent	8	and providers
	with PrEP eligibility	R	Awareness: broadly in the
59%	Expressed interest in learning more about	4	community
33/0	PrEP	-	Access: to PrEP
			information
			& services

47

Disclaimer

- Generics and brand names usedTDF (Truvada) and TAF (Descovy) generics very similar

48

You're a PA in Family Medicine

A 17-year-old nonbinary (they/them) patient presents for a school physical with their caregiver (grandmother)

- PMHx: none
- Medications: none
- NKDA, no significant family Hx
- Social Hx: senior in high school, on lacrosse team, alcohol: 5-7 beers per setting at parties, tried cocaine for first time this past summer, marijuana weekly, lives with grandmother

49

You're a PA in Family Medicine

When you get to sexual practices, grandmother leaves the room:

- Non-binary, AMAB, reports oral sex, anal receptive, anal insertive sex, insertive vaginal sex
- Using condoms for vaginal sex only
- Meets anal sex partners on Grindr and other apps
- · No prior HIV testing or STI testing
- · No history of HPV vaccine

50

You're a PA in Family Medicine

PE:

- W: 75 kg, H: 72 inches
- No significant findings

Labs:

- HIV antibody test negative in office (phew)
- 3 site STI testing collected in office

Assessment:

- Recommend HPV vaccine
- Discuss PrEP options. Patient interested in Descovy (TAF/FTC).

51

Descovy (TAF/FTC)

- FDA approved for PrEP October 2019
- Indications:
 - Adolescents and adults ≥ 35kg, high risk for HIV-1 transmission
 - *EXCLUDES: individuals having receptive vaginal sex
- Dose: TAF 25mg/ FTC 200mg daily
 - $\boldsymbol{\cdot}$ TAF is prodrug of TDF
 - Plasma exposure to TAF, intracellularly converted to TDF at higher levels
 - Lower drug levels

52

Descovy (TAF/FTC)

- Labs:
 - · Initial: r/o HIV infection, Hep B surface antigen, baseline SrCr/CrCl, STI testing, urine glucose, urine protein
 - · CrCl > 30 mL/min (Crockcroft Gault Calculation)
- Follow up
 - · Every 3 months
- Blackbox warning
 - · Acute HBV exacerbation

53

TAF vs TDF: DISCOVER Trial

- Double blind, randomize HIV seronegative
- Median age: 34
- Majority white
- Criteria:

- Subjects were seen in follow-up visits at Weeks 4, 12, and every 12 weeks thereafter; 50% followed up at 96 weeks

54

DISCOVER TRIAL for TAF vs TDF

- "TAF noninferior to TDF"
- No changes in sexual behaviors
- Safety Concerns
 - · Renal
 - · Bone Mineral Density
 - · Lipid levels

55

56

DESCOVY (N=2,694)	TRUVADA (N=2,693)
-0.01 (0.107)	0.01 (0.111)
1.8 (-7.2, 11.1)	-2.3 (-10.8, 7.2)
0.7%	1.5%
	-0.01 (0.107) 1.8 (-7.2, 11.1)

57

able 7: Percentage Change from Baseline in I		
DISCOVERI	TIP and Spine BIVID at Weeks 48 an	a 96, Observed Dat
	F/TAF	F/TDF
	Hip BMD ¹	
Baseline	N=190	N=185
Mean (SD) (g/ cm²)	1.029 (0.154)	1.02 (0.132)
Week 48	N=158	N-158
Mean (SD) % Change from Baseline	+0.183 (2.384)	-0.988 (2.435)
Week 96	N=100	N=105
Mean (SD) % Change from Baseline	+0.424 (2.612)	-1.202 (2.897)
	Spine BMD ²	
Baseline	N-190	N=188
Mean (SD) (g/cm²)	1.131 (0.161)	1.131 (0.138)
Week 48	N=159	N=160
Mean (SD) % Change from Baseline	+0.496 (2.988)	-1.123 (2.945)
Week 96	N-100	N=112
Mean (SD) % Change from Baseline	+0.877 (3.143)	-1.248 (3.918)

DISCOVER TRIAL TAF VS TDF: Lipid

- •TDF greater decreases in fasting lipids
- •TDF higher incidence of fasting lipids
- •No association with cardiovascular risk
- •Two-fold increase in lipid lowering therapy

59

TDF VS TAF?

