

PrEP 2.0

What's Next in
Biomedical
Prevention?



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University of North Carolina at Chapel Hill

School of Medicine

I have no conflicts of interest in relation to this presentation.

Dr. Hurt is supported by the National Institute of Mental Health (K23MH099941), Eunice Kennedy Shriver National Institute of Child Health & Human Development (U19HD089881), the National Institute on Drug Abuse (UG3DA044823), and the National Institute of Allergy and Infectious Diseases (P30AI50410).

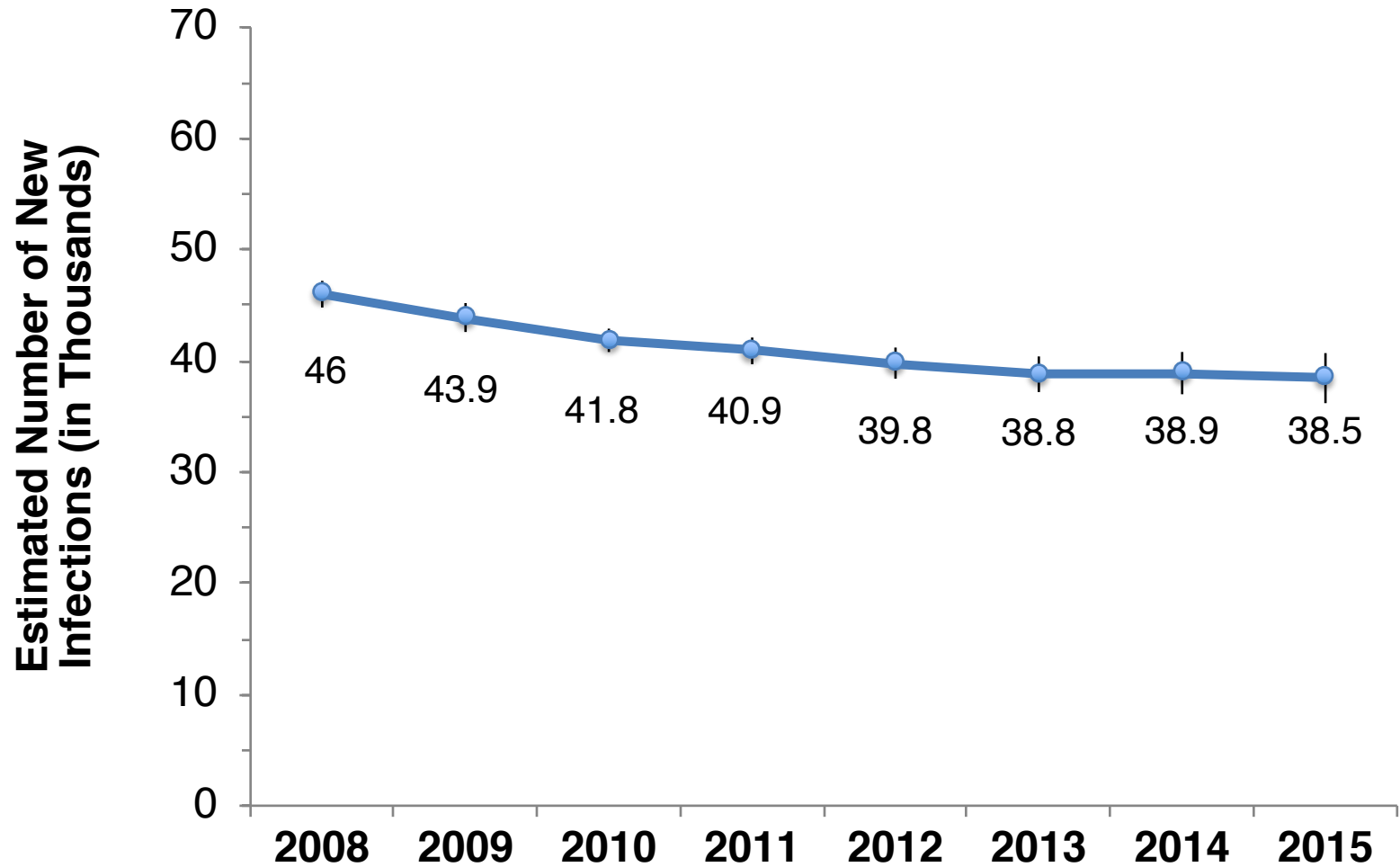
The views expressed are not necessarily those of the NIH.

Overview

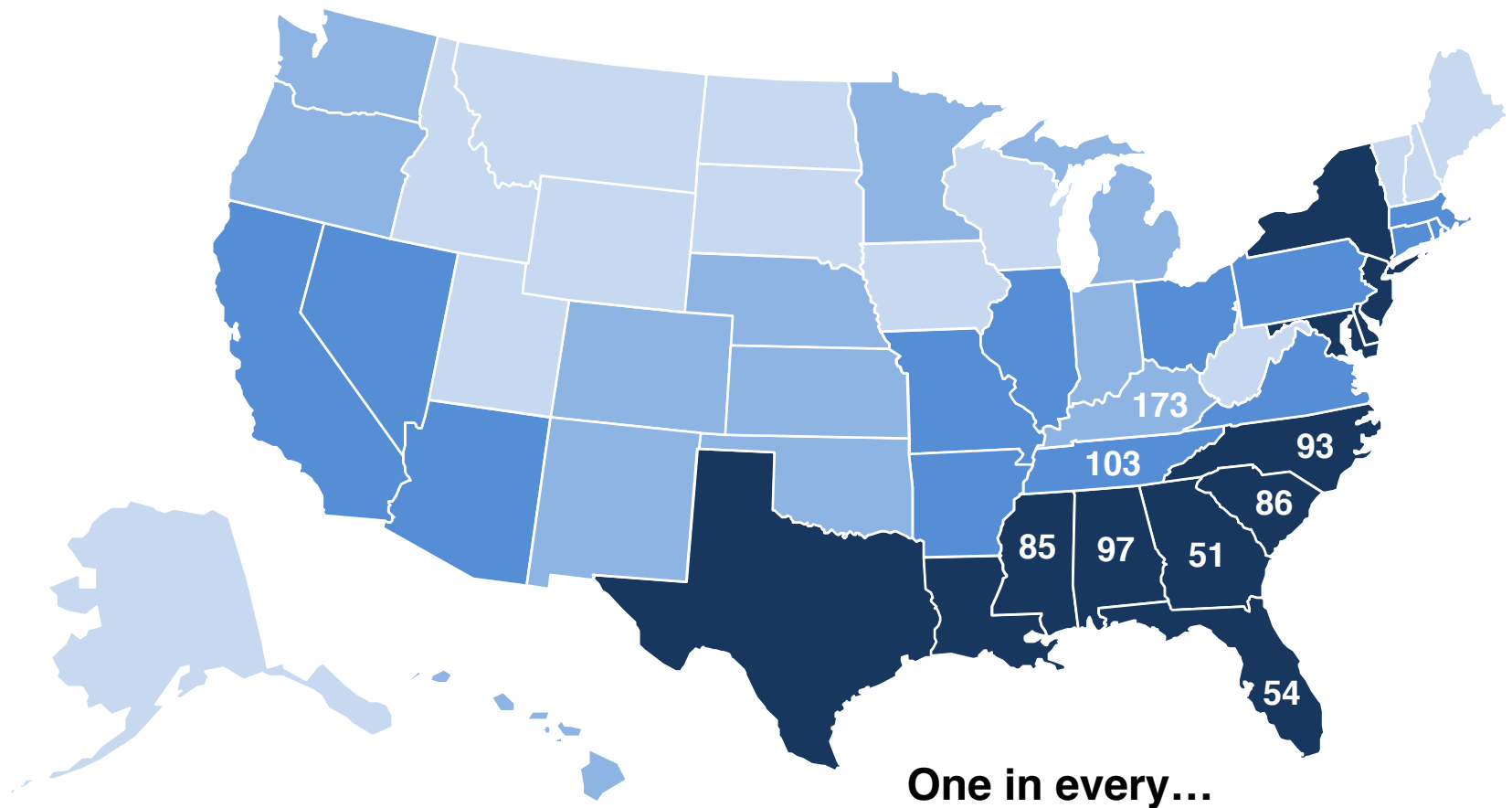
- Some HIV epidemiology for context
- Impact of existing options: U=U vs. PrEP
- Learning from contraceptives...
- What's in the pipeline?
- Challenges for the future
- Questions from you

HIV incidence in United States, 2008-2015

By CD4 model (new in 2017)



Lifetime risk of acquiring HIV



Highest – Lowest

... will acquire HIV
in her/his lifetime

Hess K et al. CROI 2016, abstract #52

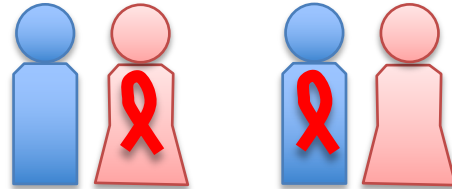
Map from CDC website: https://www.cdc.gov/nchhstp/newsroom/images/2016/CROI_lifetime_risk_state.jpg

If a patient is “undetectable,” s/he cannot transmit HIV to others

U=U undetectable=untransmittable

HPTN 052

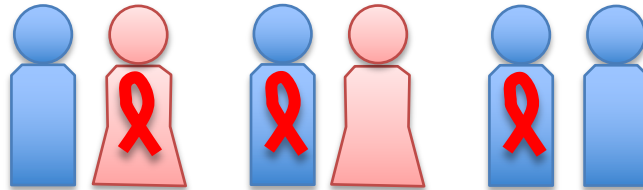
Africa (954)
Americas (278)
India (425)
Thailand (106)



93%
reduction
8509-10031 PY f/u
HR 0.07; 95%CI: 0.02, 0.22

PARTNER-1

Europe (888)



100%
reduction
1238 couple-years f/u
Upper CI bound: 0.3/100 couple-years

Opposites Attract

Australia (153)
Thailand (97)
Brazil (93)



100%
reduction
588.4 couple-years f/u
Upper CI bound: 1.59/100 couple-years

CDC is on board with “U=U”

Undetectable = untransmittable (launched July 2016)

“[P]eople who take ART daily... and maintain an undetectable viral load have **effectively no risk of sexually transmitting the virus** to an HIV-negative partner.”

 Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™



MENU

CDC A-Z



SEARCH

HIV/AIDS

HIV/AIDS > Resource Library > Dear Colleague Letters

Dear Colleague: September 27, 2017



Dear Colleague

INFORMATION FROM CDC'S DIVISION OF HIV/AIDS

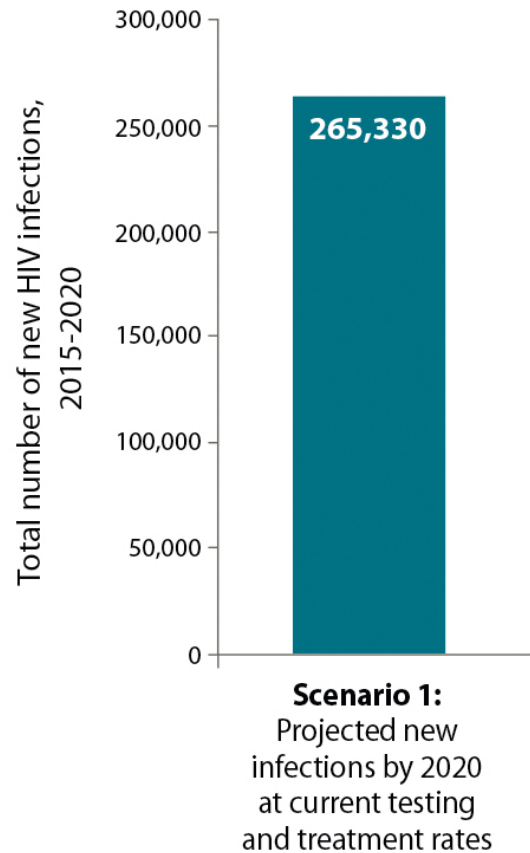
Dear Colleague,

Today is [National Gay Men's HIV/AIDS Awareness Day](#). On this day, we join together in taking actions to prevent HIV among gay and bisexual men and ensure that all gay and bisexual men living with HIV get the care they need to stay healthy. Gay and bisexual men are severely affected by HIV. More than 26,000 gay and bisexual men received an HIV diagnosis in 2015, representing two-thirds of all new diagnoses in the United States, and diagnoses increased among Hispanic/Latino gay and bisexual men from 2010 to 2014.

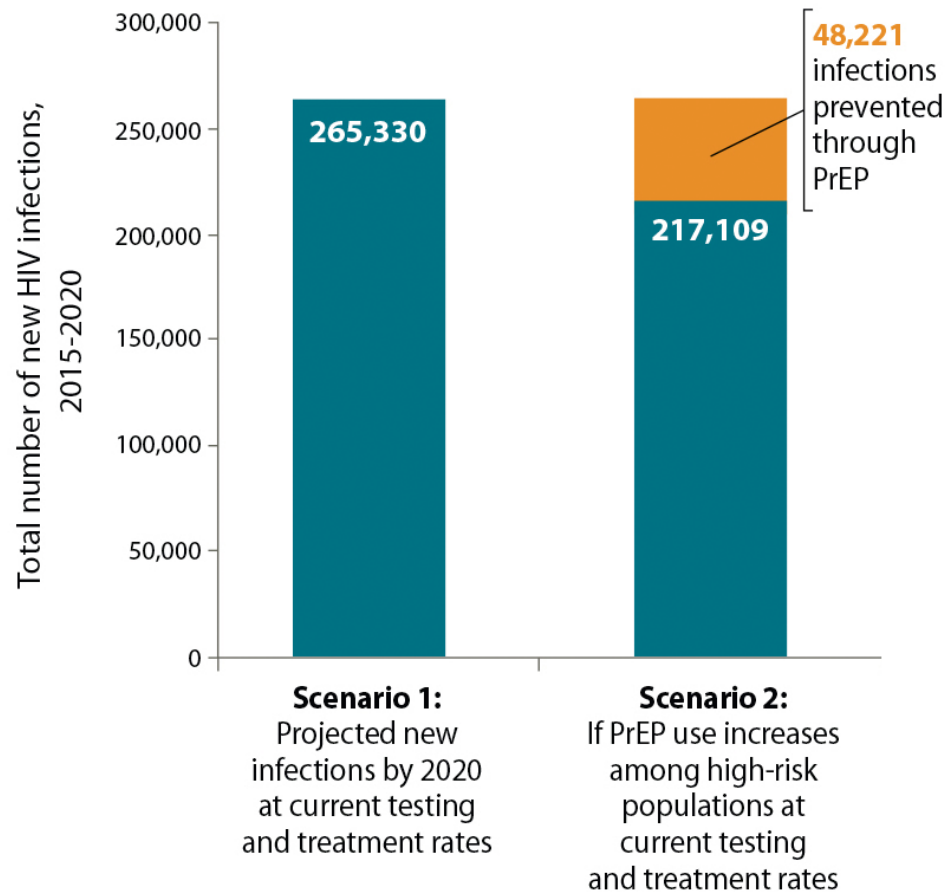
However, recent trends suggest that prevention efforts are slowing the spread of HIV among some gay and bisexual men. From 2010 to 2014, HIV diagnoses fell among white gay and bisexual men and remained stable among African American gay and bisexual men after years of increases.

