

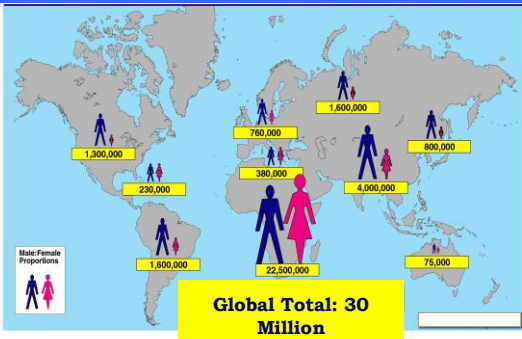
PREP EFFICACY AND IMPLEMENTATION WITHIN CLINICAL SETTINGS

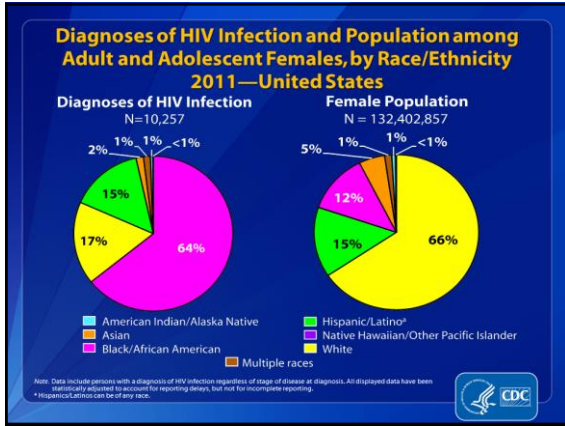
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Gifty-Maria Jane Ntim, MD, MPH
October 6, 2016

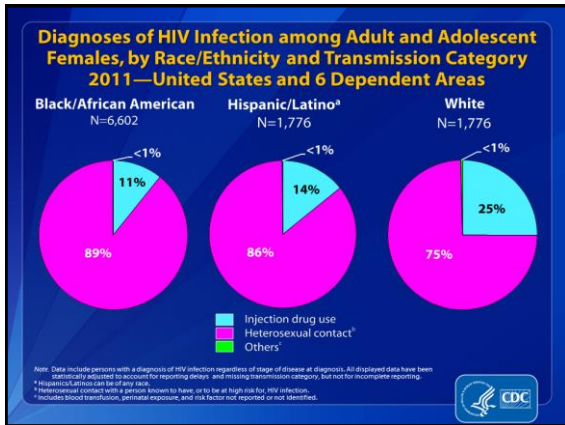
Disclosures

- I have nothing to disclose.

30.1 Million HIV-Infected Adults World Wide: 56% are Women







Vulnerability of Female Youth to HIV

- Sexually active female teenagers may be biologically more susceptible to HIV acquisition than older women
 - Highest age-specific rates of both gonorrhea and chlamydia; may increase the relative risk of acquiring HIV 2-3 fold
 - The less mature cervix commonly has larger areas of cervical ectopy than that of a more mature woman
 - Age-discrepant sexual relationships

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Prevention Modalities

Condoms	PEP	Voluntary Male Circumcision	Needle Exchange
Vaccine	Abstinence	HIV Treatment	PEP
Microbicides	HIV & STI Testing	STI Treatment	Harm Reduction

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TENOFOVIR/EMTRICITABINE (TRUVADA) WAS FDA APPROVED FOR USE FOR PREVENTION ON JULY 16, 2012

It's been over 4 years but we still aren't using it in women?!

Pre-Exposure Prophylaxis (PrEP)

- PrEP (Pre-exposure prophylaxis)
 - Strategy of administering ART to uninfected, at-risk individuals
 - Think of: Malaria prevention, birth control pill
- Tenofovir Disoproxil Fumarate (TDF) +/- Emtricitabine (FTC)
 - Safe and well-tolerated
 - Once daily dosing of co-formulated tablet supported by pharmacokinetic and pharmacodynamic studies
 - Concentration in genital/rectal tissues

Hendrix CW et al. PLoS One. 2013. Von Rompay KK et al. JAIDS. 2006.
 Lehman DA et al. JID. 2015. Von Rompay KK et al. JID. 2002.
 Grant RM et al. AIDS. 2015.

