Implementation of evidence-based interventions in HIV prevention and care: from Malawi to North Carolina

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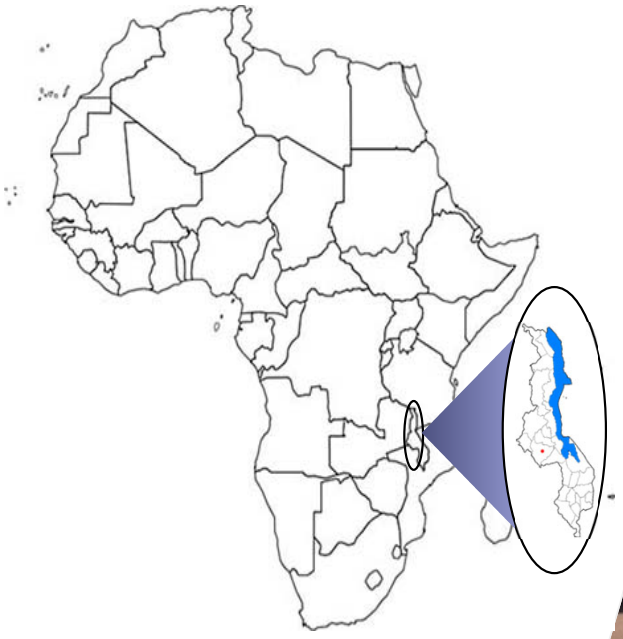
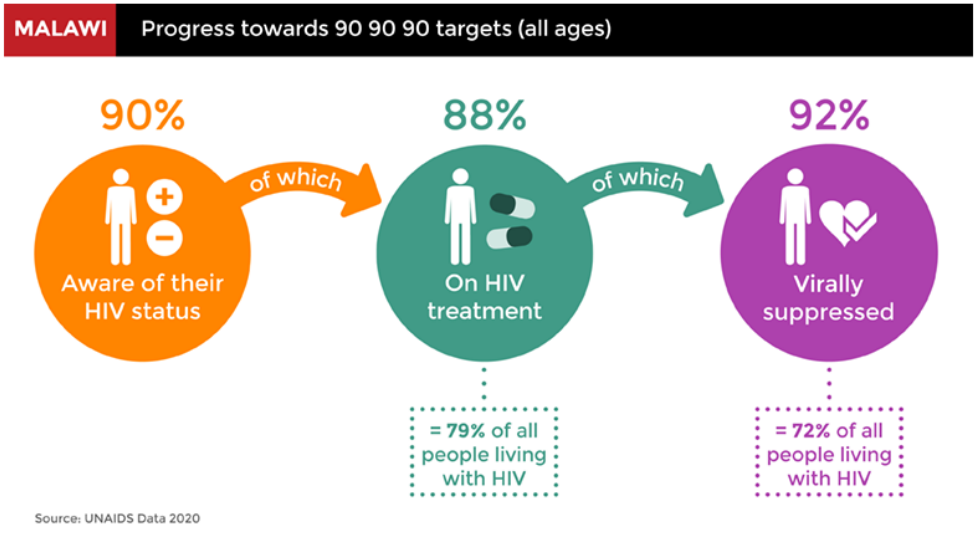
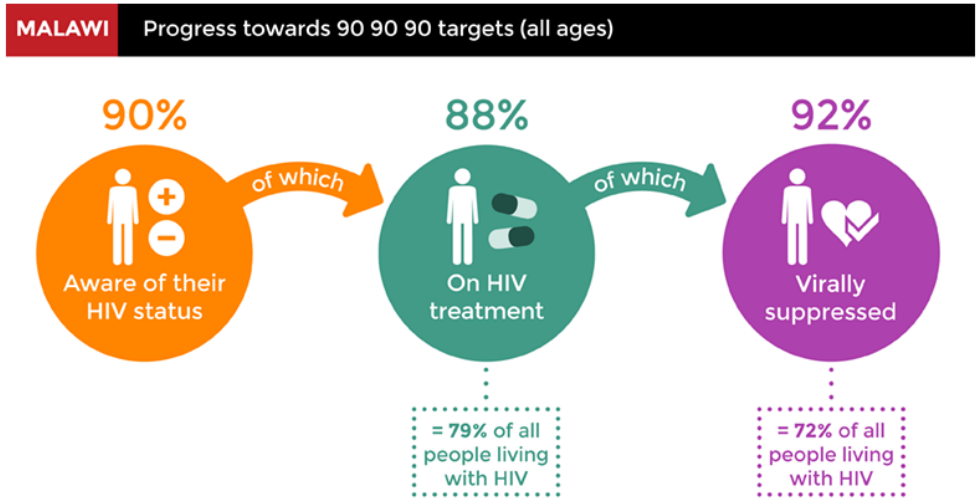
UNC
PROJECT
Lilongwe, Malawi