<https://www.cdc.gov/hiv/library/dcl/dcl/092717.html>

Potential impact of interventions, 2015-2020

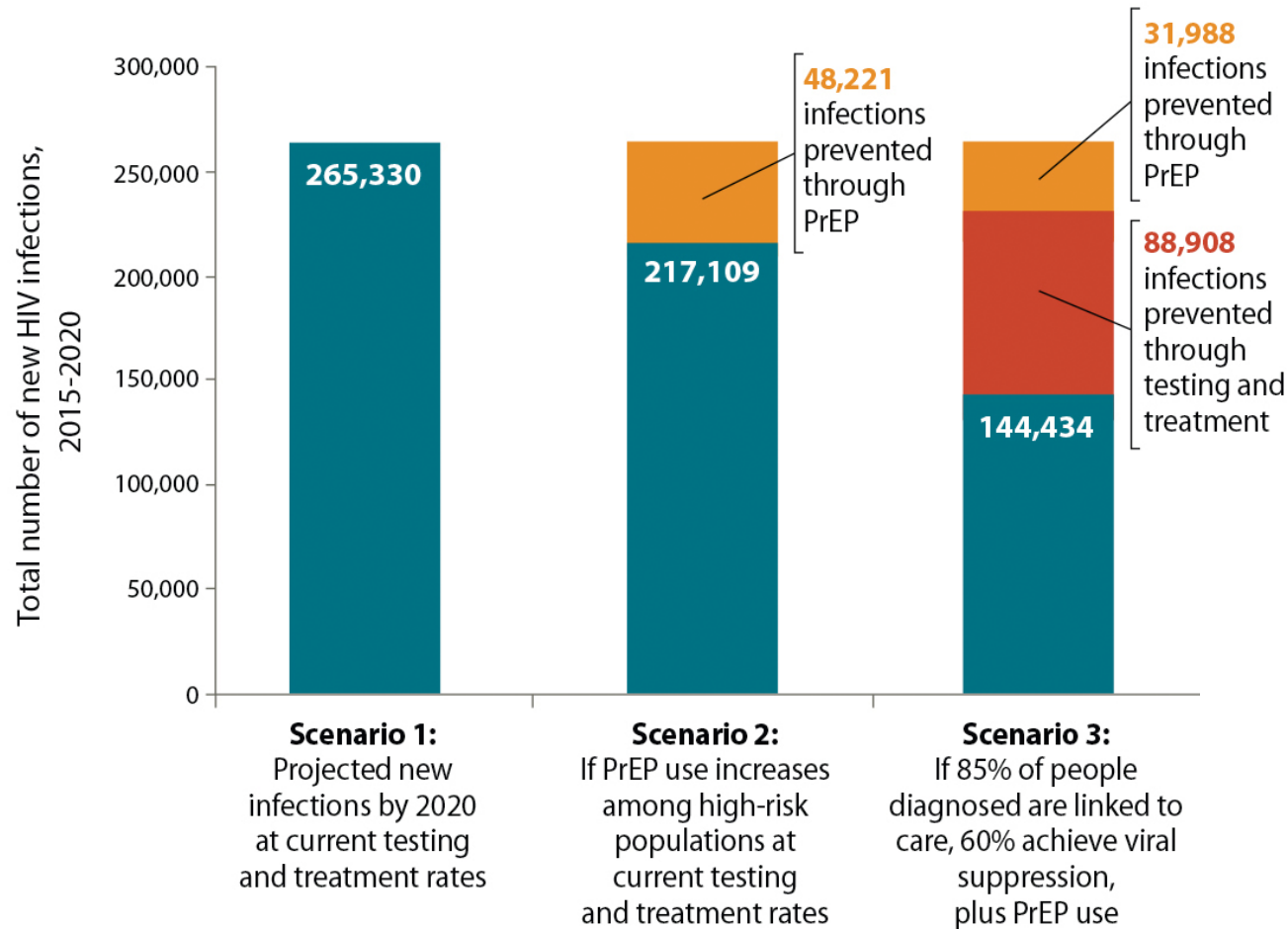


Potential impact of interventions, 2015-2020



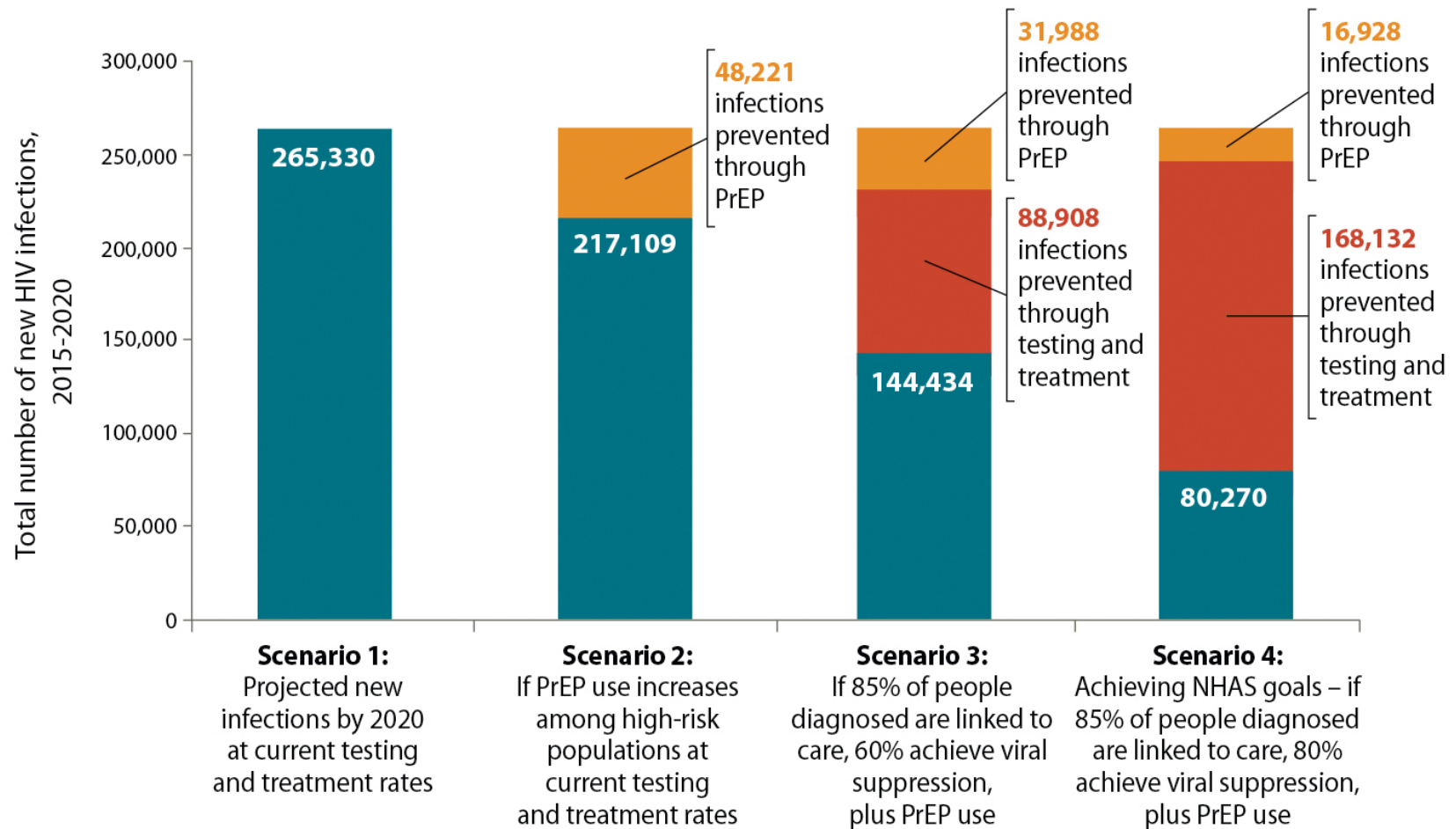
- New infections
- HIV infections prevented due to expanded testing and treatment
- HIV infections prevented due to PrEP (assumes PrEP use among high-risk populations = 40% MSM; 10% PWID; 10% HET)

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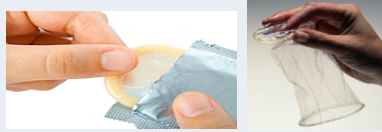


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Pregnancy Prevention

Education & behavior modification

Condoms



Rings



Birth control pill & injection



“Morning-after pill”



Spermicide



Implantable birth control



Vasectomy/Tubal Ligation

Pregnancy Prevention

HIV Prevention

Education & behavior modification

Education & behavior modification

Condoms



Condoms

Rings



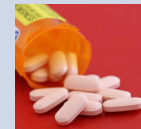
Rings

Birth control pill & injection



PrEP (oral & injectable)

“Morning-after pill”



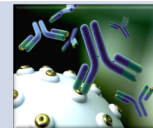
Post-exposure prophylaxis

Spermicide



Topical microbicides

Implantable birth control



Broadly neutralizing Abs
Implantables

Vasectomy/Tubal Ligation



Vaccination

Pregnancy Prevention

HIV Prevention

Education & behavior modification

Education & behavior modification

Condoms



Condoms

Rings



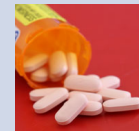
Rings

Birth control pill & injection



PrEP (oral & injectable)

“Morning-after pill”



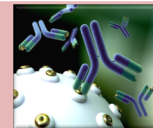
Post-exposure prophylaxis

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Topical microbicides

Implantable birth control



Broadly neutralizing Abs
Implantables

Vasectomy/Tubal Ligation



Vaccination



Oral PrEP

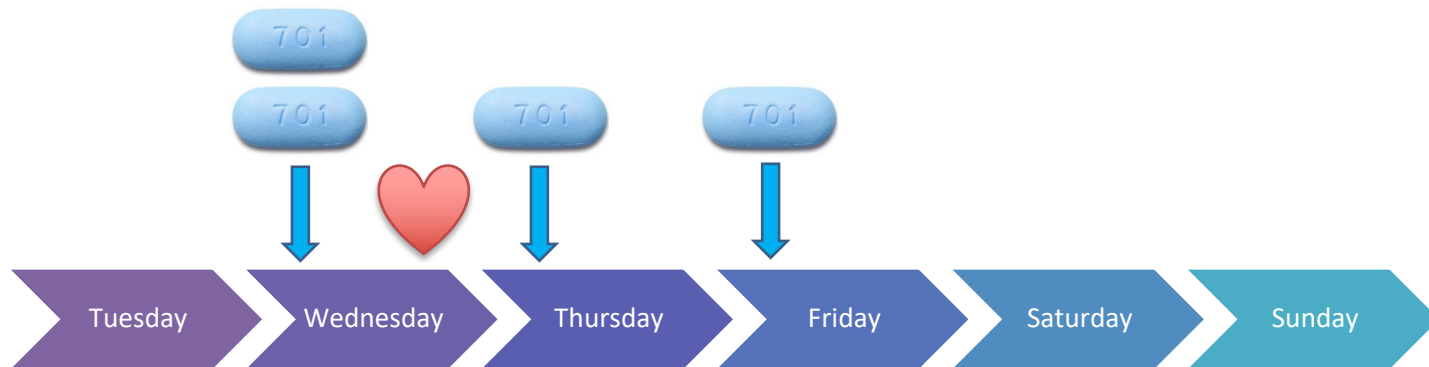
IPIRGAY

On-Demand Oral PrEP



Study design

- 2 tablets 2-24 hours before sex
- 1 tablet 24 hours later
- 1 tablet 48 hours after first intake



Molina JM, et al. *NEJM*. 2015;373(23):2237-46

Molina JM, et al. AIDS 2016, Durban, South Africa. Abstract WEAC0102

IPIERGAY

Montréal & multiple sites in France



Study Phase	N	Total F/U (PY)	Median Pills/ Month	HIV Incidence / 100 PY		Risk Reduced (%)	P
				TDF/FTC	Placebo		
Placebo controlled, randomized ^[1]	400	431.3	15	0.91	6.60	86	.002
Open-label extension ^[2]	361	518	18	0.19	6.60	97	NR
Substudy (patients with less frequent sex) ^[3]	269	134	9.5	0	9.3	100	NR

Adapted from slide by clinicaloptions.com

1. Molina JM, et al. N Engl J Med. 2015;373:2237-2246.
2. Molina JM, et al. Lancet HIV. 2017;4:e402-e410.
3. Antoni G, et al. IAS 2017. Abstract TUAC0102.

ANRS Prevenir

Multicenter, open-label cohort study in Paris



May 2017 – July 2018 (interim)

1594

Higher-risk
MSM
(target N = 3000)

45%

Daily
FTC/TDF
(1088 acts)

55%

On-Demand
FTC/TDF
(1192 acts)

0

new HIV infections in
either arm
(95% CI: 0, 0.7-0.8)

On-demand NOT approved in the US

US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2017 UPDATE

A CLINICAL PRACTICE GUIDELINE



**Do not use other than
daily dosing (e.g.,
intermittent, episodic
[pre/post sex only], or
other discontinuous
dosing)**

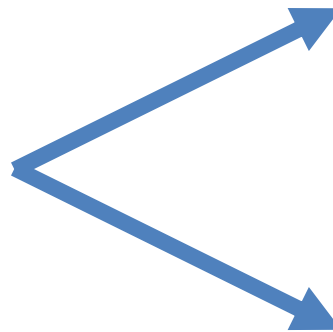
DISCOVER

RCT of FTC/TAF vs FTC/TDF

Sept 2016 – Sept 2020 (May 2019)



Adult MSM/TGW at high
risk for HIV infection
(N = 5400)



FTC/TDF
with placebo FTC/TAF



FTC/TAF
with placebo FTC/TDF

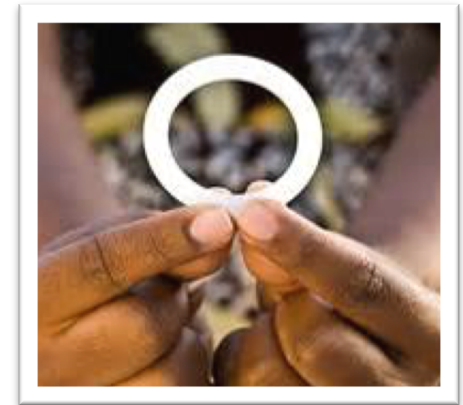
92 sites across US, Canada, Europe

96 weeks of f/u planned w/48 wk FTC/TAF open-label extension

Dapivirine vaginal ring

ASPIRE / MTN-020 & IPM 027 / Ring

Drug-eluting ring vs placebo in Sub-Saharan Africa



HIV Protection Efficacy vs Placebo, %	ASPIRE/MTN-020 ^[1] (N = 2629)	IPM 027/Ring ^[2] (N = 1959)
Overall	27 (95% CI: 1-46; <i>P</i> = .05)	30.7 (95% CI: 0.90-51.5; <i>P</i> = .04)
Age > 21 yrs	56 (95% CI: 31-71; <i>P</i> < .001)	37.5 (95% CI: 3.49-59.5)

