

Updates in HIV Treatment and Prevention

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Vanderbilt Division of Infectious Diseases

September 15, 2017

Agenda

- HIV Epidemiology in USA
- Novel Therapies
- Updates on long-acting ART
- Updates on dual therapy
- Pre-Exposure Prophylaxis
 - Current state and updates

90

90

90

Joint United Nations Program on HIV/AIDS (UNAIDS) goal to have **90%** of those living with HIV to know their status, **90%** of those to be on ART, and **90%** of those on ART to be virally suppressed by 2020

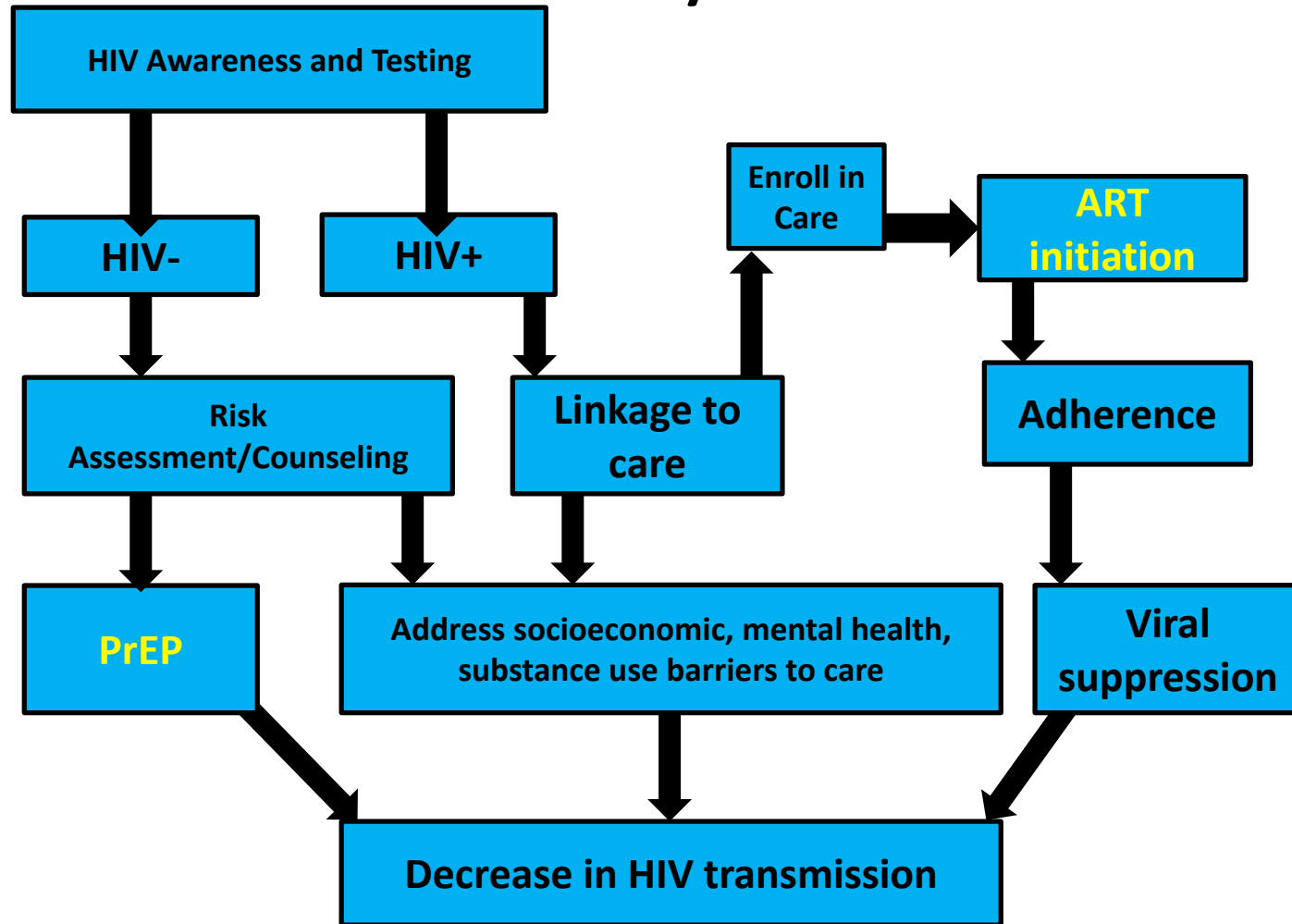
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46

38

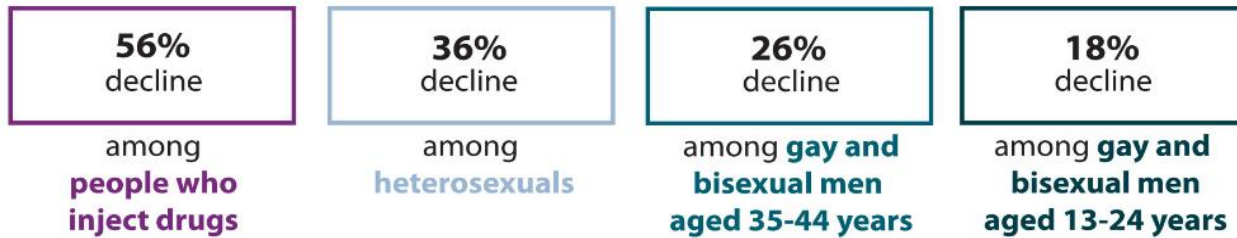
As of 2015, **60%** of those living with HIV know their status,
46% of those are on ART, and
38% of those on ART are virally suppressed.