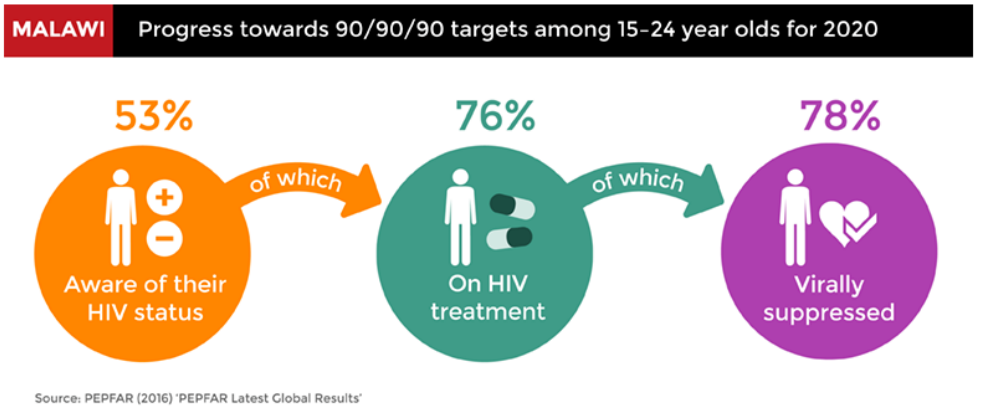


Malawi's HIV epidemic



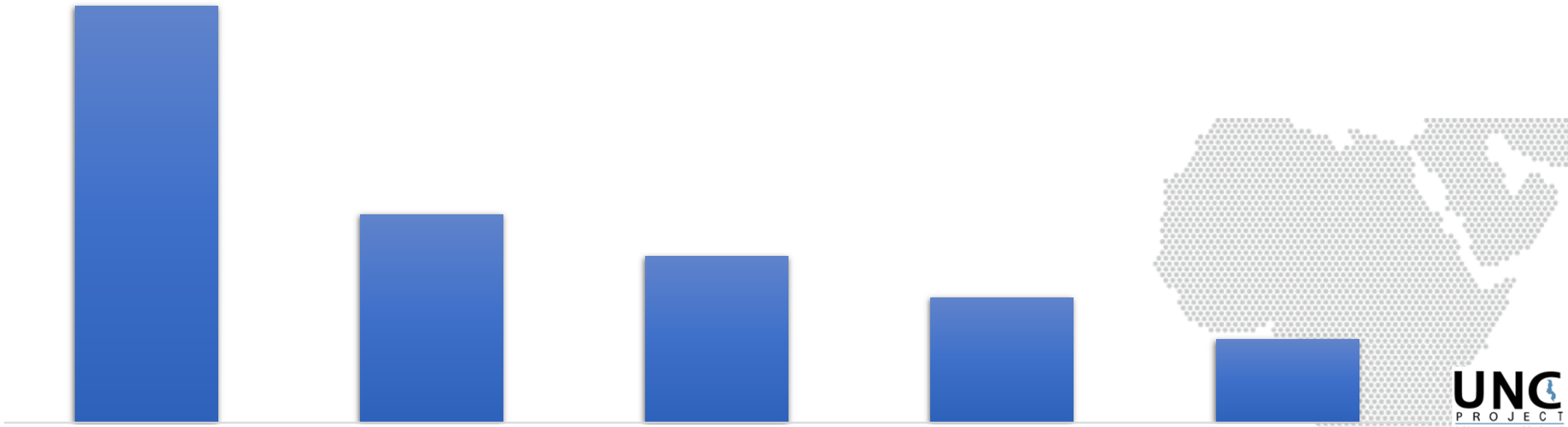
Malawi's HIV epidemic



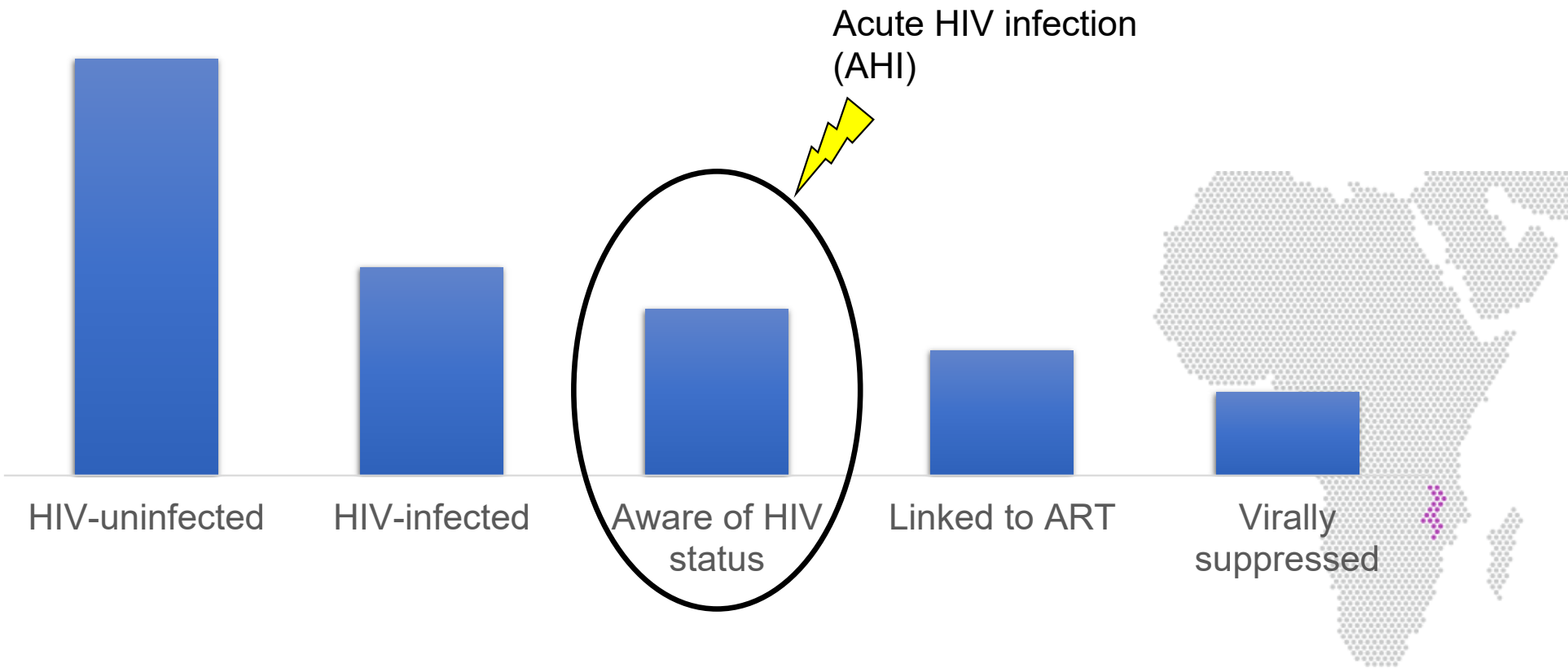


Source: PEPFAR (2016) 'PEPFAR Latest Global Results'

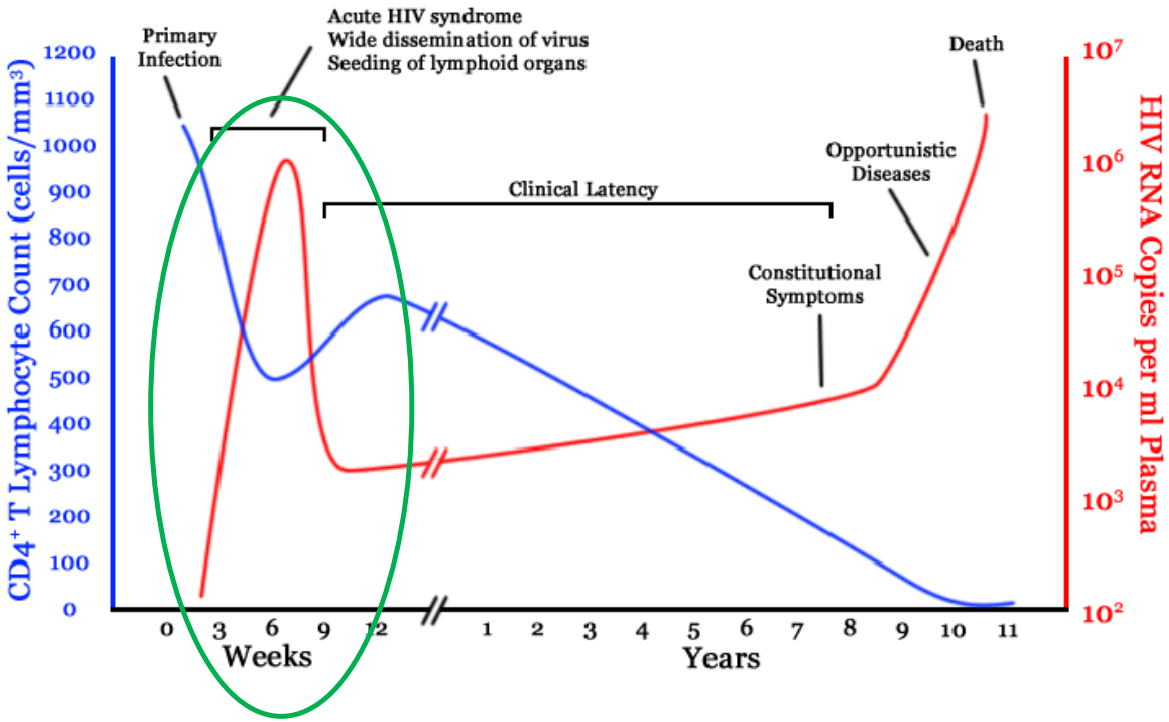
The HIV cascade – a roadmap



Increasing HIV status awareness: AHI



Acute HIV infection (AHI)