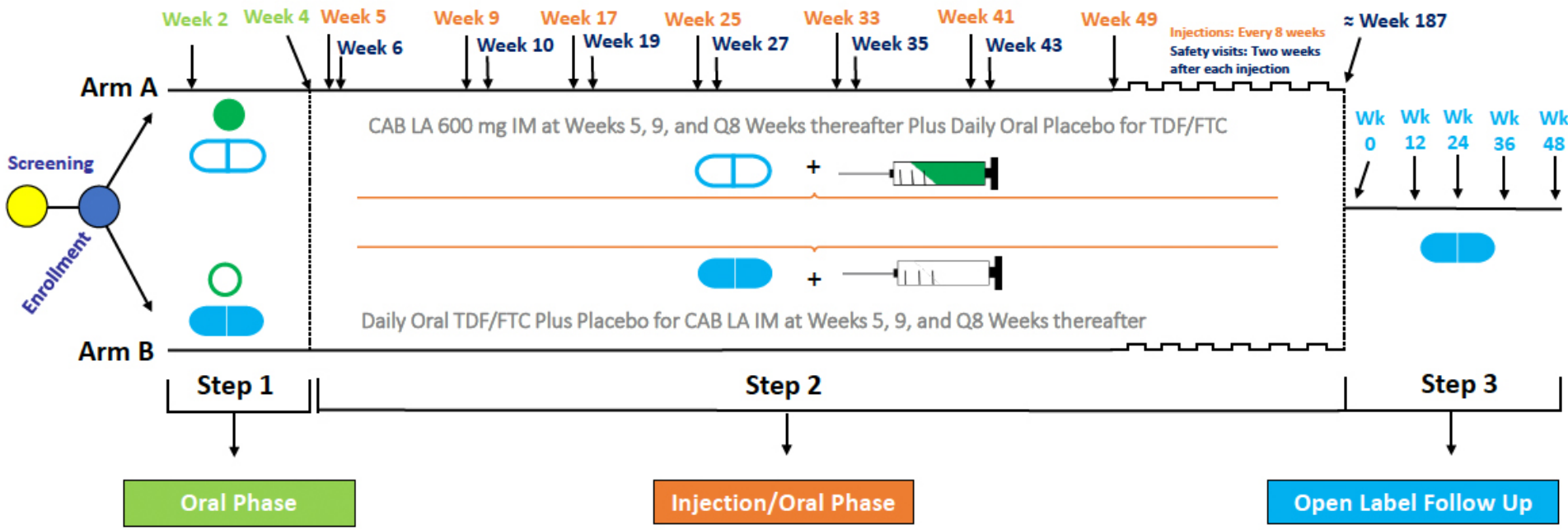
HOPE (ASPIRE) and DREAM (IPM 027/Ring) programs have open-label extension studies

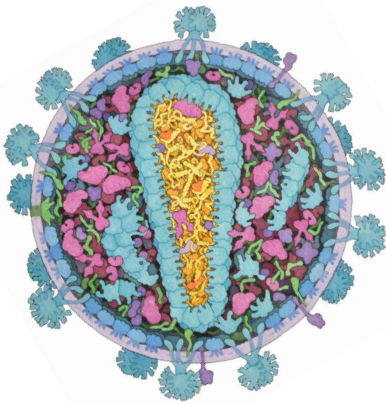
HPTN 083 & 084

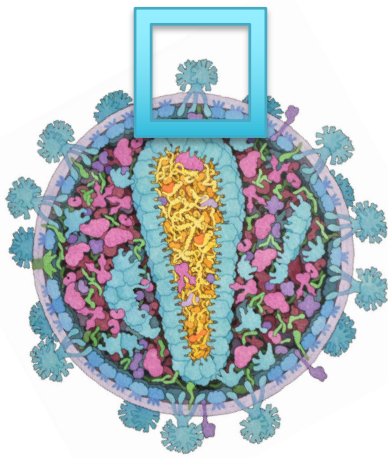
Oral FTC/TDF vs Injectable Cabotegravir-LA
MSM & TGW (083) and Cisgender Women (084)