60

Unclear

- "TAF is noninferior to TDF"
- Pre-existing renal function, BMD, hyperlipidemia
- Age?*
- Length of time on TDF?*
- New to PrEP?*

* Off label considerations

61

You're a PA in Sexual Health (LA)

A 45 year old white man presents for PrEP follow up

- PMHx: Rectal CT, negative repeat testing on multiple occasions
- Medications: Truvada (TDF/FTC) for 5 years
- NKDA, no significant family Hx
- Social Hx: Denies alcohol and drug use, non-smoker, stable housing, occupation: sex worker, travels for work monthly
- Does not want to take PrEP everyday because knows his sexual schedule due to occupation.

62

You're a PA in Sexual Health

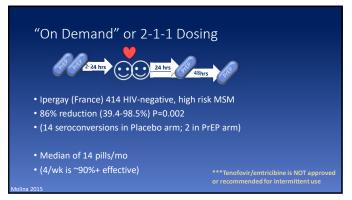
- Sexual practices include:
 - M, AMAB (assigned male at birth) reports oral sex, anal receptive, and anal insertive sex
 - Clients: 3 regular clients, engages 3 times monthly; 0% condom
 - use
 Non-clients: 100% condom use

63

You're a PA in Sexual Health

- Patient concerned about long term use of Truvada (TDF/FTC). Does not want to switch to Descovy (TAF/FTC).
 Very adamant about scheduled sexual encounters. Does not want to continue daily PrEP.
- What recommendations are appropriate for this patient?

64



65

"On Demand" or 2-1-1 Dosing

- Tenofovir/emtricibine is NOT approved or recommended for intermittent use
- Relies on anticipation of sex
- Less drug = less potential for side effects and adverse events
- Glidden et al suggest:

"[Intermittent dosing] is clearly preferable to no PrEP at all"

Gildden 201

66

What's Next: PrEP Pipeline

- Dapivirine ring (27% effective women in Sub-Saharan Africa)
- Injectable cabotegravir every 8 weeks (HPTN-083)
- Implantable PrEP (\$140 million grant)
- Topical tenofovir for MSM (Rectal Microbicides)

None of these are approved

or recommended for PrEP

Molina 2015, Baeten 2016, HPTN, Bill & Melinda Gates Foundation, MTN 201

67

You're a PA in Gastroenterology...

A 45 year old female patient presents for a second opinion

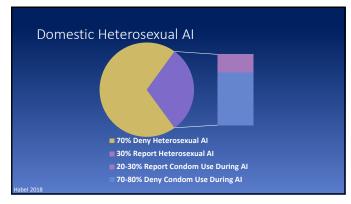
- Diagnosed with Crohns vs. UC with OSH
- BRBPR, tenesmus, mucous discharge, no significant abd Sx
- PMHx: PE (10 years prior)
- Medications: ASA 81 mg, Mesalamine suppository
- NKDA, no surgical Hx
- Family Hx: Denies family Hx of IBD
- Social Hx: single, etoh social, denies drug use, travels frequently for work,

68

You're a PA in Gastroenterology...

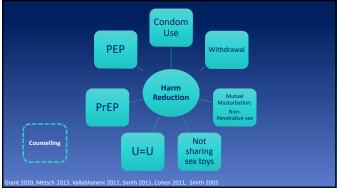
- Your culturally sensitive sexual history identifies:
 - F, AFAB, She pronouns, reports male sexual partner. No primary partner. Consistently uses condoms with RVI, **but not** for RAI, oral sex. 4 partners in the last 6 months.
- Rectal gc+, treated with ceftriaxone/azithromycin and symptoms fully resolve
- What patient education is appropriate?

69



Estimated Per-Act Probabil	ity of Acquiring HIV
from an Infected Source,	
Type of Sexual Exposure	Risk per 10,000 Exposure
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Oral intercourse	low

71



72

1.2 Million Americans Meet Eligibility for PrEP

MSM with male sexual partner in last 6 months
Al without condoms in past 6 mos OR STI in prior 6 mos OR sexual relationship with HIV+ partne
492,200

Heterosexual with opposite gender sexual partner in last 6 months Infrequent condom use with 1+ partners with HIV risk factors **OR** sexual relationship with HIV 624,000

IV drug users who injected non-Rx drugs in last 6 months
Any equipment sharing OR in treatment program in last 6 months OR risk of sexual acquisition
115,000

Smith 201

73

Take Home Points

- HIV prevention IS the responsibility of health care providers, especially in primary care
- Biomedical HIV prevention options vary and meet the needs of a diverse patient population
- Tenofovir/emtricitibine as daily pre-exposure prophylaxis for HIV is highly effective, safe, and easy to manage in a primary care setting

74

"No more excuses,

We have the tools to end the epidemic:

It is up to us to do it."