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Safety: Well tolerated

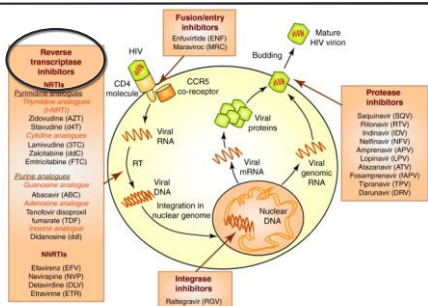
- Start-up syndrome
 - 1-18.5% with nausea, vomiting ± dizziness
- Renal safety
 - 0.2% had elevations in creatinine among 5469 participants randomized to TDF/FTC
- Bone safety
 - 0.4 to 1.5% loss of BMD across total hip, spine, femoral neck and trochanter
 - Return towards baseline with withdrawal
 - Not associated with increased fracture risk

Longer term follow-up in diverse populations needed

Grant RM, et al. N Engl J Med. 2010. Marrazzo JM, et al. N Engl J Med. 2015.
 Baeten JM, et al. N Engl J Med. 2012. Solomon MM, et al. AIDS. 2014.
 Thigpen M, et al. N Engl J Med. 2012. Liu AY, et al. PLoS One. 2011.
 Van Damme L, et al. N Engl J Med. 2012. Kasende M, et al. PLoS One. 2014.

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How does TDF/FTC work?



TRENDS in Pharmaceutical Sciences

PrEP	PEP
<ul style="list-style-type: none"> Given before exposure to prevent infection 2 antiretrovirals given once daily (other regimens under study) Given continuously during periods of increased risk Highly effective at preventing HIV in those who are adherent Given to any individual at increased risk 	<ul style="list-style-type: none"> Given after exposure to prevent infection 3 antiretrovirals ("ART") from at least 2 different classes Given for 28 days from the time of exposure Highly effective at preventing HIV in those who are adherent Can be given for occupational and non-occupational exposures

Clinical Trials of Oral PrEP

	iPrEx	TDF 2	Partners PrEP
Population	MSM and TG females	Heterosexual men and women	Heterosexual HIV serodiscordant couples
Location	US, Brazil, Ecuador, Peru, South Africa, Thailand	Botswana	Kenya and Uganda
Sample size	2,499	1,219	4,758
Intervention	Daily oral TDF/FTC*	Daily oral TDF/FTC*	Daily oral TDF or TDF/FTC*
Efficacy of TDF/FTC (ITT analysis)	44% 36 vs. 64 (95% CI, 15-63%)	62% 9 vs. 24 (95% CI, 22-83%)	75% 17 vs. 13 vs. 52 (95% CI, 55-87%)

Grant et al. *N Engl J Med* 2010
Thigpen et al. *N Engl J Med* 2012
Baeten et al. *N Engl J Med* 2012

*** All as part of a comprehensive prevention package***

- HIV testing
- Risk-reduction counseling and condoms
- Diagnosis and treatment of symptomatic STIs (gonorrhea, chlamydia, syphilis, and HSV-2), as well as screening in asymptomatic individuals and partners
- +/- Referral for PEP if reporting a recent exposure to HIV
- +/- Hepatitis B vaccination

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Clinical Trials in Women Only

	FemPrEP	VOICE
Location	Kenya, South Africa, and Tanzania	Uganda, South Africa, Zimbabwe
Sample size	2,120	5,029
Intervention	Daily oral tablet (TDF/FTC)*	Daily oral tablet (TDF or TDF/FTC) or vaginal gel (TDF)*
Efficacy of TDF/FTC (ITT analysis)	6% 33 vs. 35 (95% CI, -52-41%)	-4.4% 61 vs. 60 (95% CI, -149-27%)