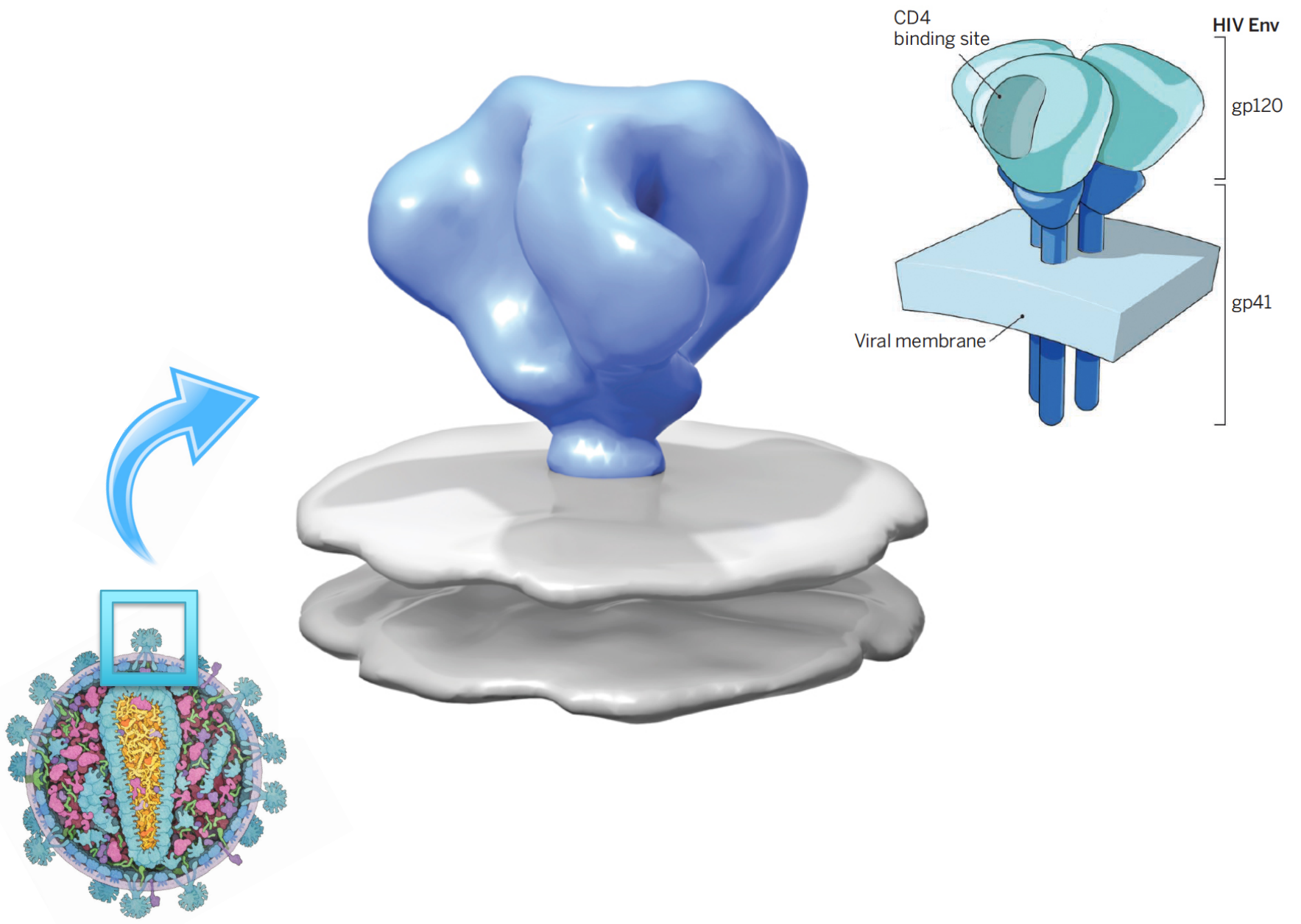


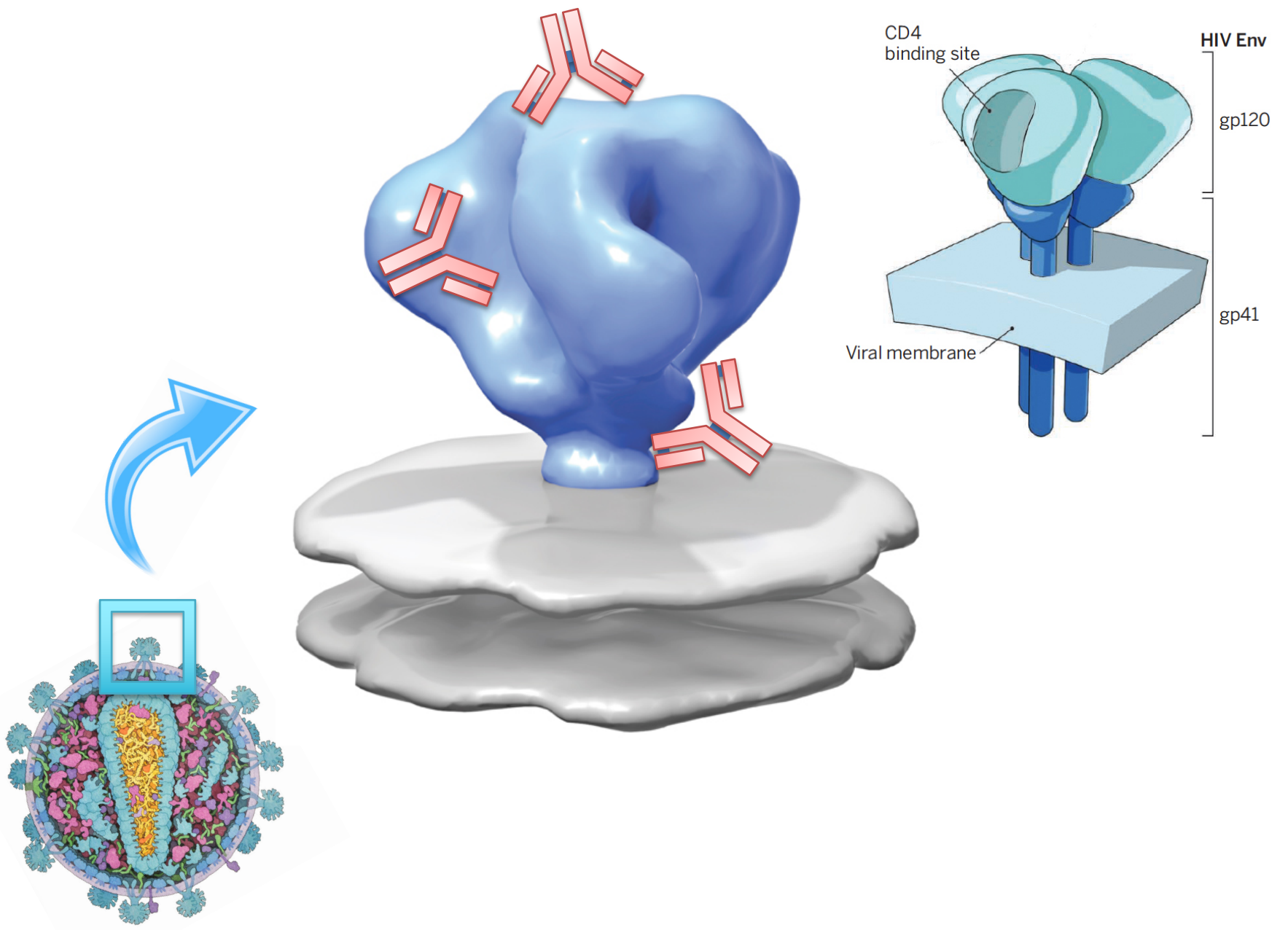
Blinded Injections & Safety Visits

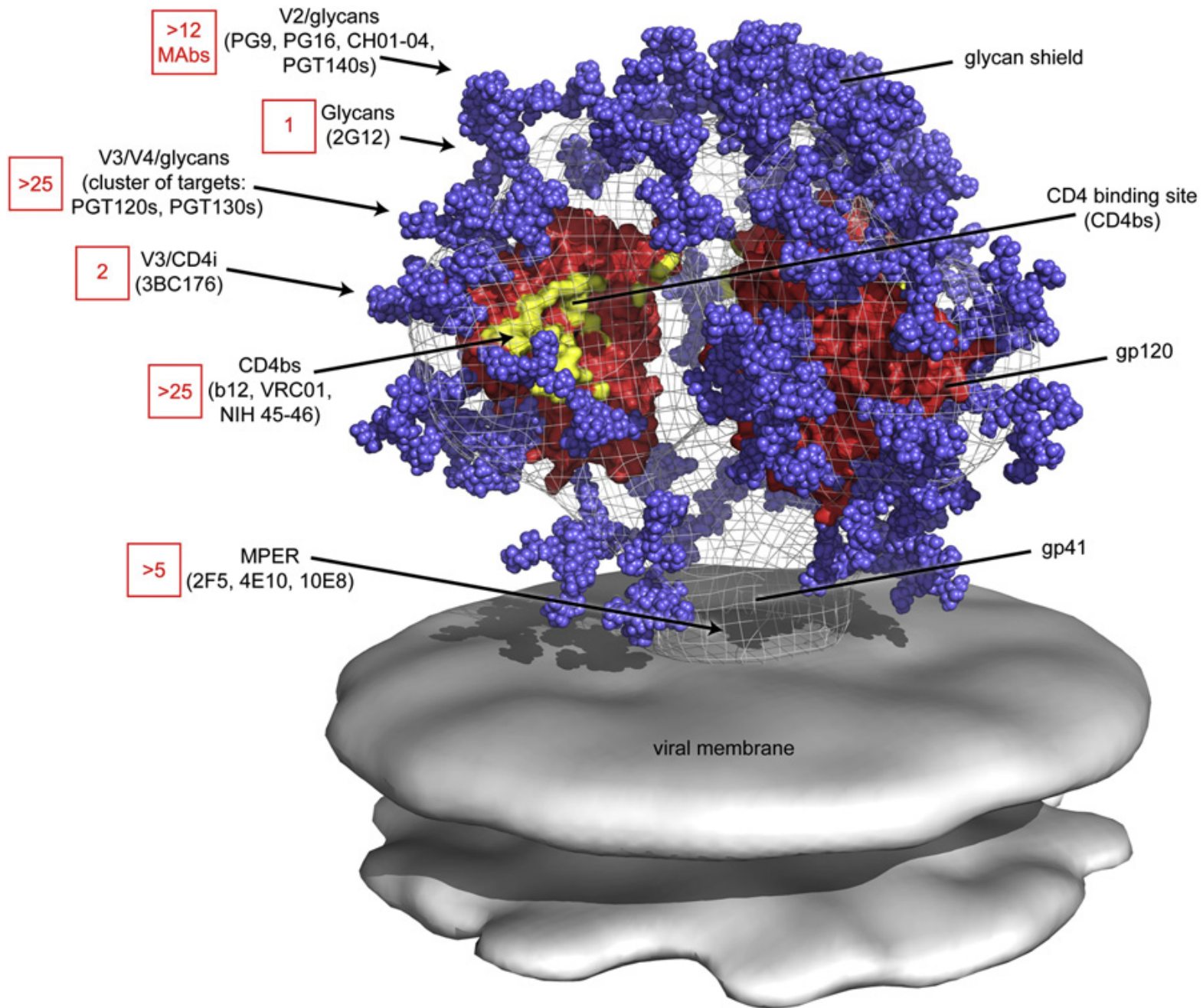




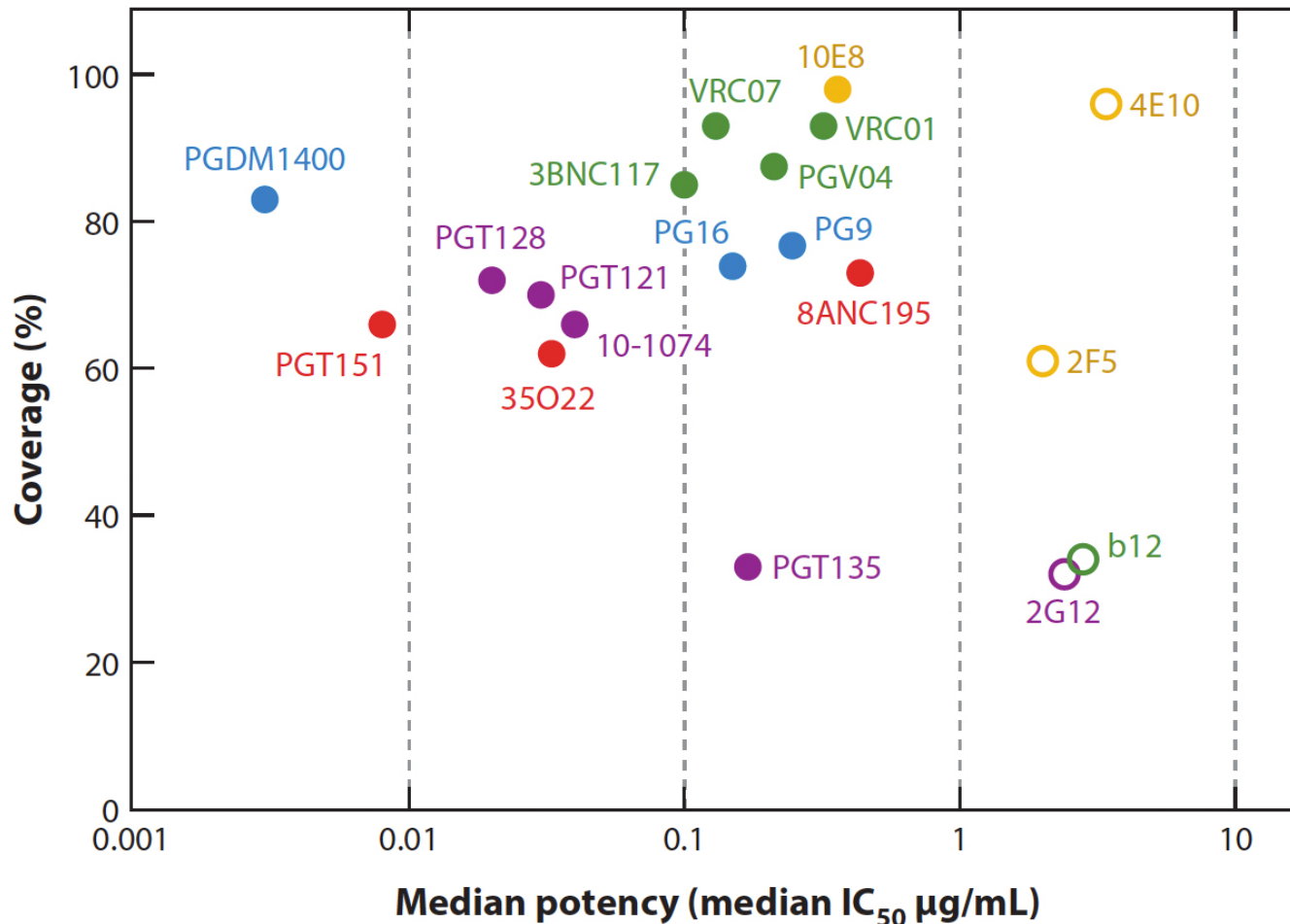








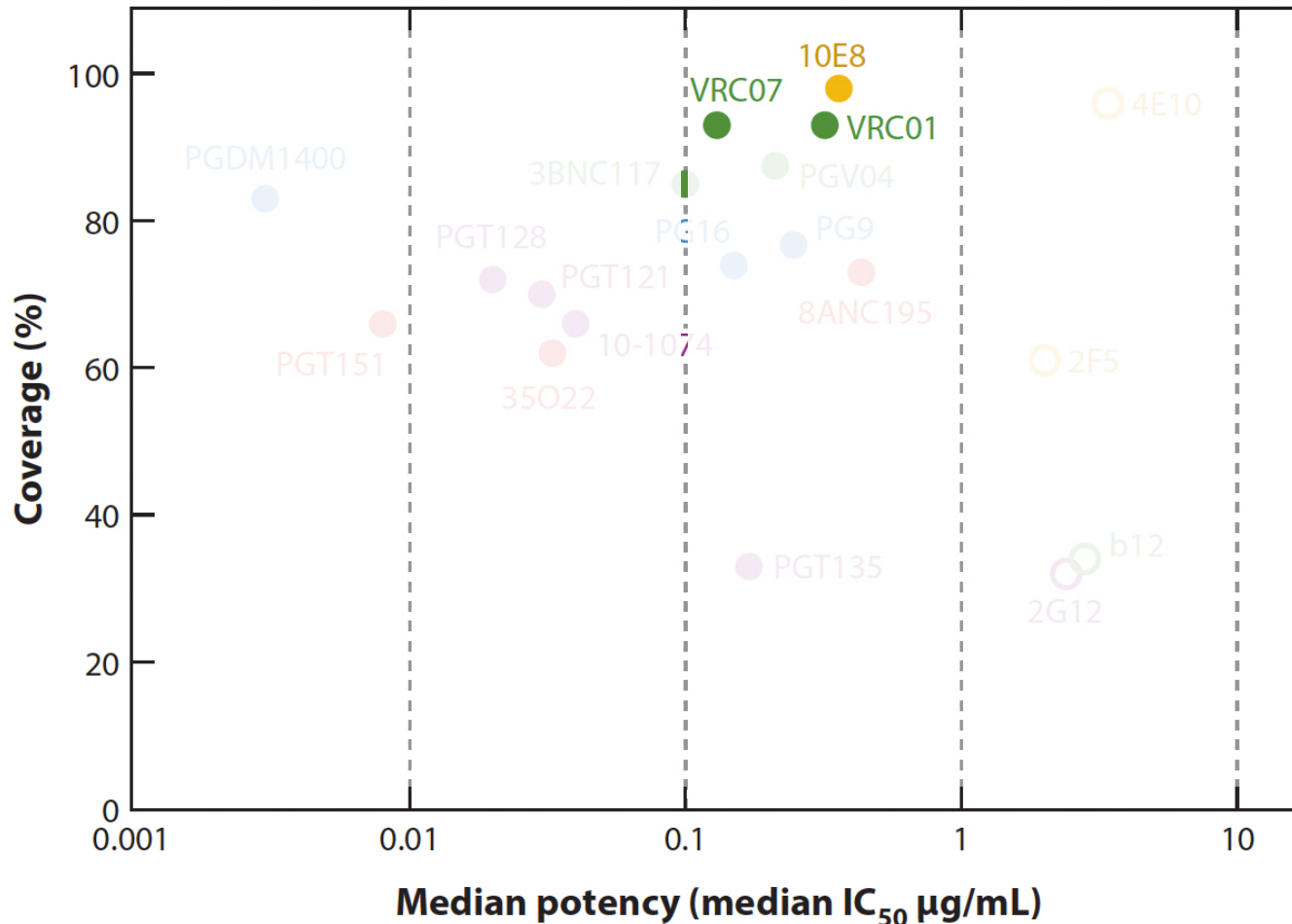
Breadth & potency of bnAbs are important



Open circle: 1st generation mAb
Filled circle: 2nd generation mAb

CD4 binding site
Apex-specific
Membrane proximal external region (MPER)
High-mannose patch
gp120-gp140 interface

Breadth & potency of bnAbs are important



Open circle: 1st generation mAb
Filled circle: 2nd generation mAb

CD4 binding site **High-mannose patch**
Apex-specific **gp120-gp140 interface**
Membrane proximal external region (MPER)

HPTN 081 & 085

VRC01 for Cis-Women (081) and MSM & TGW (085)

Co-sponsored with HVTN (703 & 704)



- IV infusion of VRC01 every 8 weeks for 10 visits
- Blood work monthly (including HIV testing)
- STI testing and behavioral assessments every 4-8 weeks
- Total study involvement 22 months



HIV VACCINE
TRIALS NETWORK



HVTN/HPTN is investing in bnAbs

HVTN 127 / HPTN 087

Phase I study – currently enrolling

VRC07-523LS (CD4bs)

Intravenous, intramuscular, and subcutaneous

HVTN 131 / HPTN 090

Phase I study – opening early 2019

VRC07-523LS (CD4bs) plus 10E8VLS (MPER)

Subcutaneous and intravenous

Efficacy Trial

2018

2019

2020

2021

 Vaginal Ring
Dapivirine Ring

HOPE (MTN 025)

Open-label trial of the once-monthly slow-release dapivirine vaginal ring; ongoing in 2,500 women in Malawi, South Africa, Uganda, Zimbabwe

DREAM (IPM 032)

Open-label trial of the once-monthly slow-release dapivirine vaginal ring; ongoing in 1,400 women in South Africa and Uganda

 Antibody
VRC01

AMP (HVTN 704/
HPTN 085)

Randomized controlled trial of the VRC01 antibody infused every two months; ongoing in 2,700 MSM and transgender men & women in Brazil, Peru, Switzerland, US

AMP (HVTN 703/
HPTN 081)