ART and PrEP alone are not the only keys

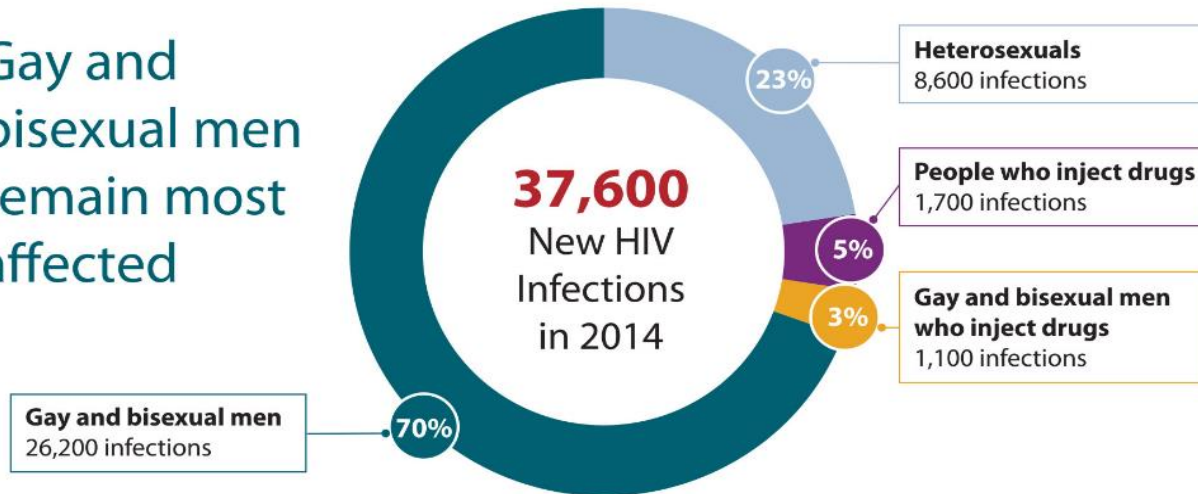


Estimated annual HIV infections in the U.S. declined **18%**

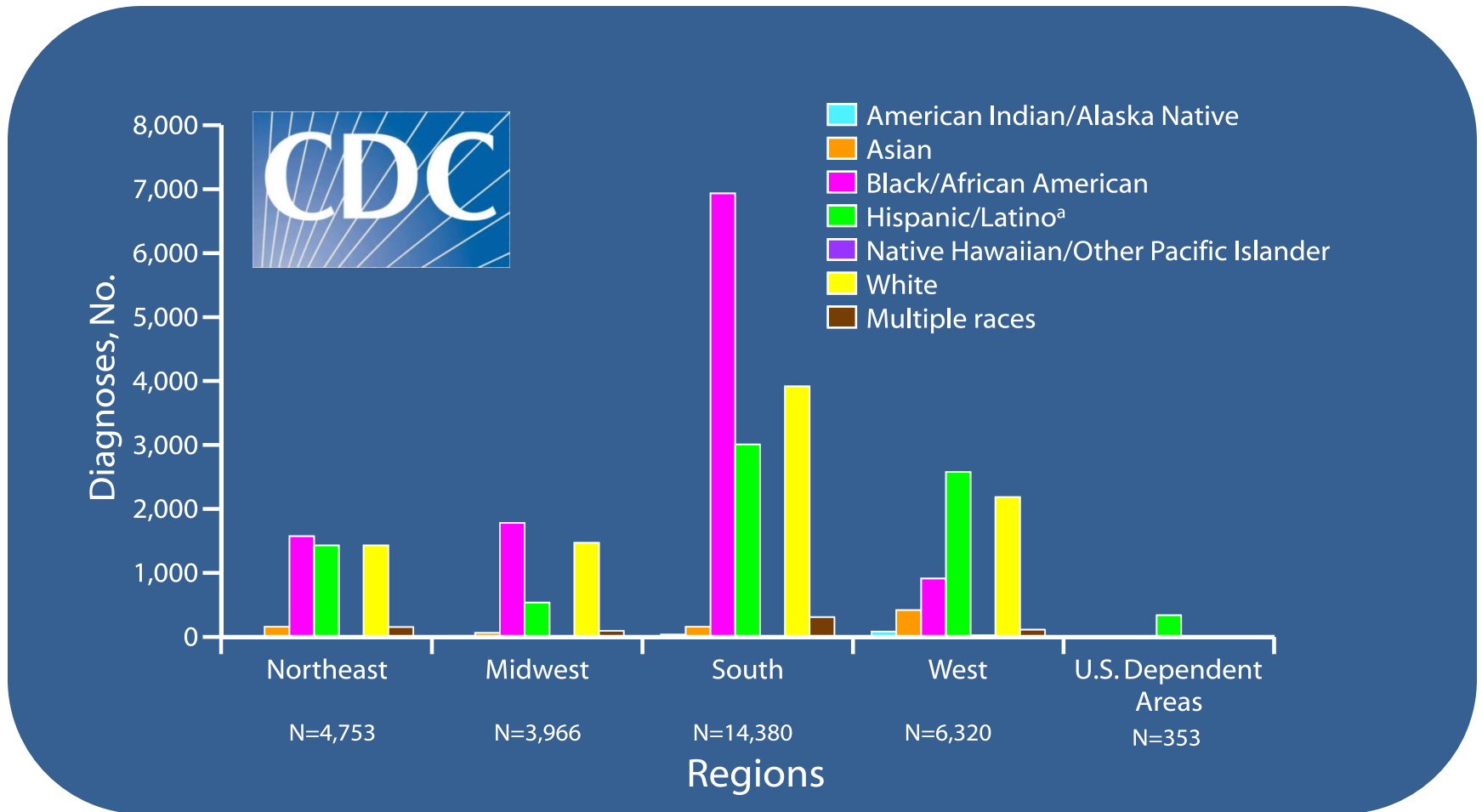
Between 2008 - 2014 infections fell from 45,700 to 37,600