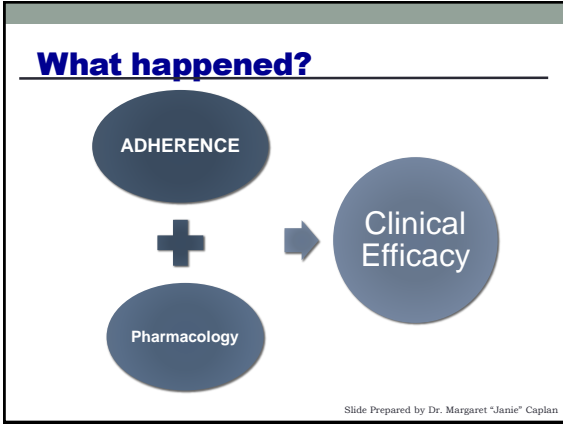
Van Damme et al. N Engl J Med 2012
Marrazzo et al. N Engl J Med 2015

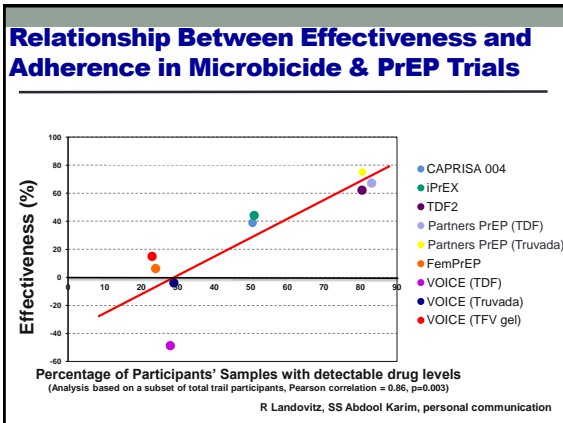
Women in Clinical Trials

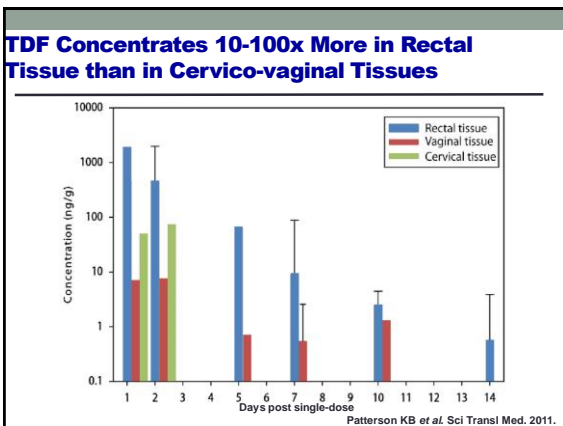
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Efficacy of TDF/FTC (ITT analysis)	44% 36 vs. 64 (95% CI, 15-63%)	Men: 80% (25-97) Women: 49% (-22-81)	75% 17 vs. 13 vs. 52 (95% CI, 55-87%)

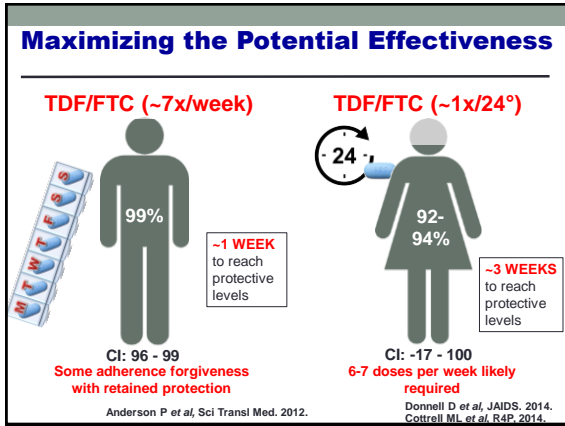
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Dosing Strategies

- **Intermittent dosing is NOT recommended.**
 - IPERGAY study: "On Demand" PrEP with TDF/FTC, only in MSM¹
 - HPTN067 (ADAPT): non-daily PrEP in South African women²
 - Prelim data: Daily dosing fostered better adherence, better coverage of potential sexual exposure, and more sustained use
- **Take Home Point: Daily dosing in women!**