Randomized controlled trial of the VRC01 antibody infused every two months; ongoing in 1,900 women in Botswana, Kenya, Malawi, Mozambique, Tanzania, South Africa, Zimbabwe

 Oral PrEP
F/TAF
(Descovy)

DISCOVER

Randomized controlled trial of once-daily F/TAF as PrEP; ongoing in 5,400 MSM and transgender women in Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, UK, US

End September 2020

 Long-Acting
Injectable
Cabotegravir


HPTN 083


Randomized controlled trial of injectable cabotegravir every two months; ongoing in 4,500 MSM and transgender women in Argentina, Brazil, Peru, South Africa, Thailand, US, Vietnam

HPTN 084

Randomized controlled trial of injectable cabotegravir every two months; ongoing in 3,200 women in Botswana, Kenya, Malawi, South Africa, Uganda, Zimbabwe

 Open-label

 Randomized Controlled

 Open-label and Randomized

 Ongoing

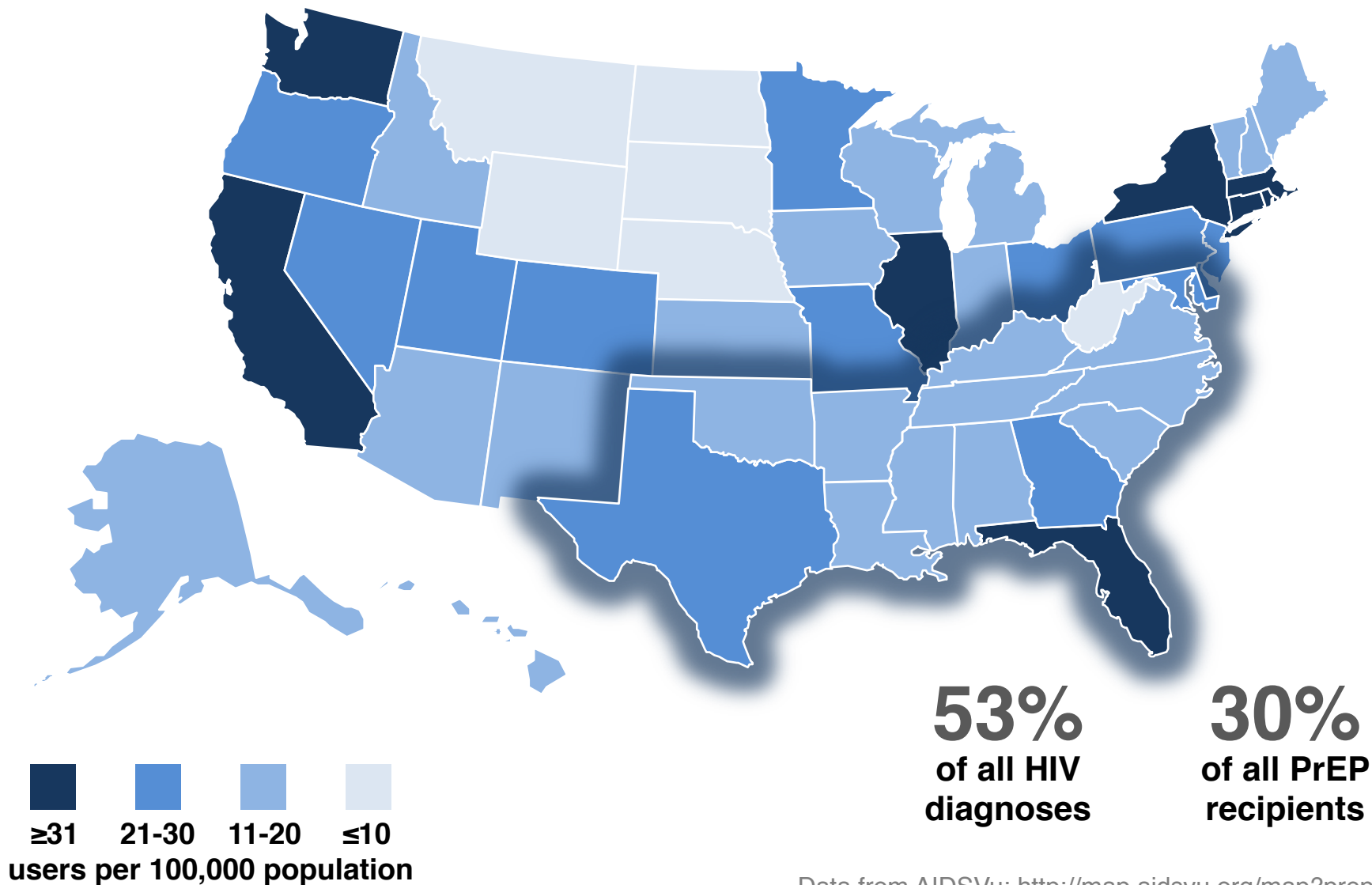
AVAC

Global Advocacy for HIV Prevention



Challenges for the future

PrEP users per 100,000 population, 2016



Data from AIDSvu: <http://map.aidsvu.org/map?prep=1>
<https://www.cdc.gov/hiv/statistics/overview/geographicdistribution.html>

Addressing disparities in access & uptake



“The Louisville Flood” by Margaret Bourke-White, 1937
<https://rarehistoricalphotos.com/there-no-way-like-american-way-1937/>

Optimizing delivery methods

- Infrequent administrations
- Self-administration?
- Minimizing injection-site reactions
- Manageable volume of product(s)



FTC/TDF is approved for adolescents



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 021752/S-055

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Kim Lindstrom, PhD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lindstrom:

Please refer to your Supplemental New Drug Application (sNDA) dated November 15, 2017, and received November 16, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets, 200/300 mg, 167/250 mg, 133/200 mg, and 100/150 mg.