Gay and bisexual men remain most affected

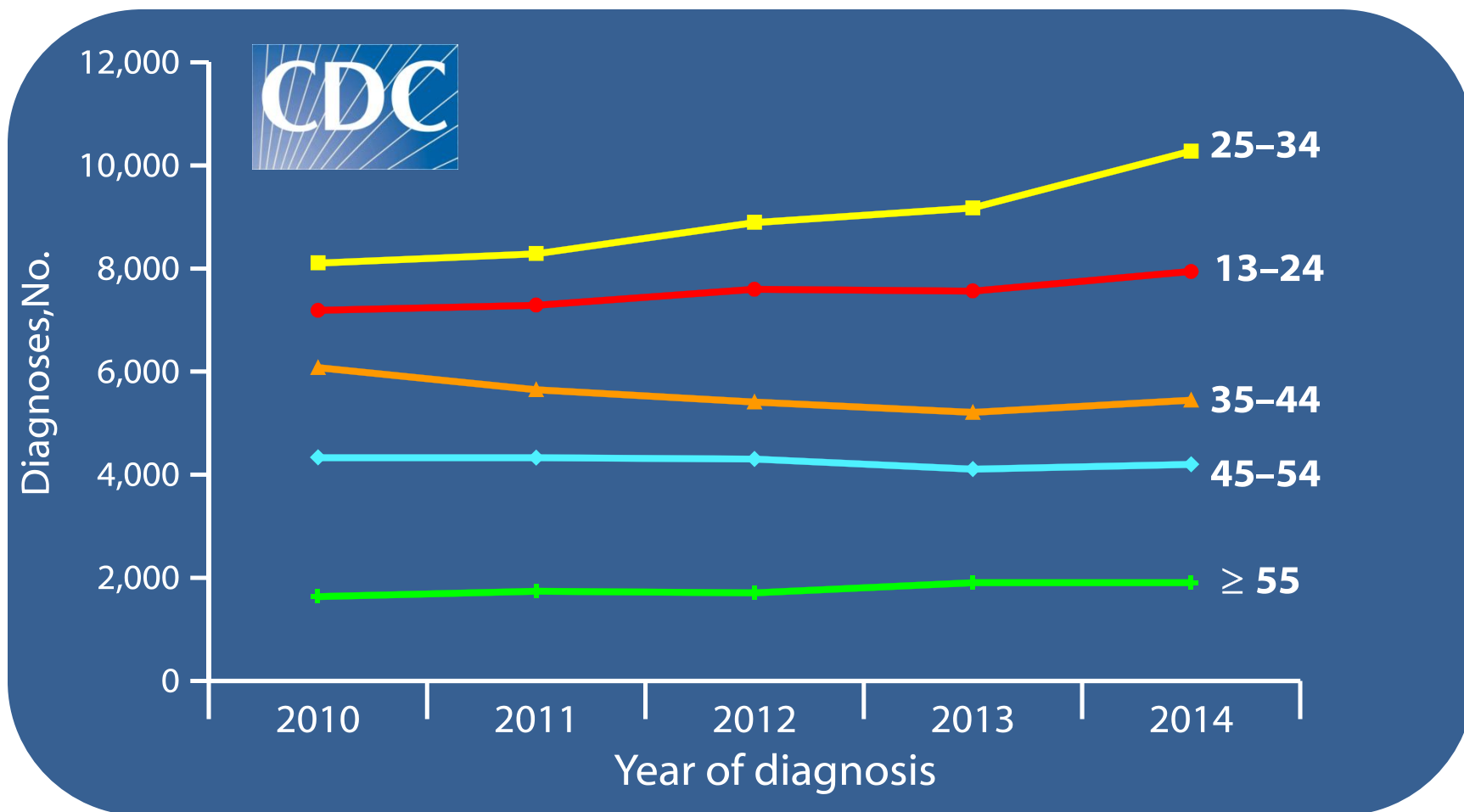


Diagnoses of HIV Infection among Men Who Have Sex with Men, by Region of Residence and Race/Ethnicity 2014 - United States and 6 Dependent Areas



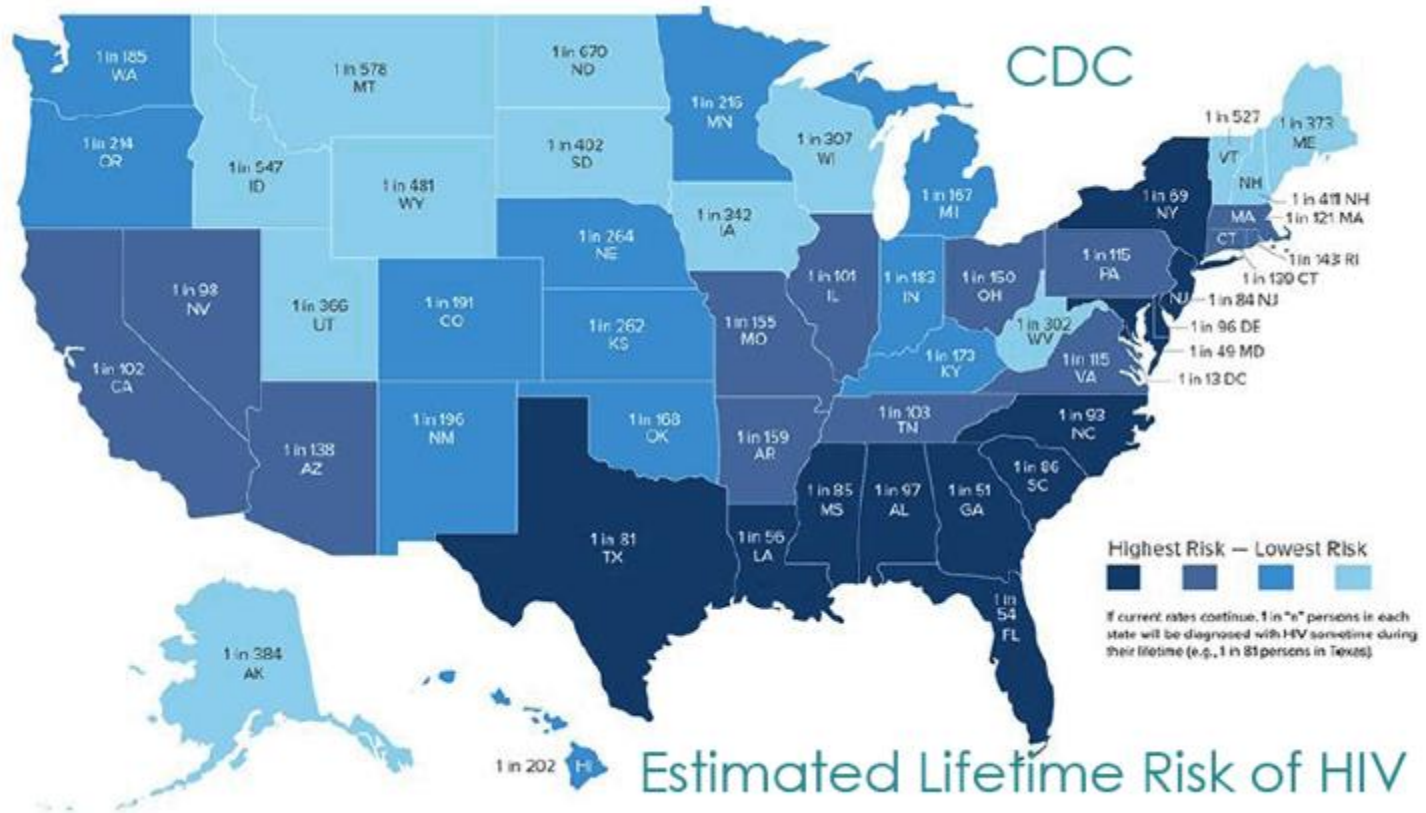
Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact *and* injection drug use. ^a Hispanics/Latinos can be of any race.