-Anthony S. Fauci Director of the NIAID at NIH

75

•	Resources
Finding a PrEP Provider	www.preplocator.org www.greaterthan.org/get-prep/
Uninsured/underinsured/ Copay Assistance	www.panfoundation.org www.copays.org www.health.ny.gov/ (PrEP-AP) Manufacturer rebate programs
FREE CME: Preventing HIV Inf The Role of Pre-Exposure Prop http://www.medscape.org/vi	

Question 1

Order the below interventions from most effective to least effective intervention for reducing risk of HIV transmission

- 1. Condoms, PrEP, UVL, Counselling
- 2. PrEP, Condoms, UVL, Counselling
- 3. Counselling, Condoms, PrEP, UVL
- 4. UVL, PrEP, Condoms, Counselling

CONDOMS: Consistent condom use
UVL: Viral Suppression of partners with HIV
PREP: Tenofovir/emtricitabine pre-exposure prophylaxis (PrEP)
COUNSELLING: Safe Sex Counselling by their PCP

77

Question 2

Your patient presents for 3 month follow up for tenofovir/emtricitabine PrEP and reports increased number of sexual partners and decreased condom use. All of the following are appropriate, except:

- 1. Encourage your patient to undergo asymptomatic STI screening every 3-6 mos and sooner if needed
- 2. Discontinue tenofovir/emtricitabine PrEP
- 3. Discuss tenofovir/emtricitabine PrEP adherence
- 4. Draw bloodwork for HIV and Creatine

78

Question 3

A patient on tenofovir/emtricitabine PrEP presents to the ED within 72 hours of potential HIV exposure, what is the most appropriate practice?

- 1. Discontinue tenofovir/emtricitabine PrEP and test at 6 wks, 3 mos, and 6 mos
- 2. Continue patient on tenofovir/emtricitabine, and add raltegravir for 28 days as PEP
- 3. Reassure the patient that their risk of HIV acquisition is minimal and they should continue daily tenofovir/emtricitabine PrEP
- 4. Check a viral load (HIV RNA) for earliest detection of HIV

79

References

80

References

81

Raifman, Julia RG, Colin Flynn, and Danielle German. "Healthcare Provider Contact and Pre-exposure Prophylavis in Baltimore Men Who Have Sex With Men." American Journal of
Preventive Medicine 52.1 (2017):55-63.
Sales, Jessica M., et al. "Patient recommendations for PrEP information dissemination at family planning clinics in Atlanta, Georgia." Contraception (2019).
Molina, Jean-Michel, et al. "On-demand preexposure prophylaxis in men at high risk for HIV-1 infection." New England Journal of Medicine 373.23 (2015): 2237-2246.
Glidden, David V., Peter L. Anderson, and Robert M. Grant. "Pharmacology supports "on-demand" PrEP." The Joncet. HIV 3.9 (2016): e405.
Hare C, et al. The Phase 3 Discover Study: Daily F/TAF or F/TDF for HIV Preexposure Prophylaxis. CROI, March 2019, Abstract 104. Seattle.
Baeten, Jared M., et al. "Use of a vaginal ring containing daplyirine for HIV-1 prevention in women." New England Journal of Medicine 375.22 (2016): 2121-2132.
Habel, M. A., et al. "Heterosexual Anal and Oral Sex in Adolescents and Adults in the United States, 2011-2015." Sexually transmitted discuses 45.12 (2018):775.
Centers for Disease Control and Prevention. HIV Risk Behaviors. December 2015. Available at: https://www.cdc.gou/biv/risk/estimates/riskbehaviors.html. Accessed April 2019.
Metsch, Lisa R, et al. "Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical trial." JAMA 310.16 (2013):1701-1710.
Vallabhaneni S et al. Seroadaptive behavior: association with seroconversion among HIV- MSM. Nineteenth Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, abstract 140, 2012.
Smith, Dawn K., et al. "Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States." JAIDS Journal of Acquired Immune Deficiency Syndromes 68.3 (2015): 337-344.
Dentarry synthesis 66.3 (2013): 337-344. Cohen MS, Chen YO, McCaluly M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Enel J Med. 2011: 365(6):493-505.
Comen was, chem 10, indicadiny wil, et al. Prevention of nov-1 finection with early antivercental therapy. In Engl 3 Med. 2011; 365(6):493-305.



03