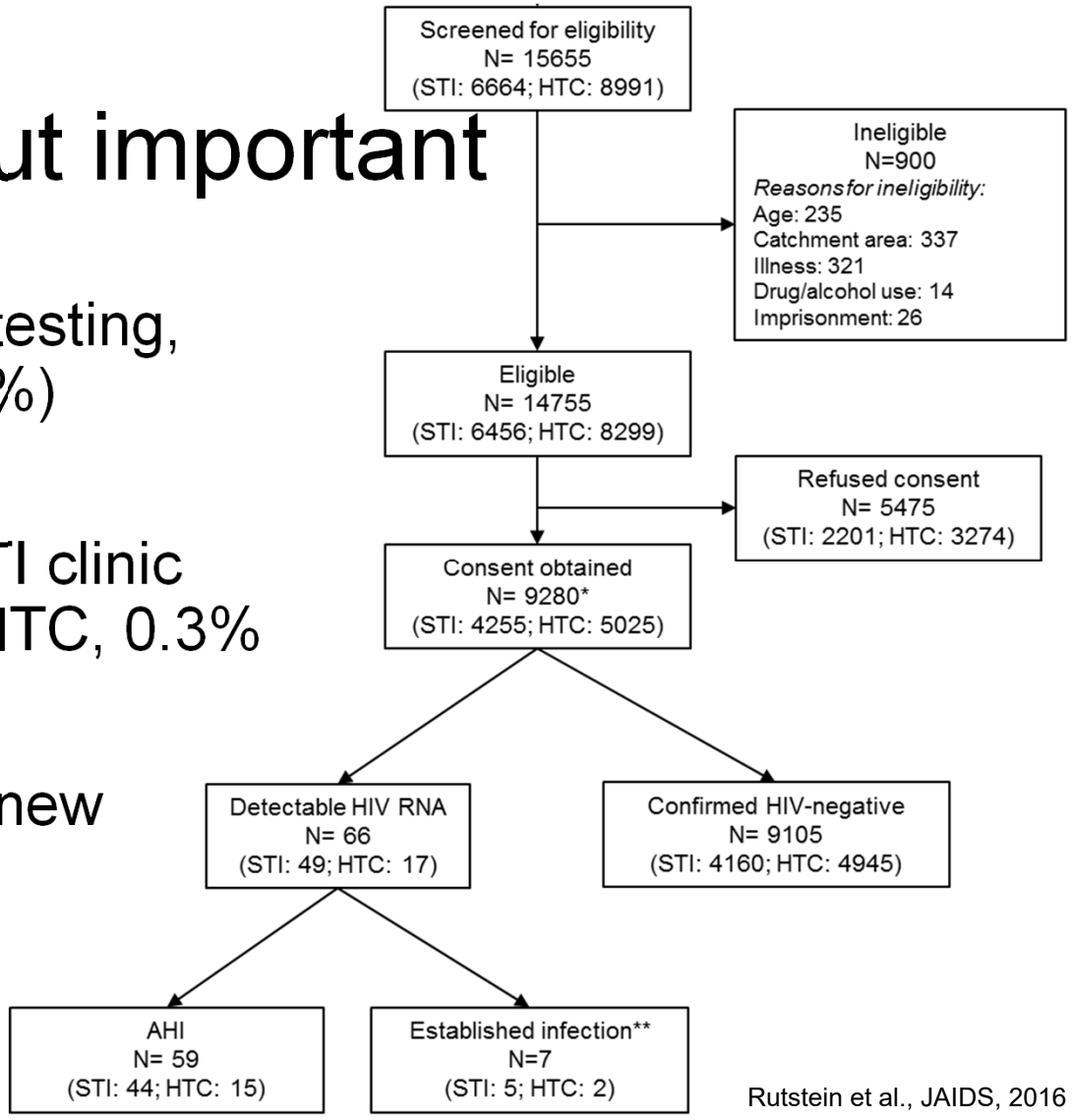


AHI: hard to find, but important

Among 9280 undergoing AHI testing,
59 with AHI (prevalence: 0.64%)

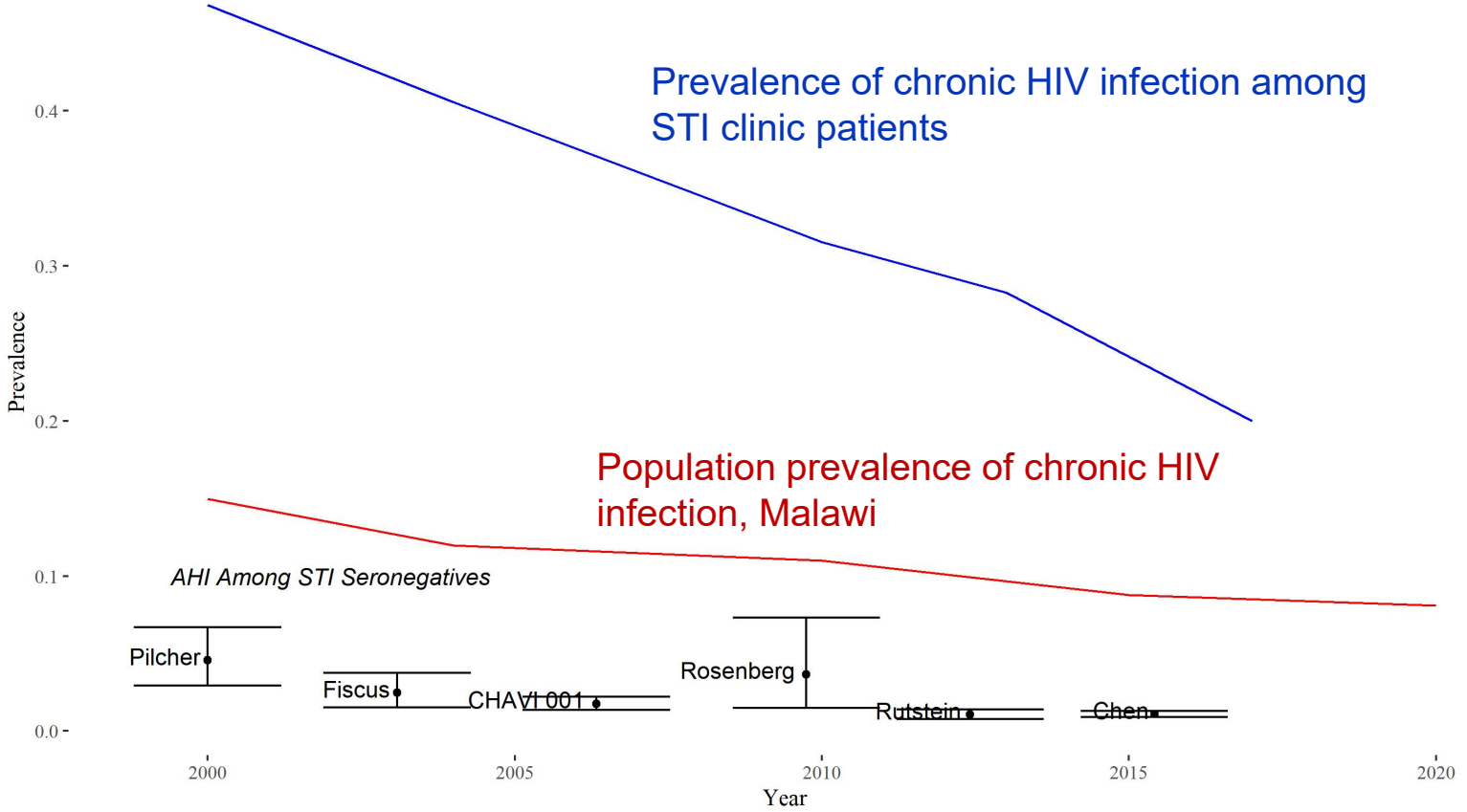
44/59 (75%) identified from STI clinic
Prevalence @ STI, 1.0% vs. HTC, 0.3%