We acknowledge receipt of your Risk Evaluation and Mitigation Strategy (REMS) assessment, received on November 16, 2017, and your amendments.

This efficacy supplement provides the following revisions to the labeling for Truvada® and proposes a Major Modification to the approved REMS:

- Expansion of the Pre-Exposure Prophylaxis (PrEP) indication to include adolescents weighing at least 35 kg who are at risk of HIV-1 acquisition.
- Updates to Section 8 of the U.S. Prescribing Information (PI) to align with the Pregnancy and Lactation Labeling Rule (PLLR).
- Revised REMS materials to reflect expansion of the patient population based on the proposed revision to the PrEP indication. The proposed REMS Major Modification includes the Single Shared System (SSS) REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We have previously granted a waiver of the requirements of 21 CFR [redacted] regarding [redacted] information.

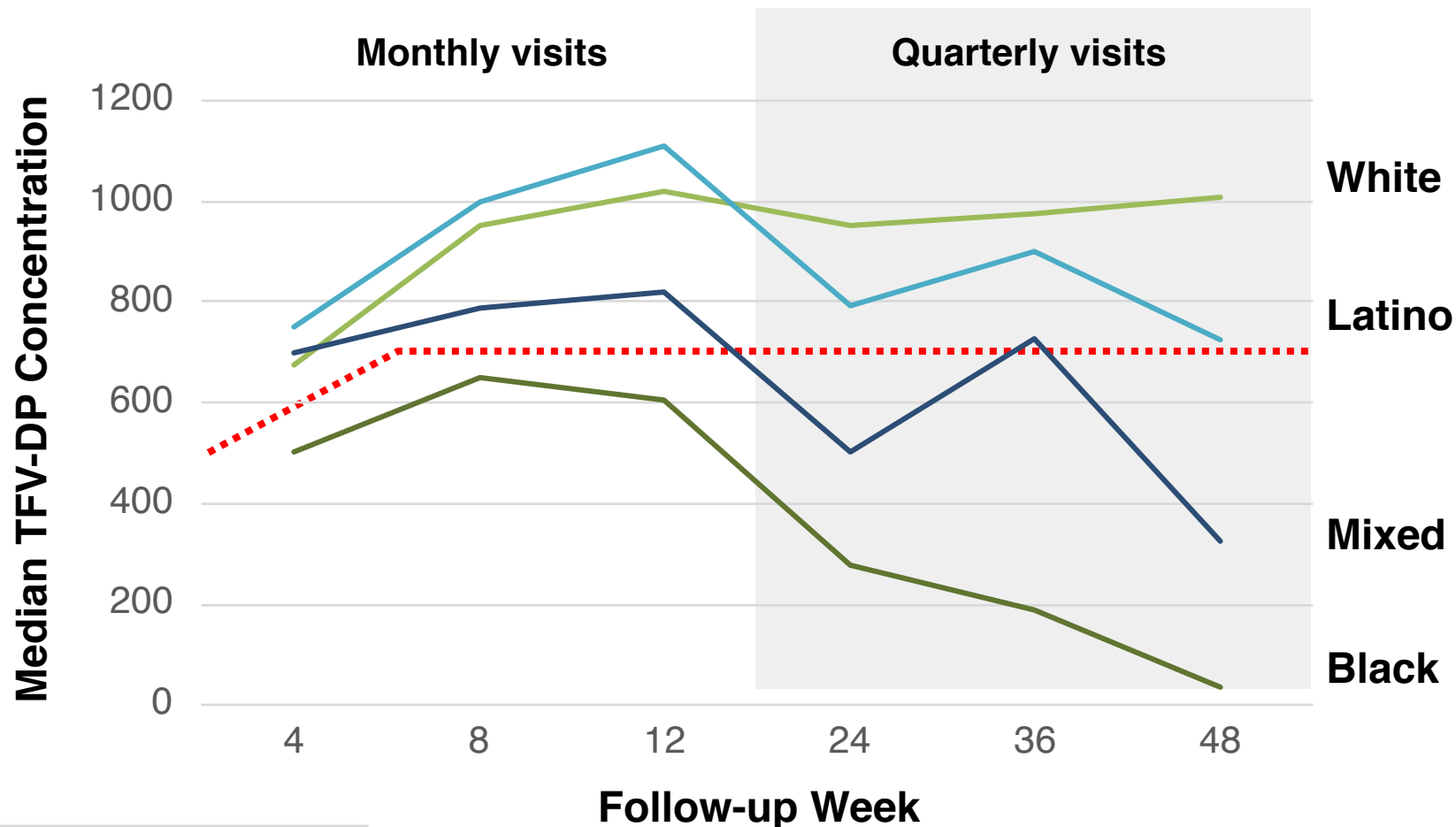
Indicated... in combination with safer sex practices ... to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg.