1. Molina JM, et al. CROI. 2015.

2. Bekker LG, et al. CROI. 2015.

Risk Compensation

- **Theory that people adjust their behaviors in response to perceived level of risk**
 - Historical example: Birth control and concern that its increased availability would promote risky sexual behavior
 - Studies have not supported this theory.
 - Recent study (Secura et al. 2014) found giving women free birth control did not result in increased sexual promiscuity.
- **Does PrEP use result in increase in risky behavior (e.g. less condom use)?**
 - PrEP trials have not seen risk compensation.
 - **HOWEVER**, in these trials, participants knew they might be getting a placebo.
 - What will happen in the real world setting?

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Guidelines for PrEP: #1 WHO?

- Other things to consider when estimating a woman's risk:
 - History of multiple STIs (rectal or vaginal gonorrhea; syphilis)
 - Previous PEP use
 - Sex for goods, money or services
 - Partner who has been incarcerated; partner from a region with >1% HIV prevalence; interpersonal partner violence

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Guidelines for PrEP: #1 WHAT?

- The ONLY FDA approved regimen is
 - Tenofovir (TDF) 300 mg + emtricitabine (FTC) 200mg [Truvada]
 - Medication should be used daily
 - Use of other antiretrovirals instead of or in addition to TDF/FTC is not recommended

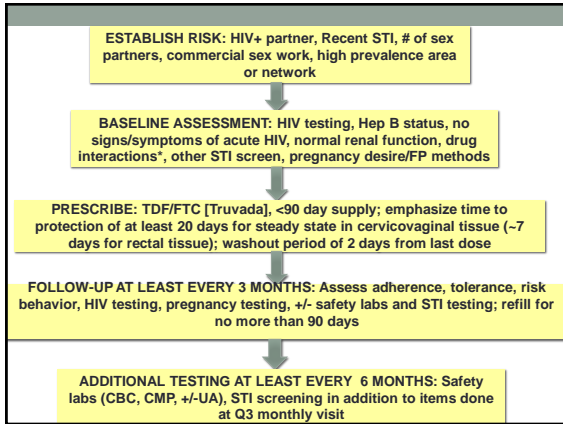


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Guidelines for PrEP: #3 HOW?

- Establish Risk
- Baseline Assessment
- Prescribe
- Intensive follow-up (every 30 days)
- Maintenance follow-up (every 3 months)

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Counseling: Baseline

- **Short term side effects:** Gastrointestinal start-up syndrome (diarrhea, nausea, anorexia and/or weight loss - time limited 2-4 weeks)
- **Long term side effects:** renal dysfunction, bone mineral density loss (1% over 12 months and reversible)
- Concern for resistance if seroconversion occurs "through" TDF/FTC (Truvada) → complicates subsequent treatment of HIV infection
- Lack of protection against other STIs and pregnancy
- Adherence/Missed doses - take if recognized in same calendar-day, otherwise skip dose and resume regular dosing next calendar day → do NOT double-dose
- Risk behavior/Risk reduction

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Baseline Assessment

Assessment	Rationale
Risk Assessment for HIV acquisition	Is PrEP necessary?
Medical History, concomitant meds (including OTC and herbs) and Physical Exam	Screen for factors that could increase risk of toxicity (renal disease, bone disease); assess risk for active HIV or acute HIV
Laboratory Assessment: CBC, Cr/LFTs (CMP), Hepatitis B/C antibody status (+/-A); HIV antibody +/- viral load	Establish baseline health, rule out undiagnosed conditions, rule out chronic or acute HIV; VL in high risk pts*
STI screen (syphilis, chlamydia, gonorrhea)	Rule out concomitant STI; STIs increase risk of HIV transmission and acquisition
Pregnancy desire/contraceptive use	Avoid PrEP in pregnancy unless high risk
Assessment of adherence and follow-up challenges	Ability to adhere/remains in care