AHI accounted for 2.3% of all new
HIV diagnoses @ STI

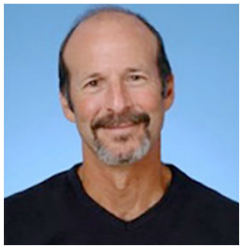


Rutstein et al., JAIDS, 2016

Frequently detected AHI at STI clinic



Griffin Bell



Irving Hoffman

~1 in every 100 HIV seronegative patients at STI clinic have AHI

Pilcher et al, 2004; Fiscus et al, 2007; Rosenberg et al, 2012; Rutstein et al, 2016, Chen et al, 2021

STI clinic EMR, Malawi DHHS

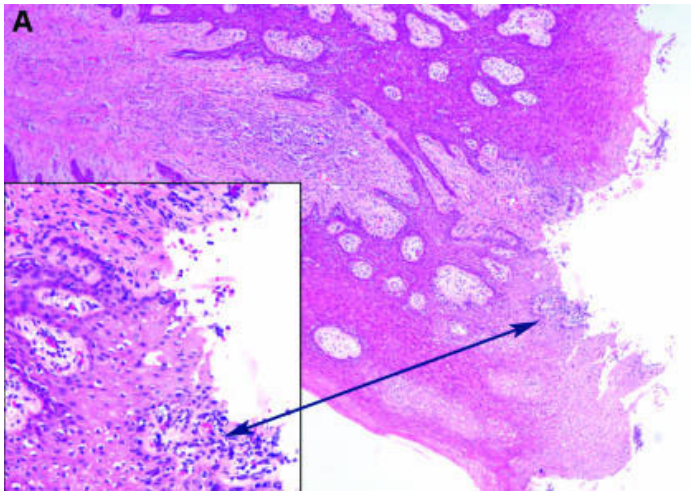
Syndemic “classical” STI/HIV: stronger together

Biological, behavioral, and epidemiological interactions

STIs enhancing efficiency of transmission via infectiousness (higher genital VL) or susceptibility

Mucosal inflammation and ulceration → exposed epithelium with concentrated inflammatory cells

AHI Risk Score:	**Points**
Discordant rapid antibody tests:	4
Fever, body ache, >1 partner:	1 (each)
Diarrhea, **GUD** :	**2 (each)**



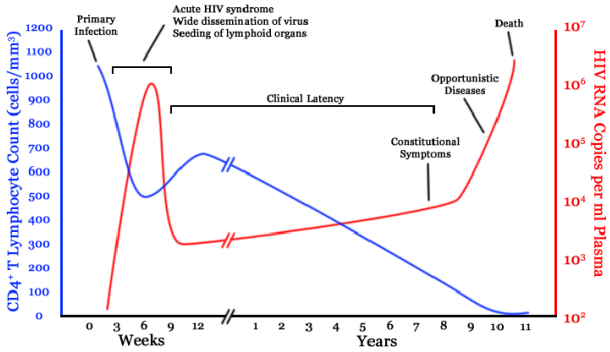
Powers et al., Improved detection of acute HIV-1 infection in sub-Saharan Africa: development of a risk score algorithm, *AIDS*, 2007

Weiler et al., Genital Ulcers Facilitate Rapid Viral Entry and Dissemination following Intravaginal Inoculation with Cell-Associated Simian Immunodeficiency Virus SIVmac239, *Journal of Virology*, 2008

Leveraging AHI for contact tracing

Recent exposure to person with HIV

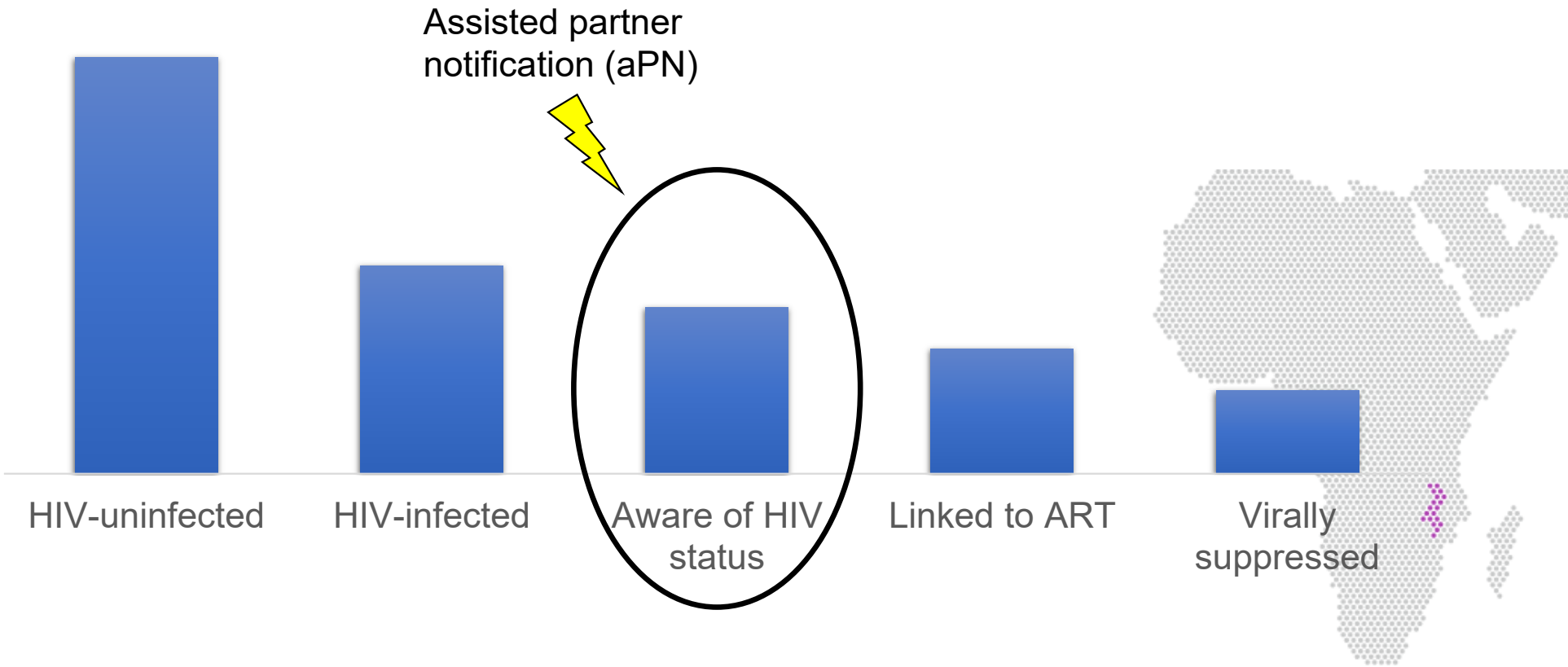
High risk of onward transmission



Evaluating social contact tracing from STI clinic, **30% of contacts of persons with AHI had HIV**

Rosenberg et al, STI Patients Are Effective Recruiters of Undiagnosed Cases of HIV: Results of a Social Contact Recruitment Study in Malawi, *JAIDS,* 2014

Increasing HIV status awareness: aPN



Spectrum of partner notification

Provider Referral = A counsellor or other health care provider will call or visit your partner and offer them HIV testing services.

Contract Referral = You and the counsellor will work together to notify your partner. You will have 14 days to tell your partner. After which, the counsellor will contact your partner and offer them HIV testing services.

Dual Referral = The counsellor/provider will sit with you and your partner and support you as you tell your partner about your HIV.