15 May 2018

Adherence in young adults is a challenge

Project PrEPare 2 (ATN 110), Oct 2012 - Feb 2015

18-22
years old

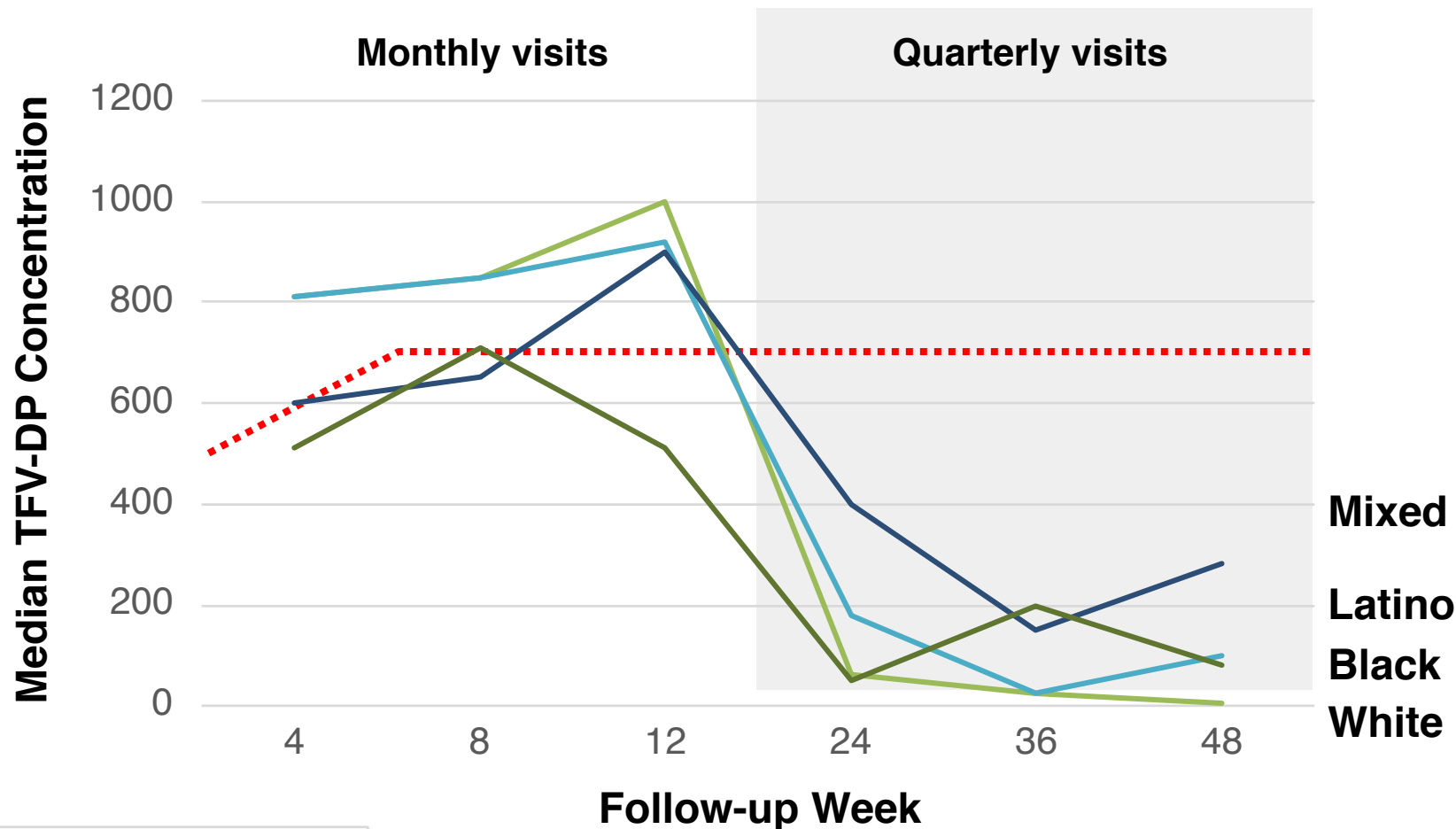


..... ≥ 4 doses per week

Adherence in teens is a bigger challenge

Project PrEPare 3 (ATN 113), Aug 2013 – Mar 2016

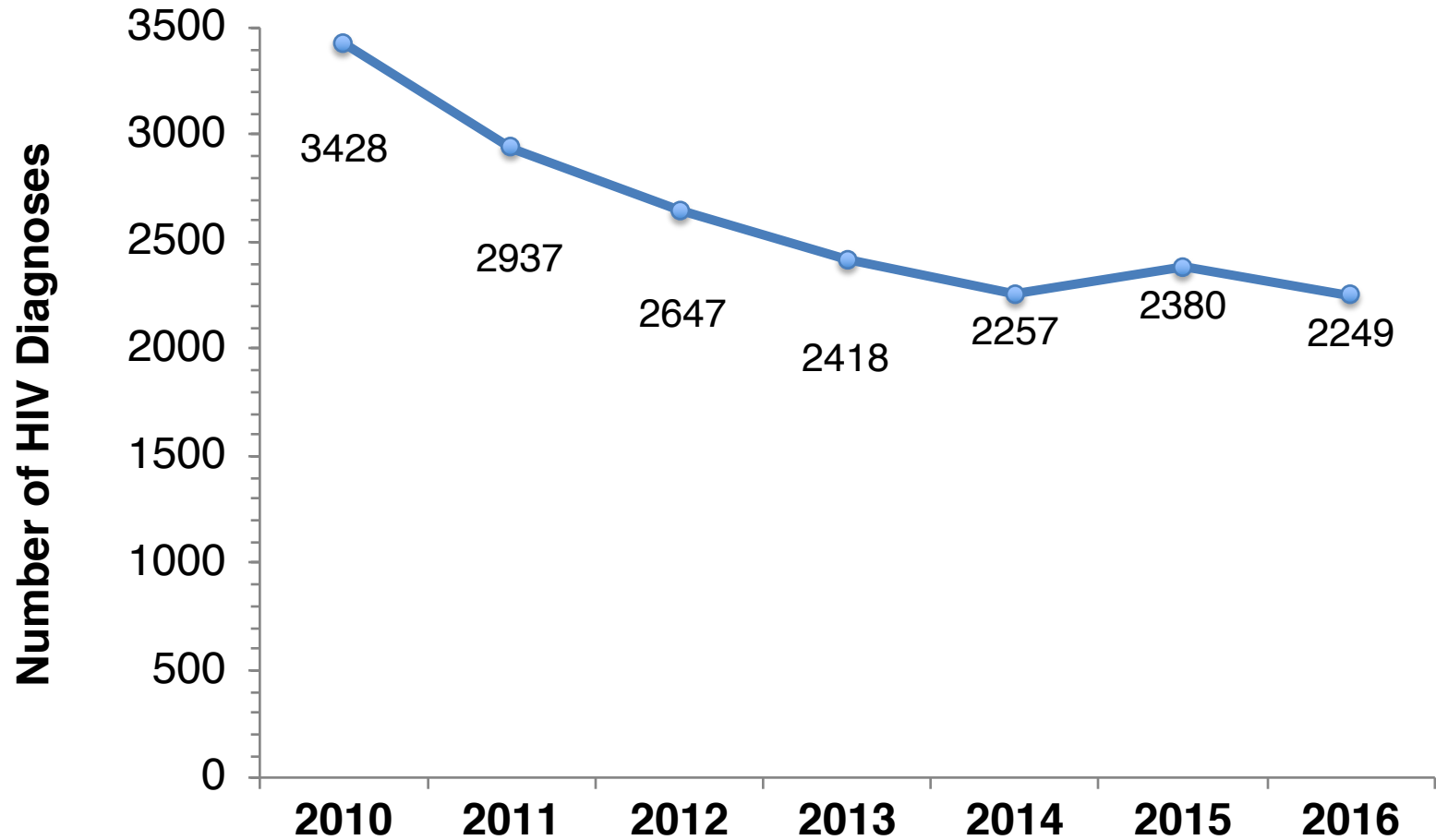
15-17
years old



..... ≥ 4 doses per week

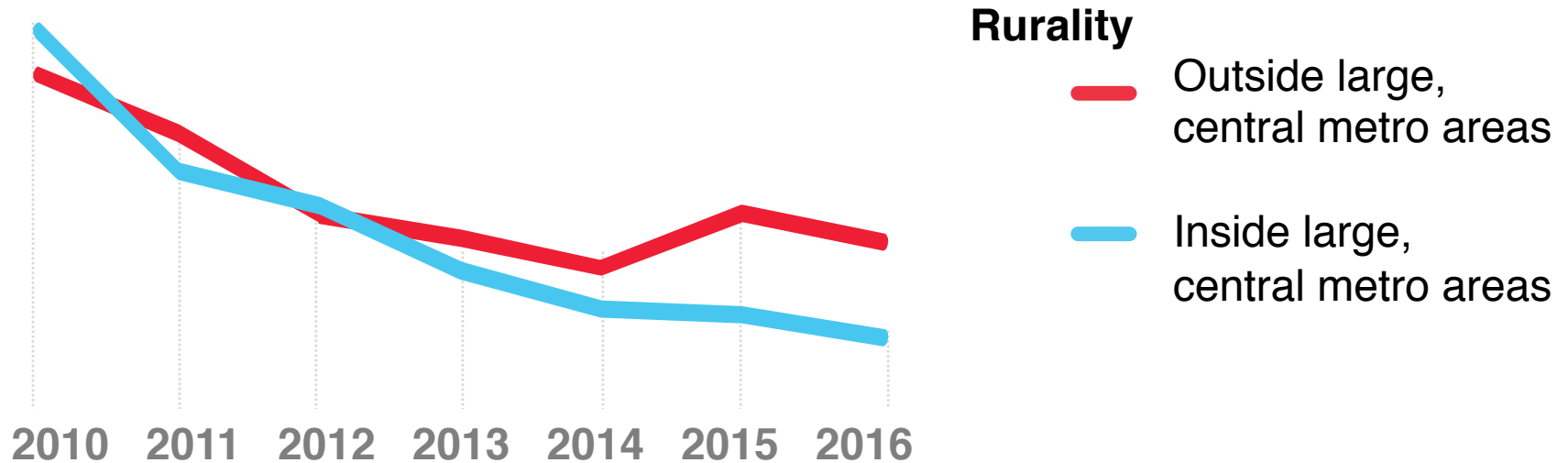
Epi trends among PWID are worrisome

HIV diagnoses, persons who inject drugs, 2010-2016



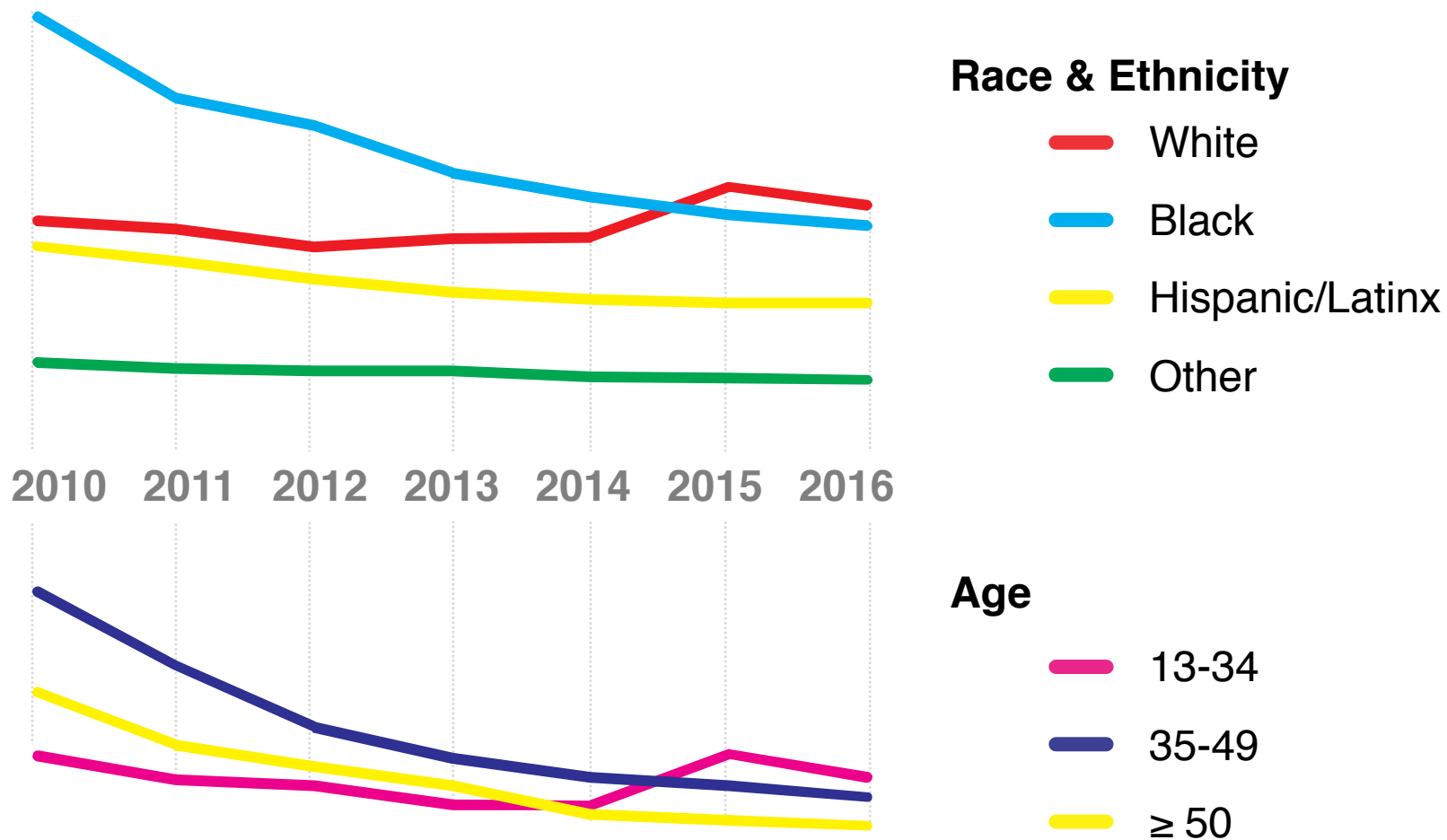
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Questions?

Please email me!

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