Lab Monitoring

- **“Safety Labs”**: At least every 3-6 months
 - CBC/diff, Cr, LFTs
 - UCLA protocol: at monthly f/u in 1st 3 months: Cr and repeat HIV antibody
- **HIV testing***: At least every 3 months → antibody testing and viral load if signs/symptoms/concern about recent infection or seroconversion
- **Pregnancy testing**: At least every 3 months
- **STI screens**: At least every 6 months, more frequently if risk or symptoms (syphilis, gonorrhea, chlamydia)

**PrEP should not be refilled unless HIV status is confirmed every 3 months*

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Note on Hepatitis B

- TDF/FTC is active against hepatitis B
- Establishing Hepatitis B status is important prior to PrEP
 - HBsAb (surface antibody) negative clients should be referred for appropriate vaccination.
- Individuals with Hepatitis B who stop TDF/FTC can have severe flares, which can manifest as fulminant hepatitis/hepatic failure.
- HBsAg (surface antigen) positive clients should be referred to hepatology to be co-followed (but may be started on TDF/FTC)

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Counseling: Follow-Up

- **Adherence**
- **Tolerance**
- **Risk behavior/risk reduction**
- **Pregnancy desire/contraception**
- **Breastfeeding concerns**

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PrEP Adherence Counseling


- **Education**
 - Management of side effects; adherence and efficacy; signs/symptoms of acute HIV
- **Support**
 - Time dose based on patient's routine; reminders and devices to minimize missed doses; identify and address barriers to adherence
- **Monitor**
 - Normalize missed doses without minimizing impact on efficacy; reinforce success; ongoing assessment of barriers

REF-USPHS/CDC PrEP Guidelines 2014

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Efficacy Depends on Adherence

- Next Step Counseling¹
- CDC Guidance²
- Text messaging^{3,4}
- "Smart" devices^{5,6}



1. Amico KR et al. AIDS Behav. 2012.
 2. CDC Clinical Practice Guidelines. 2014.
 3. Finlayson DJ et al. PLoS ONE. 2014.
 4. Moore D et al. CCG 595.
 5. Bekker LG et al. HPTN 067.
 6. Gulick RM et al. HPTN 069.

Drug Interactions

Medication/Class	TDF	FTC
Hormonal Contraception	No effect/no dose adjustment	No data/no dose adjustment
Acyclovir, valacyclovir	May decrease excretion of TDF. No dose adjustment needed	No data/no dose adjustment
NSAIDs and other drugs that reduce renal function, compete for active renal tubular secretion, or are nephrotoxic	Serum concentrations of these meds and/or TDF may be increase. Monitor renal function	No data/no dose adjustment
Tizanidine (Zanaflex)	Increased concentration of Tizanidine (avoid or start at low dose)	No data/no dose adjustment

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PrEP and Pregnancy

- In clinical trials, women becoming pregnant on TDF/FTC have been taken off the study drug → limited data
- Women globally are treated for HIV with TDF/FTC + a third antiretroviral
 - No signal for major congenital defects
 - Investigation into bone impact in infants/children
- PrEP is being used for conception in serodiscordant couples (would refer to specialist when PrEP is used for this purpose)
- Counsel patients; assess pregnancy desire and provide education

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PrEP and Breastfeeding

- TDF/FTC poses no substantial safety risk to infants of mothers who use PrEP during breastfeeding since the levels of TDF/FTC in breast milk are much lower than amount of medication in proposed daily pediatric dose of prophylaxis against vertical HIV acquisition.

Mugwanya et al PLoS Med 2016

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Cost & Coverage?

- Consider only 30 day supply when starting (no more than 90 day)
- Medication cost without insurance or assistance upwards of \$1300-1600/month
- However, most insurances including Medi-Cal cover PrEP; it is not covered under FamilyPACT
- Medi-Cal no longer requires pre-authorization (as of April 2014); private insurances may require pre-authorization
- Co-payments range from 0-30%

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Cost & Coverage?