Passive Referral = You tell your partner about your HIV and encourage him or her to come to the health facility for an HIV test. Can be done with a referral slip

Provider assisted notification 2x as effective as passive referral

Enrolled 245 index patients

302 names sexual partners (252 with locator information)

Active notification arms 2x as likely to have returning partners

Contract notification likely cost-effective (4080 USD per transmission averted)

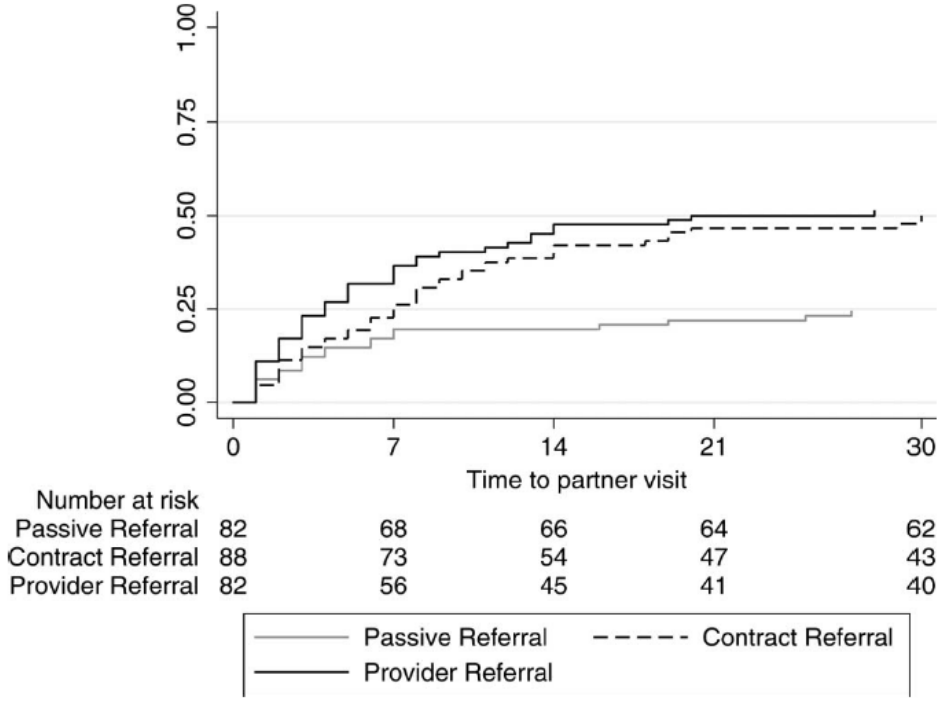


FIGURE 1. Shows the cumulative proportion of partners of partners presenting for testing for each method of partner notification. Time to partner visit is the number of days following the index patient enrollment visit.

Brown, L. et al., HIV Partner Notification Is Effective and Feasible in Sub-Saharan Africa: Opportunities for HIV Treatment and Prevention, JAIDS, 2011

Rutstein, SE et al, *Health Policy & Planning,* 2014;29:115-126

2016 WHO Recommendations

Voluntary assisted partner notification services should be offered as part of a comprehensive package of testing and care offered to people with HIV
(strong recommendation, moderate quality evidence).

aPN: One size fits…most?

Courtney Maierhofer

aPN promotes earlier HIV testing among partners, but is resource intensive

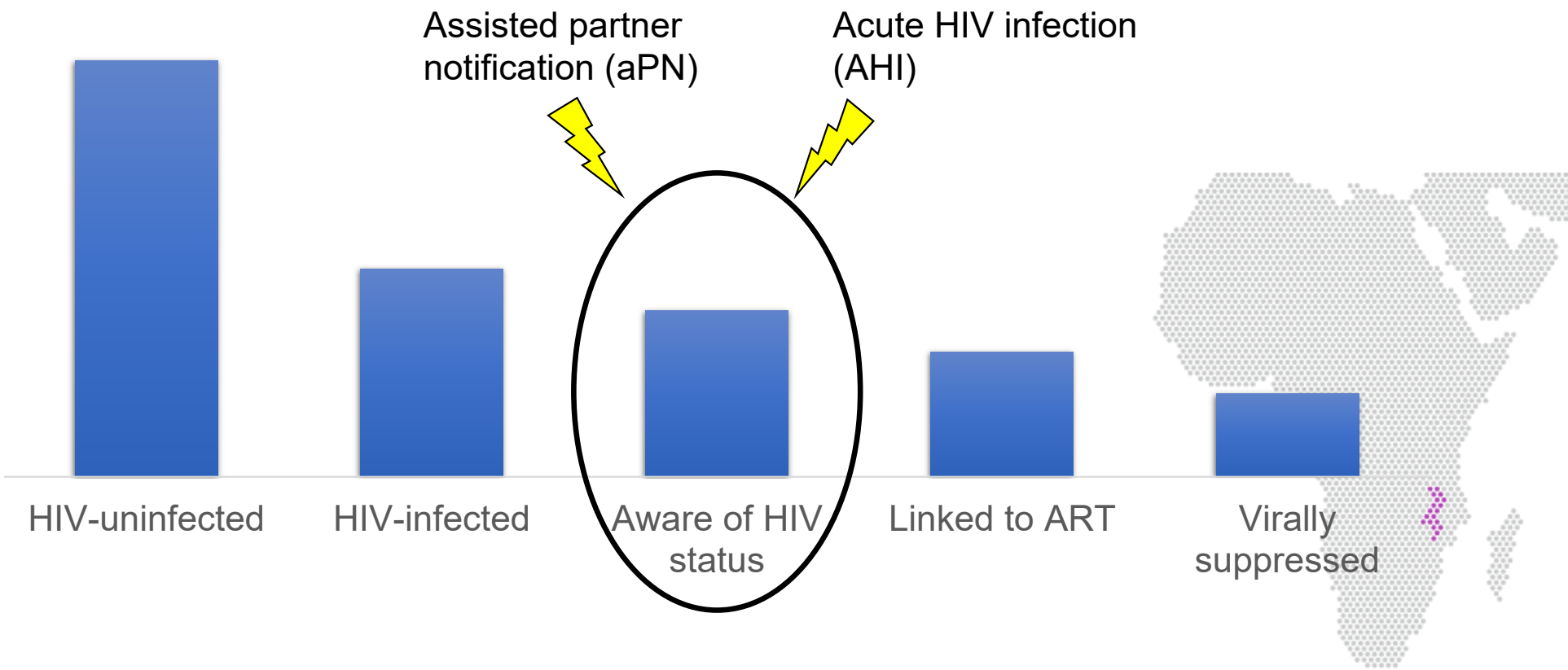
In Kenya, differences in partner HIV testing uptake according to index rurality, sex, HIV status (new vs previously diagnosed)

Analysis of aPN by referring participant characteristics at Malawi STI clinic (iKnow study)