Diagnoses of HIV Infection among Men Who Have Sex with Men, by Age Group, 2010–2014—United States and 6 Dependent Areas

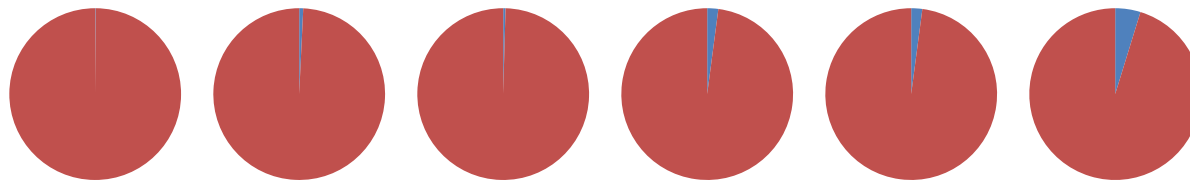


Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting. Data on men who have sex with men do not include men with HIV infection attributed to male-to-male sexual contact *and* injection drug use.

HIV Risk by State



HIV Risk by Race/Ethnicity and MSM



White women
1 in 880

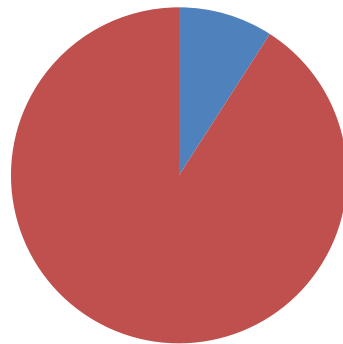
White men
1 in 132

Hispanic women
1 in 227

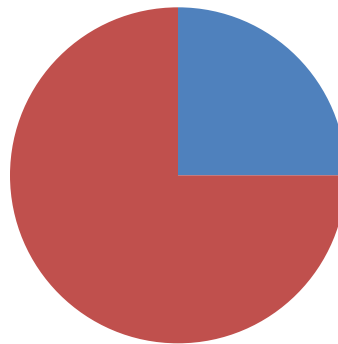
Hispanic men
1 in 48

Black women
1 in 48

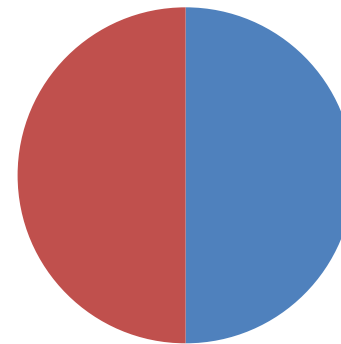
Black men
1 in 20



White MSM
1 in 11



Hispanic MSM
1 in 4



Black MSM
1 in 2

If you care about HIV...

You should be worried.

You should care about prevention.

You should know about treatment.

You should be excited about the future.

ART Refresher

The NRTI Backbones:

Truvada[®] = tenofovir disoproxil fumarate (TDF)/emtracitabine =



Descovy[®] = tenofovir alafenamide (TAF)/emtracitabine =



Epzicom[®] = abacavir/lamivudine =




ART Refresher




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First Line, Multiple Daily Pills:

Truvada[®] OR Descovy[®] + dolutegravir =  OR  + 

Truvada[®] OR Descovy[®] + raltegravir =  OR  + 

Truvada[®] OR Descovy[®] + darunavir + ritonavir =  OF  +  + 

Truvada[®] OR Descovy[®] + Prezcoibix[®] =  OR  + 

New HIV drugs (from existing classes)

Bictegravir

- Integrase strand transfer inhibitor (INSTI)
- Highly potent, well-tolerated and as effective as dolutegravir
- Favorable resistance profile compared to other INSTIs
- Phase II study comparing bictegravir vs. dolutegravir in treatment-naïve
 - At 48 weeks, 97% achieved viral suppression in bictegravir group, vs. 91% in dolutegravir group
 - Not powered to evaluate non-inferiority

Sax P et al. *Randomized trial of bictegravir or dolutegravir with FTC/TAF for initial HIV therapy*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 41, 2017.

Jones G et al. *GS-9883, a Novel HIV-1 integrase strand transfer inhibitor (INSTI) with optimized in vitro resistance profile*. ASM Microbe, abstract 413, 2016.

Bictegravir

- Phase III study (1490):
 - bictegravir + tenofovir alafenamide + emtracitabine (BIC/TAF/FTC) vs DTG/TAF/FTC
 - 645 ART-naïve, blinded
 - Non-inferiority at 48 weeks
 - Similar adverse events rates
- Phase III study (1489)
 - BIC/TAF/FTC vs DTG/ABC/3TC (*Triumeq*)
 - 629 ART-naïve randomized, blinded
 - Non-inferiority at 48 weeks
 - Nausea and neuropsychiatric adverse events higher in DTG/ABC/3TC group

Sax PE et al. Phase 3 randomized, controlled clinical trial of bictegravir coformulated with FTC/TAF in a fixed-dose combination (B/F/TAF) vs dolutegravir (DTG) + F/TAF in treatment-naïve HIV-1 positive adults: week 48 results. 9th International AIDS Society Conference on HIV Science, Paris, abstract TUPDB0201LB, 2017.

Gallant J et al. A phase 3 randomized controlled clinical trial of bictegravir in a fixed dose combination, B/F/TAF, vs ABC/DTG/3TC in treatment-naïve adults at week 48. 9th International AIDS Society Conference on HIV Science, Paris, abstract MOAB0105LB, 2017.