- Drug Assistance program via manufacturer (Gilead Sciences)
 - Co-pay assistance program for non-state and non-federally funded drug assistance programs (www.GileadCoPay.com); 1-877-505-6986
 - Other resources for those without insurance (www.truvada.com/truvada-patient-assistance)
- ***Assistance with patient navigation is key***

Ongoing Research

- **Other oral antiretrovirals as PrEP**
 - Maraviroc (HPTN069)
- **Long Acting Therapies**
 - Dapivirine ring
 - Injectables – Rilpivirine; Cabotegravir
 - Immunotherapies – VRC01
- **Intermittent (i)PrEP**
- **Combinations of interventions**

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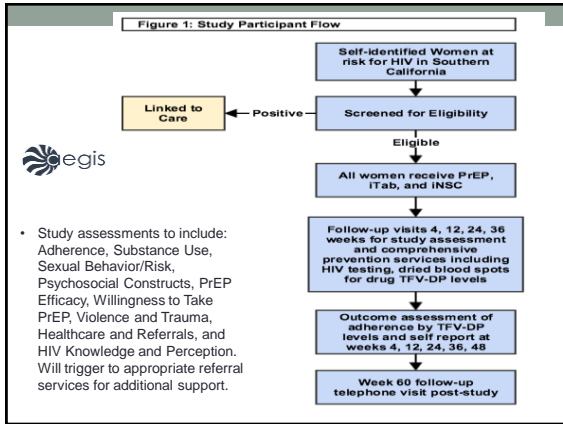
Ongoing Research

Local Demonstration Project: **AEGiS -- PrEP Adherence Enhancement Guided by iTAB and Drug Levels for Women**

- Los Angeles and San Diego
- Truvada® as part of a combination prevention package with enhanced adherence support in the forms of counseling, text messaging, and drug levels for 135 heterosexual, cis-gender women at risk of HIV infection
- UCLA sites (2): APLA Gleicher/Chen Health Center and T.H.E. Health Center



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Case

- A 22 year old healthy female presents to clinic for IUD placement.
- She has one male partner who is HIV-positive and on antiretroviral therapy (ART).
- Her partner's viral load is 'undetectable' most of the time; his highest viral load over the last year has been 350 copies/ml.
- They use condoms 'most of the time' but she remains anxious about HIV transmission.

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What do you recommend?

- No PrEP needed, his viral load is undetectable or low so there is low risk of transmission
- Three-drug PrEP with tenofovir/emtricitabine/rilpivirine (Complera)
- Two-drug PrEP with tenofovir/emtricitabine (Truvada)
- Single drug PrEP with an integrase inhibitor (raltegravir or dolutegravir)

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What do you recommend?

- A. No PrEP needed, his viral load is undetectable or low so there is low risk of transmission
- B. Three-drug PrEP with tenofovir/emtricitabine/rilpivirine (Complera)
- C. Two-drug PrEP with tenofovir/emtricitabine (Truvada)**
- D. Single drug PrEP with an integrase inhibitor (raltegravir or dolutegravir)

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Conclusions

- PrEP is highly effective when taken as prescribed
- We need to reach at-risk populations
 - We need more data in women at risk
 - In partnership with communities
- No single intervention is going to end the HIV epidemic
- PrEP scale-up is a global health imperative as part of combination prevention efforts

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PrEP Resources

- Guidelines -- CDC
www.cdc.gov/hiv/prevention/research/prep/
- Additional CDC Guidance for Providers
www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf
www.cdc.gov/hiv/pdf/PrEPproviderSupplement2014.pdf
- PrEP Support Hotline for Clinicians: PrEPLine, 1-855-448-7737 (1-855 HIV-PrEP).
The CCC Pre-Exposure Prophylaxis Service, 11 a.m. – 6 p.m. ET
National Clinicians Consultation Center <http://nccc.ucsf.edu>
- US Women & PrEP Working group
<http://www.prepwatch.org/us-women-prep-working-group/>
- Gilead website and drug assistance program
www.truvada.com
www.gileadcopay.com
www.pparx.org

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THANK YOU!