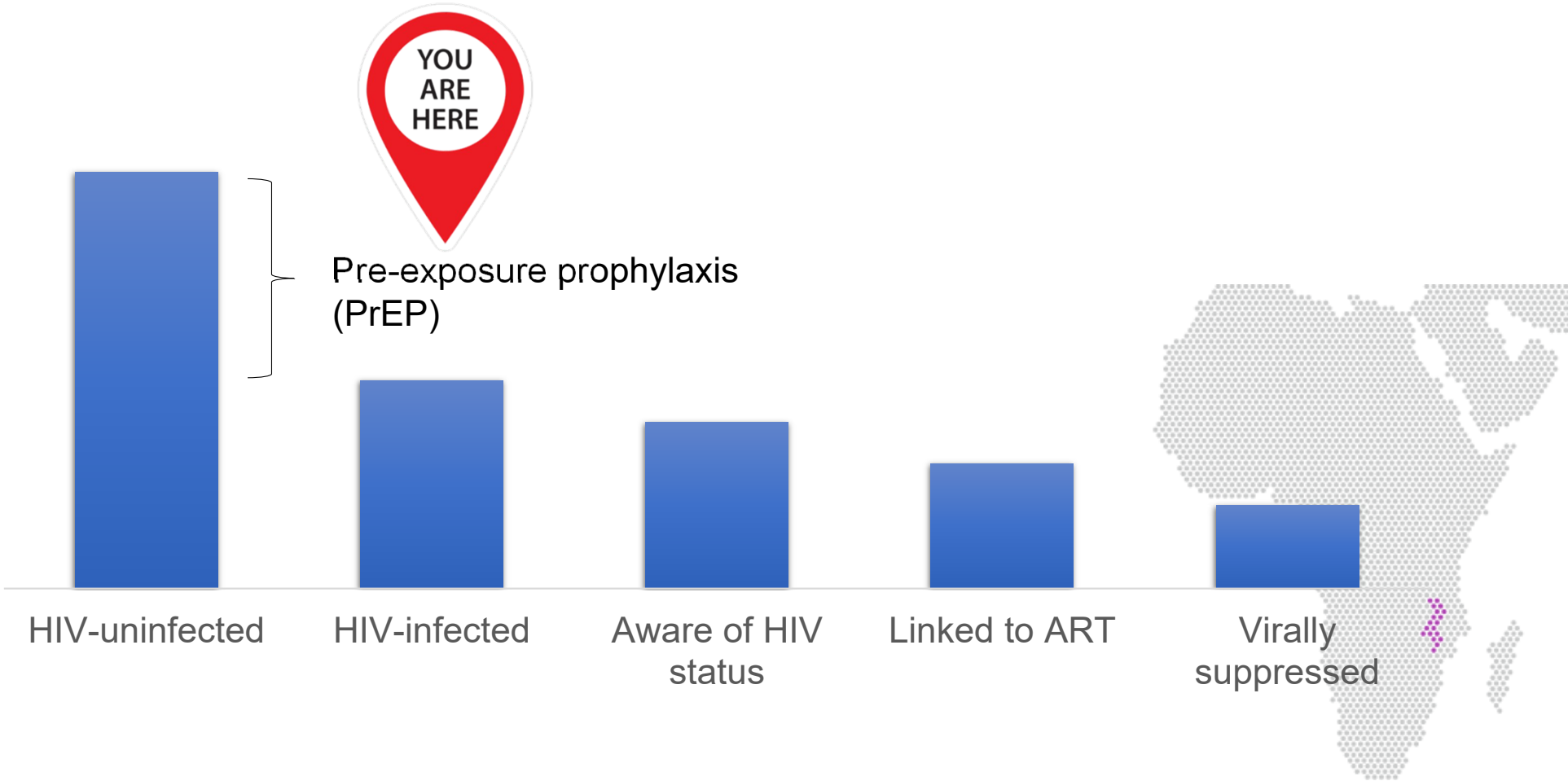
- Contract notification may increase referrals for women and those with previously diagnosed infection

Masyuko et al, *JIAS*, 2019

Efficient use of resource intensive strategies to improve HIV case finding



An ounce of prevention…



PrEP drugs

Nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs)

TDF/FTC (Truvada): Tenofovir disoproxil fumarate (TDF) + Emtricitabine (FTC)

TAF/FTC (Descovy): Tenofovir alafenamide fumarate (TAF) + Emtricitabine (FTC)

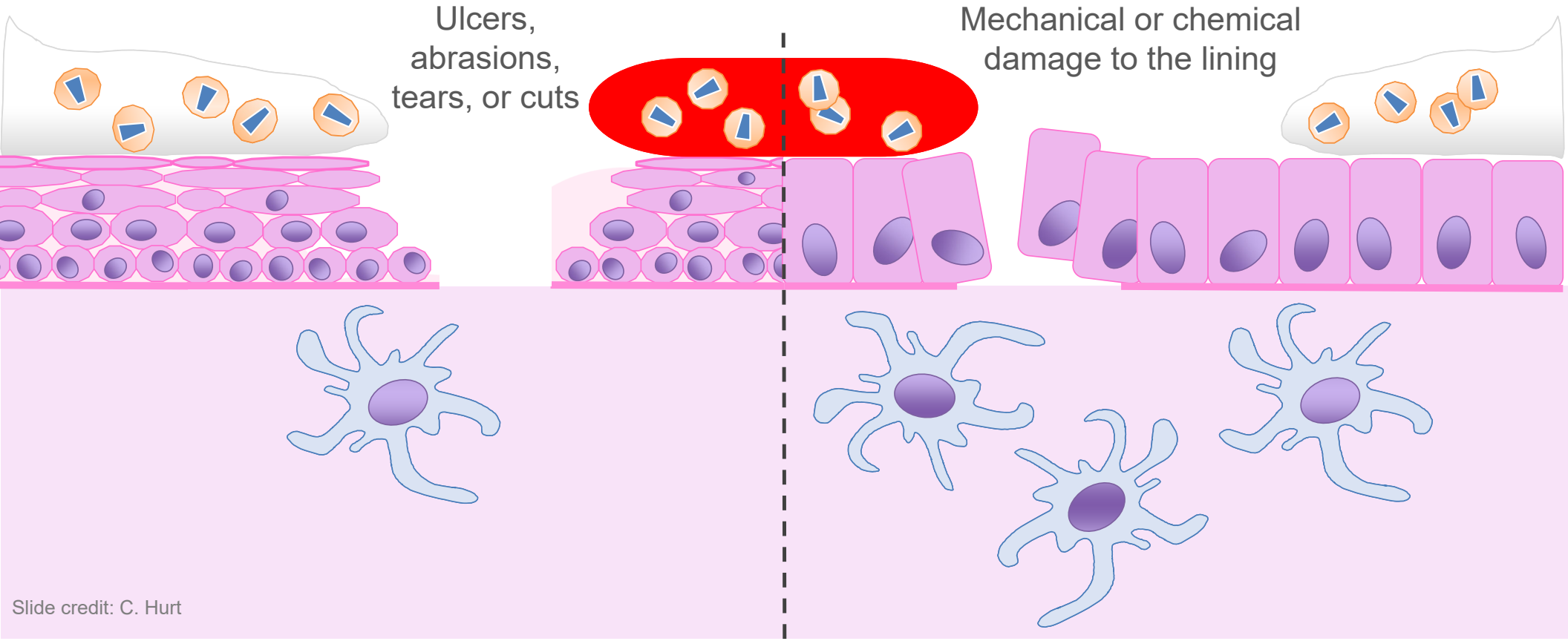
Non-nucleoside reverse transcriptase inhibitor (NNRTI)