Bictegravir

- *Bictegravir/tenofovir alafenamide/emtracitabine* is under FDA priority review for approval, due February 12, 2018



*Wordcloud

Doravirine

- NNRTI with fewer CNS adverse effects than EFV
- Can be used in the setting of the most common NNRTI resistance mutations (K103N, Y181C, G190A)
- DRIVE-FORWARD – phase III study
 - 766 participants randomized to 2 NRTIs + doravirine vs. 2 NRTIs + DVR/r
 - Doravirine was non-inferior to DRV/r at 48 weeks
 - Doravirine yielded a more favorable lipid profile than DRV/r

Doravirine

- **DRIVE-AHEAD**

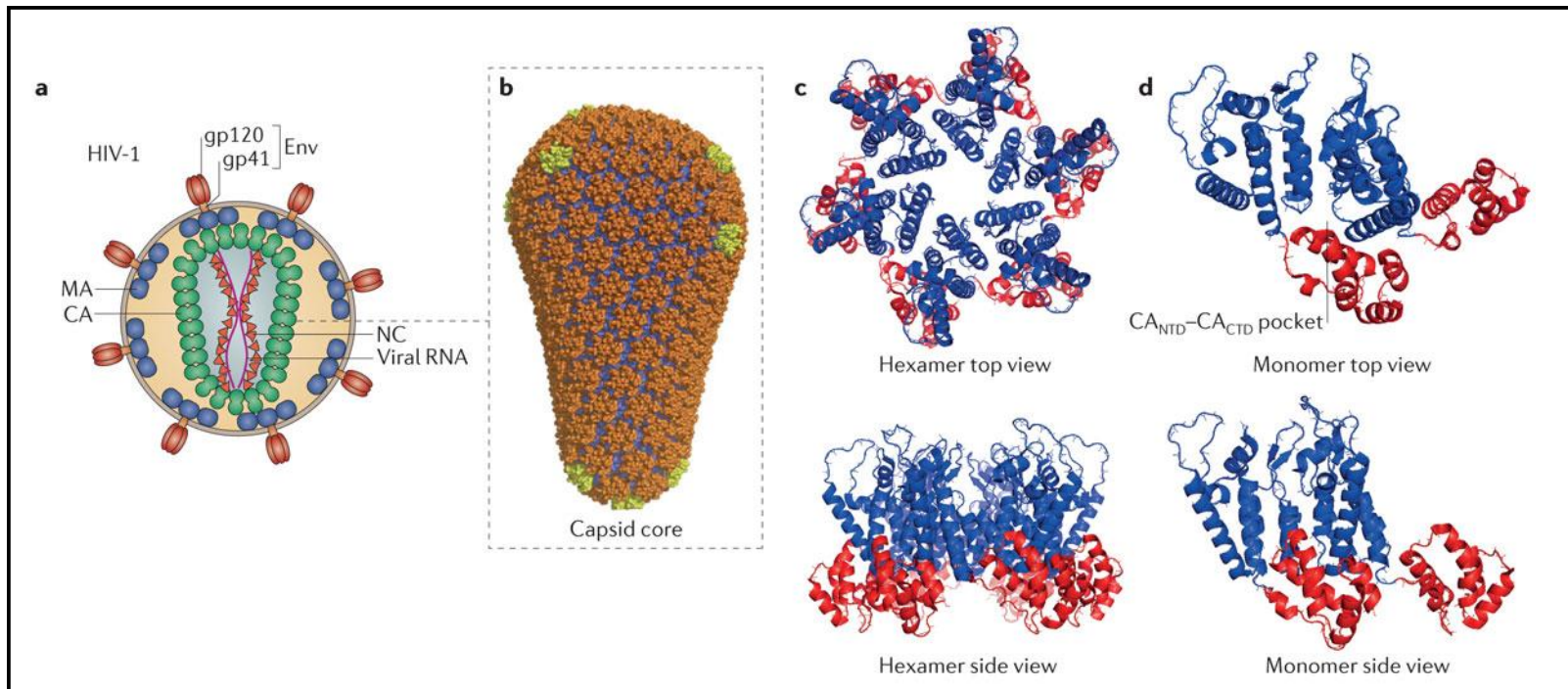
- Phase III study evaluating DOR/TDF/3TC vs TDF/FTC/EFV (*Atripla*) in ART-naïve participants
- DOR-regimen was non-inferior at 48 weeks
- Fewer neuropsychiatric adverse events with DOR-regimen

- **DRIVE-SHIFT**

- Phase III study evaluating switch from boosted PI-based regimen to DOR/TDF/3TC
- Results due March 2018

Novel drug therapies

HIV Capsid Inhibitor



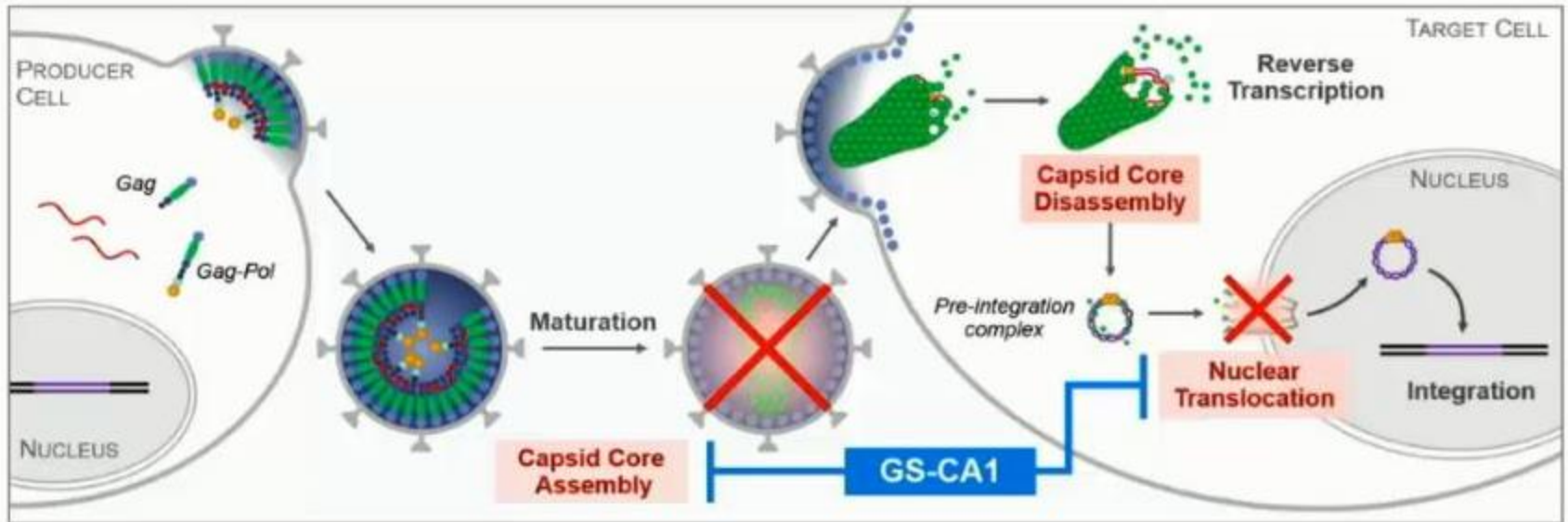
Nature Reviews | Microbiology

HIV Capsid Inhibitor

- GS-CA1
 - Capsid proteins self-assemble into hexamers, which assemble to form capsid core
 - GS-CA1 binds at interface of two adjacent molecules within a capsid hexamer
 - Interferes with capsid assembly, disassembly, and translocation of viral genetic material into nucleus

GS-CA1

GS-CA1 Mode of Action Summary



GC-CA1

- High barrier to resistance (and has HIV-2 activity)
- Very long half-life (in rats, a single parenteral administration maintained therapeutic plasma concentrations for >10 weeks)
- Monkey/human PK data are needed
- More potent than available ART

Long-acting ART

Cabotegravir LA

- INSTI
- Injectable depot formulation with and elimination half-life of 25–54 days
- Under investigation for both HIV treatment and prevention
- Phase II trial (ÉCLAIR) indicates dosing every 8 weeks

Rilpivirine LA

- NNRTI
- Injectable crystalline nano-suspension with plasma elimination half-life 44-61 days
- Under evaluation for HIV treatment (use in prevention remains indeterminate)

LATTE-2

Cabotegravir LA + Rilpivirine LA

- Background:
 - CAB LA + RVP LA was non-inferior to EVF-containing 3-drug oral regimen (LATTE-1)
- Methods
 - After 20-week induction on oral CAB/ABC/3TC, 286 participants randomized 2:2:1 to:
 - CAB LA 400mg/RPV LA 600mg Q 4 weeks
 - CAB LA 600mg/RPV LA 900mg Q 8 weeks
 - Continue daily oral CAB/ABC/3TC

LATTE-2

- Results

- Viral suppression at 96 weeks:

- CAB LA 400mg/RPV LA 600mg Q 4 weeks – 87%
- CAB LA 600mg/RPV LA 900mg Q 8 weeks – 94%
- Continue daily oral CAB/ABC/3TC – 84%

- Intermittent IM ART was non-inferior to oral therapy

- >99% in IM groups reported satisfaction, 78% in oral group reported satisfaction with regimen

MK-8591

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- In HIV+ humans, single oral dose resulted in viral suppression for 10 days
- Potential to suppress ongoing replication of HIV in lymph nodes
- Potential for use as less frequently-dosed PrEP

Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435, 2017.

Friedman E, Schuermann D, Rudd DJ, Fox-Bosetti S, Zhang S, Robberechts M, et al. A single monotherapy dose of MK-8591, a novel NRTI, suppresses HIV for 10 days. In: Conference on Retroviruses and Opportunistic Infections (CROI 2016). Boston, Massachusetts; 2016.

Elsulfavirine

- Long-acting NNRTI, $T_{1/2} \sim 8$ days
- Phase IIa, randomized, placebo-controlled trial comparing Elsulfavirine + TDF/FTC (N=60) to EFV/TDF/FTC (N=60) in ART-naïve patients
- At 48 weeks, both regimens demonstrated viral and immunologic efficacy
- Elsulfavirine regimen was better tolerated
- Studies evaluating less frequent dosing are pending

Dual therapy

Dolutegravir + Rilpivirine

- SWORD 1 & 2
 - Over 1000 treatment-experienced participants randomized to:
 - DTG + RPV
 - Stay on current 3- or 4-drug regimen
 - 95% dolutegravir + rilpivirine group maintained viral suppression at 48 weeks (equivalent to control arm)
 - No clear resistance emergence
 - Potential NRTI and PI-sparing regimen

Dolutegravir + Lamivudine

- ACTG A5353
 - Pilot study on DTG/3TC in ART-naïve
 - 120 participants enrolled
 - 31% with HIV RNA >100,000 cpm
 - At 34 weeks, 96% achieved viral suppression (HIV RNA <50 cpm)

Two large trials currently enrolling to evaluate this regimen vs first line triple therapy regimens in treatment-naïve patients (GEMINI-1 and GEMINI-2)

Dolutegravir + Lamivudine

- LAMIDOL
 - 104 treatment-experienced participants switched to dolutegravir + lamivudine
 - 101 maintained viral suppression at 40 weeks

And don't forget...

- Cabotegravir LA + rilpivirine LA (LATTE-2)

Pre-Exposure Prophylaxis (PrEP)

PrEP is primary prevention

It is intended to PREVENT
the onset of a disease in
those who are AT RISK

It is a concept, fulfilled by medication
that has been FDA-approved for this
purpose

What is PrEP?

- Right now, PrEP is Truvada®
 - Fixed dose combination of tenofovir disoproxil fumarate (TDF) 300mg/emtricitabine (FTC) 200mg
 - Developed by Gilead
 - FDA-approved for use as PrEP on June 6, 2012
- Generic TDF/FTC approved 6/2017