Dapivirine

Integrase strand inhibitors

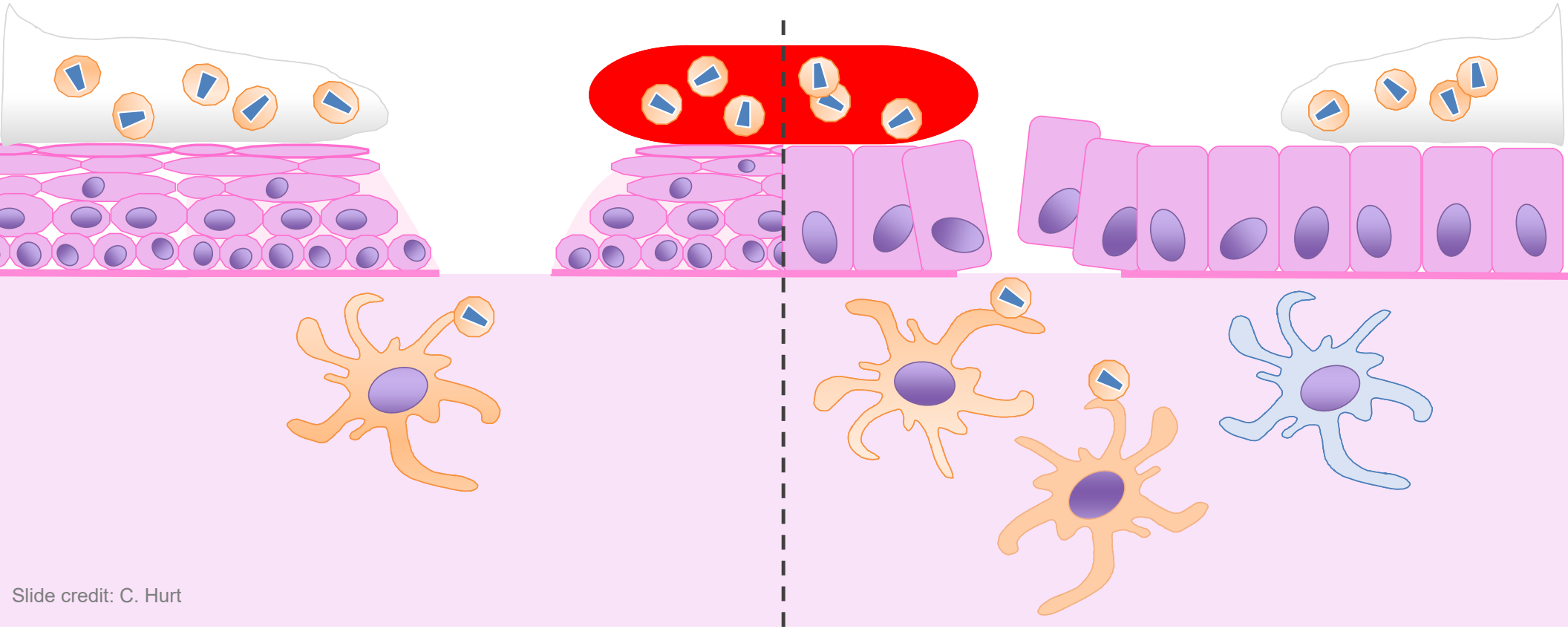
Cabotegravir (Apretude)