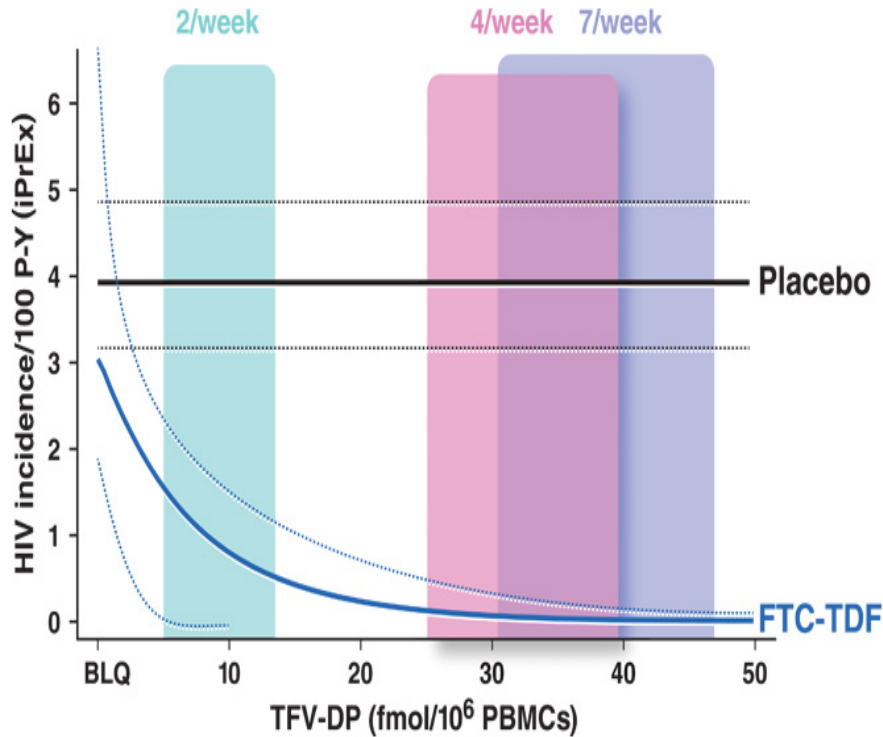
Also approved in Australia, Canada, France, Norway, Belgium, Netherlands, Peru, Israel, Kenya, Botswana, Zimbabwe and South Africa

Coming soon in: Brazil, Nigeria, Zambia, Malawi, Uganda, India, Thailand, United Kingdom, Italy

Is PrEP Effective?

Study	Population	Dosing	Risk Reduction
iPrEX	MSM	Daily	44% (92% with ideal adherence)
TDF2	Heterosexual men and women	Daily	62.2%
Partners	Sero-discordant heterosexual couples	Daily	75% (90% with ideal adherence)
Bangkok Tenofovir Study Group	Intravenous drug users	Daily	48.9% (74% with ideal adherence)
IPERGAY	MSM	On-demand	86%

Dosing matters



Using drug concentrations in iPrEX and STRAND, pharmacokinetic models predict **76%** risk reduction with 2 doses/week, **96%** with 4 doses/week, and **99%** with 7 doses/week.

Who benefits from PrEP?

CDC Recommendations (for MSM)

- Adult man
- Without acute or established HIV infection
- Any male sex partners in past 6 months
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (receptive or insertive) in past 6 months
- Any STI diagnosed or reported in past 6 months
- Is in an ongoing sexual relationship with an HIV-positive male partner

CDC Recommendations (for heterosexual men and women)

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

CDC Recommendations (for IDU)

- Adult person
- Without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in past 6 months

AND at least one of the following

- Any sharing of injection or drug preparation equipment in past 6 months
- Been in a methadone, buprenorphine, or suboxone treatment program in past 6 months
- Risk of sexual acquisition

Who benefits from PrEP?

- Sero-discordant sexual activity (couples)
- Multiple sex partners (especially sex partners with unknown HIV status or at risk for HIV) with inconsistent or no condom use
- History of sexually transmitted infections
- Exchange of sex for money or commodities
- Injection drug use

How to provide PrEP

Encounter	To do
Month 0	<ul style="list-style-type: none">• Screen for HIV• Confirm HBV and HCV status• Check serum creatinine• Screen for STIs• Counseling• Prescribe
Month 3	<ul style="list-style-type: none">• Screen for HIV• Check serum creatinine• Counseling• Prescribe
Month 6	<ul style="list-style-type: none">• Screen for HIV• Screen for STIs• Counseling• Prescribe
Month 9	<ul style="list-style-type: none">• Screen for HIV• Check serum creatinine• Counseling• Prescribe
Month 12	<ul style="list-style-type: none">• Screen for HIV• Screen for STIs• Counseling• Prescribe

Labs:

- HIV screen: 5
- Serum creatinine: 3
- STI screen: 3

Prescriptions/Refill
authorizations: 5

Discussions: 5+

Billing and Coding

- ICD-10 did not take into account medical prevention of HIV
- Suggested codes:
 - Z71.7 - Human immunodeficiency virus [HIV] counseling
 - Z20.6 - Contact with and (suspected) exposure to human immunodeficiency virus [HIV]
 - Z11.3 - Encounter for screening for infections with a predominantly sexual mode of transmission
 - Z79.899 - Other long term (current) drug therapy
 - Z51.81 – Encounter for therapeutic drug level monitoring
- Not suggested
 - Z72.52 – High risk homosexual behavior

Alternative Agents for PrEP

Among the agents discussed in this talk, which are under investigation as PrEP?

- A. Cabotegravir
- B. Bictegravir
- C. Doravirine
- D. Rilpivirine
- E. GC-CA1

Tenofovir Alafenamide (TAF)?

- Achieves high intracellular concentrations, but lower plasma and tissue concentrations than TDF
 - 13-fold lower than TDF in rectal tissues
 - 11-fold lower than TDF in cervicovaginal fluid

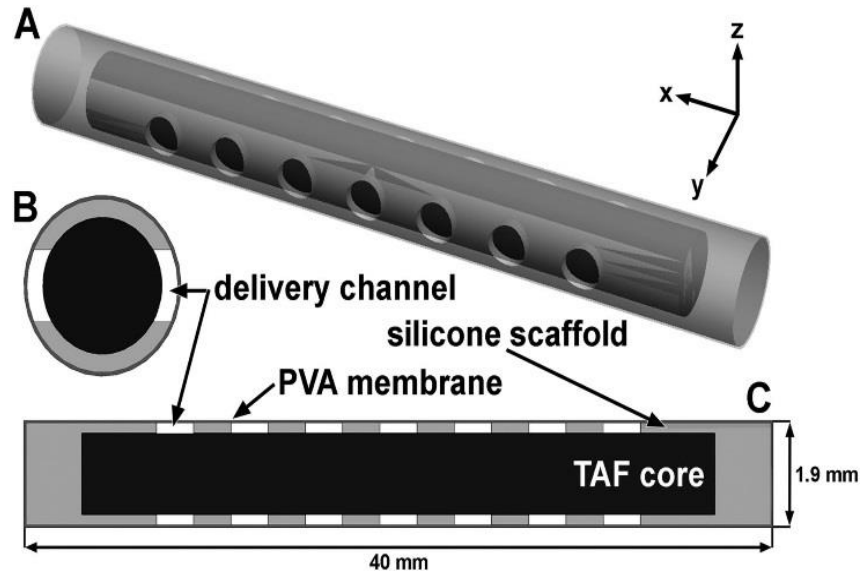
Due to low plasma and tissue concentrations, TAF's use in PrEP is uncertain

Tenofovir Alafenamide (TAF)?

- However...
 - An animal study suggests efficacy
 - 6 macaques received TAF/FTC before and after rectal weekly exposure of SHIV or up to 19 weeks
 - 6 macaques received placebo
 - None of the 6 receiving TAF/FTC acquired SHIV, while all 6 receiving placebo did

Tenofovir Alafenamide (TAF)

- Formulation as subdermal implant in development



Cabotegravir

- Integrase inhibitor with long half-life
- Long acting, depot-controlled nanosuspension has an even longer half-life (25-54 days)
- Use as PrEP in phase 2 trials:
 - Oral lead-in
 - Will likely need every 2 months (6 injections/year)
 - Injection site reactions common
 - Most patients still preferred this over daily oral PrEP

MK-8591

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- Weekly dosing with MK-8591 (N=8) vs placebo (N=8) in macaques
 - All subjected to repeated intra-anal exposure to SHIV
 - After 12 weeks, all in control group were infected with SHIV, 0 in MK-8591 group were infected

Grobler J et al. *MK-8591 concentrations at sites of HIV transmission and replication*. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 435, 2017.

Markowitz M. *Weekly Oral MK-8591 Protects Male Rhesus Macaques against Repeated Low Dose Intrarectal Challenge with SHIV109CP3*. 9th IAS Conference on HIV Science (IAS 2017), July 23-26, 2017, Paris

Dapivirine vaginal ring

- Non-nucleoside reverse-transcriptase inhibitor
- Empowering women in HIV-endemic countries
- A recent phase III trial demonstrated disappointing HIV risk reduction (only up to 37%)

Pharmacy-Driven PrEP Initiatives

ONE-STEP PrEP®

- “One-Step PrEP” in Seattle, WA
 - Pharmacist provides screening, counseling and provision of PrEP under the remote oversight of physician
 - Between 2015-2016, initiated PrEP in 245 patients, 43% without a PCP
 - Retention was 75%
 - Financially sustainable for pharmacy

Walgreen's

- As of 7/2017, select sites offer PrEP counseling, STI screening, and Truvada[®] provision
- Sites are those with existing Walgreens Healthcare Clinics with APNs, PAs
- Sites include:
 - Cincinnati, Cleveland, Columbus, Dallas, Denver, Kansas City, Knoxville, Las Vegas, Louisville, Memphis, **Nashville**, Orlando, Philadelphia, Phoenix, Tucson, Washington D.C., and Wichita.
- <https://www.walgreens.com/topic/scheduler/hiv-prep.jsp>

PrEP Locator

PrEP Locator  Find Your Provider

[About Us](#) [About PrEP](#) [Locator Data](#) [FAQ](#) [Add Provider](#) [Add Locator To Your Site](#) [Contact](#)

PrEP access assistance

Vanderbilt Infectious Disease Clinic
1211 21st Avenue S
Medical Arts Building
Nashville, TN 37203
615-936-1174
Distance from your location: 0.3 miles

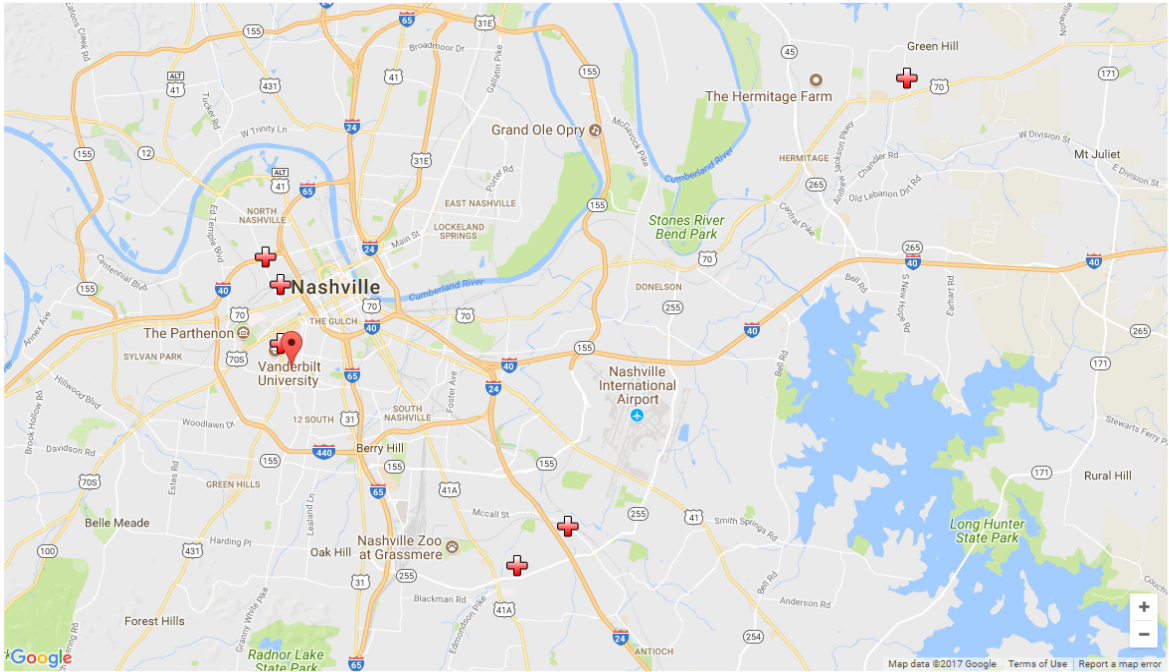
Planned Parenthood Nashville Health Center
412 Dr. D.B. Todd Jr. Blvd
Nashville, TN 37203
615-321-7216
Distance from your location: 1.4 miles

Meharry Community Wellness Center
1005 Dr. D.B. Todd Jr Blvd
Suite 333
Nashville, TN 37209
615-327-5788
Distance from your location: 2 miles

Middle Tennessee Internal Medicine Associates - Tracy Osbourne MD
510 Recovery Road
Suite 201
Nashville, TN 37212
615-833-7080
Distance from your location: 6 miles

Neighborhood Health @ MyHouse
42 Metroplex Drive
Building 4
Nashville, TN 37211

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[Suggest a provider for the directory](#)



Thank you!

Questions?