Disruptions in mucosal linings are “portals of entry” for HIV



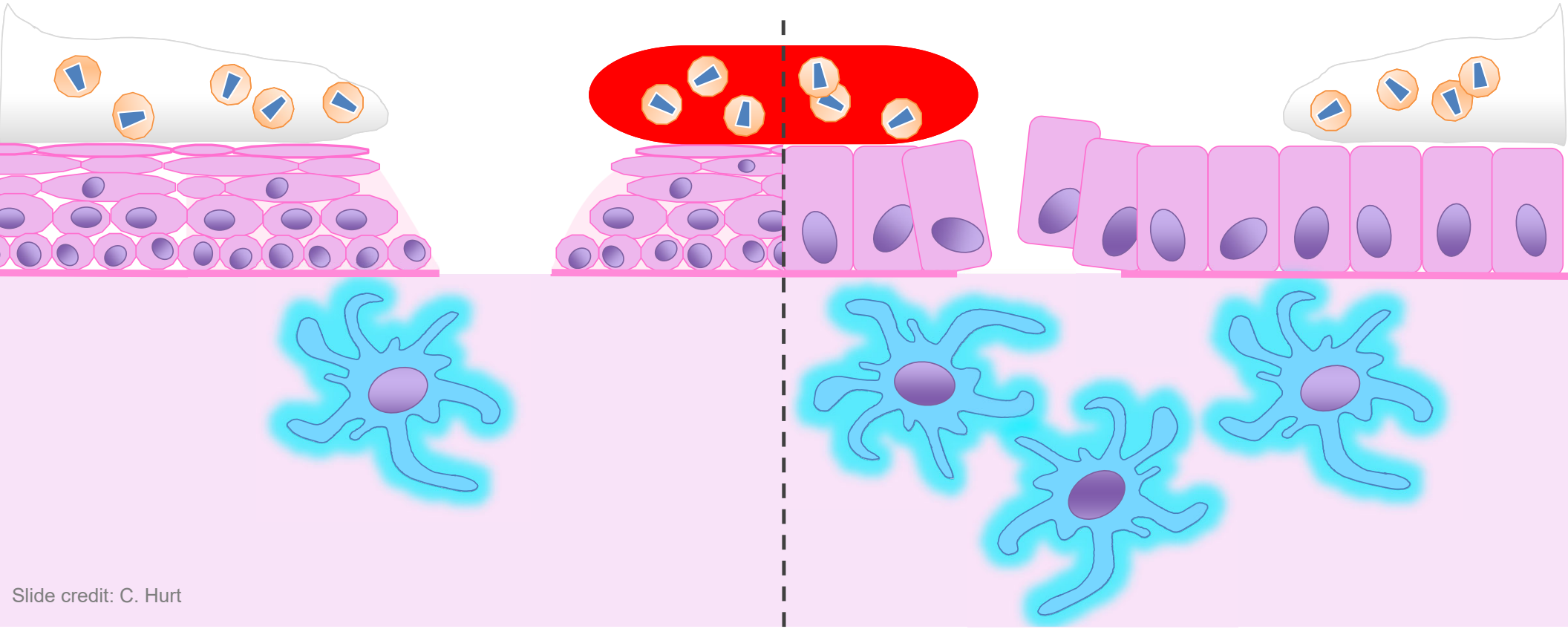
Slide credit: C. Hurt

Cells beneath the mucosal lining are the first to become infected



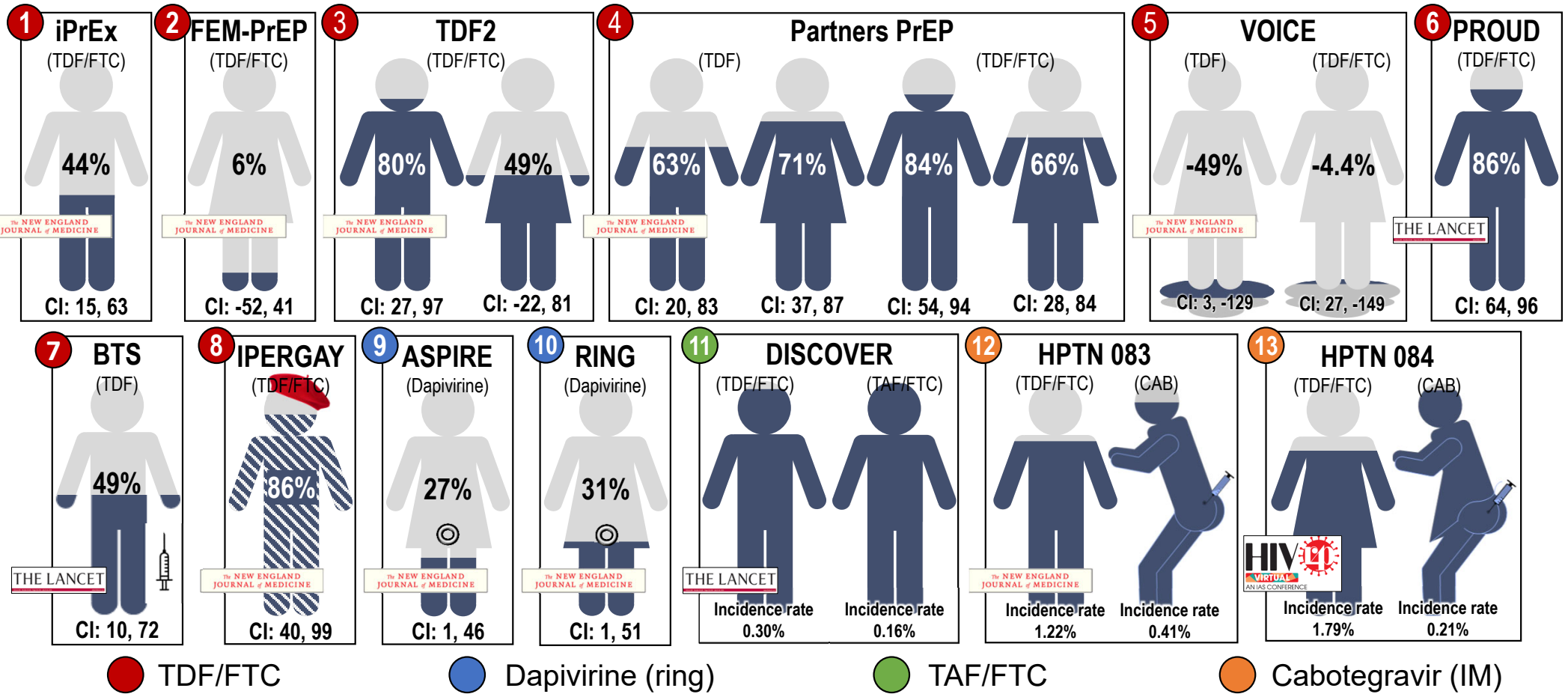
Slide credit: C. Hurt

HIV medicines administered before an exposure can prevent systemic infection



Slide credit: C. Hurt

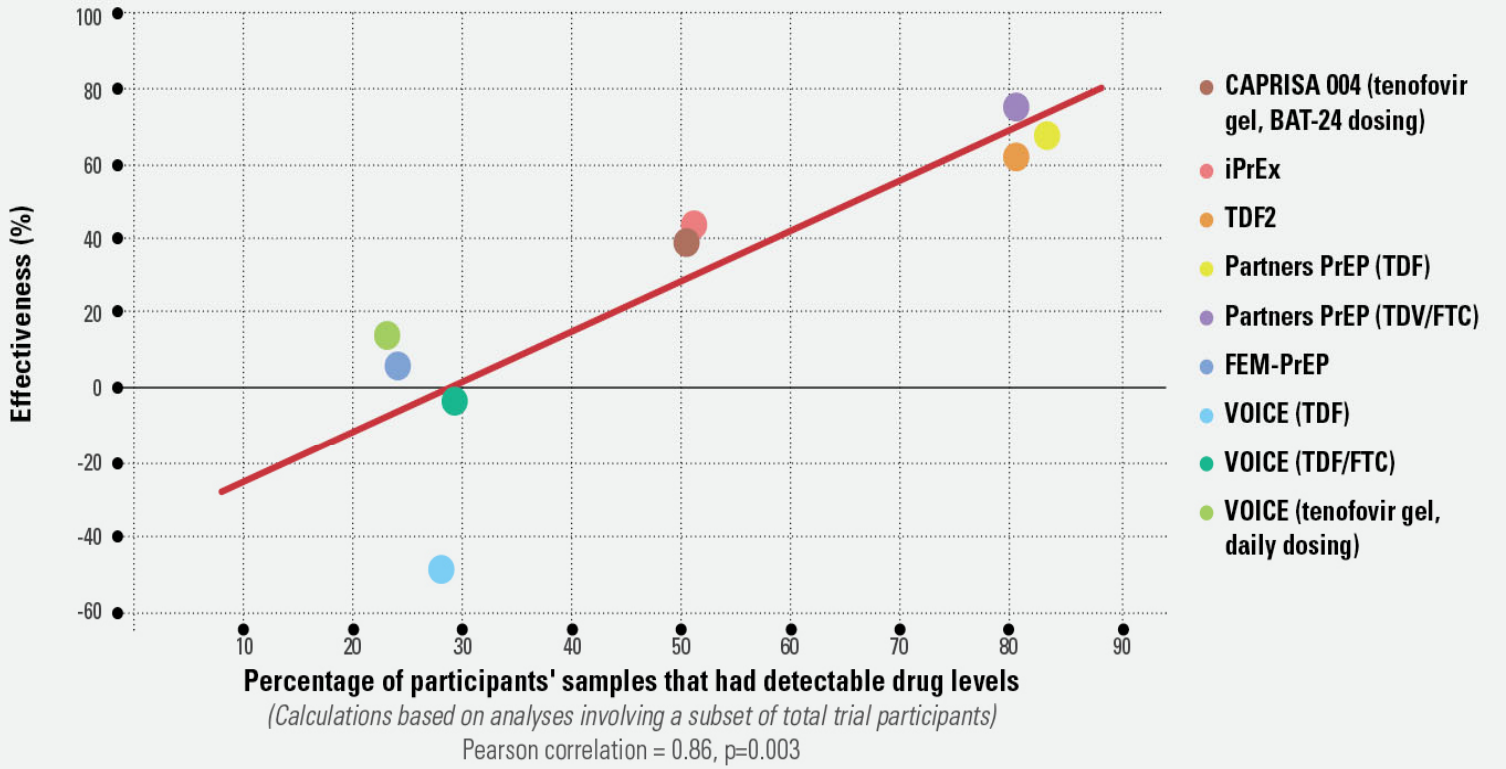
Effectiveness in randomized clinical trials



Adapted from Landovitz

1. Grant et al. NEJM. 2010.
2. Van Damme et al. NEJM. 2012
3. Thigpen et al. NEJM 2012.
4. Baeten et al. NEJM. 2012
5. Marrazzo et al. NEJM. 2015
6. McCormack et al. Lancet 2016
7. Choopanya et al. Lancet. 2013
8. Molina et al. NEJM. 2015
9. Baeten et al. NEJM. 2016
10. Nel et al. NEJM. 2016
11. Mayer et al. Lancet 2020.
12. Landovitz et al. NEJM. 2021
13. Delaney-Moretlwe et al. HIV R4P. 2021

Daily oral tenofovir works…if you take it

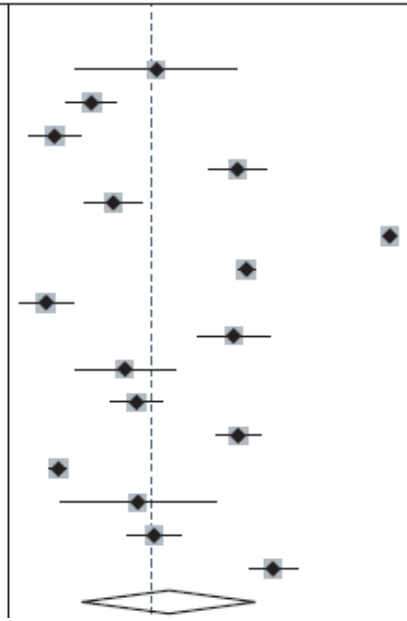


Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

Early discontinuation is the rule, not the exception

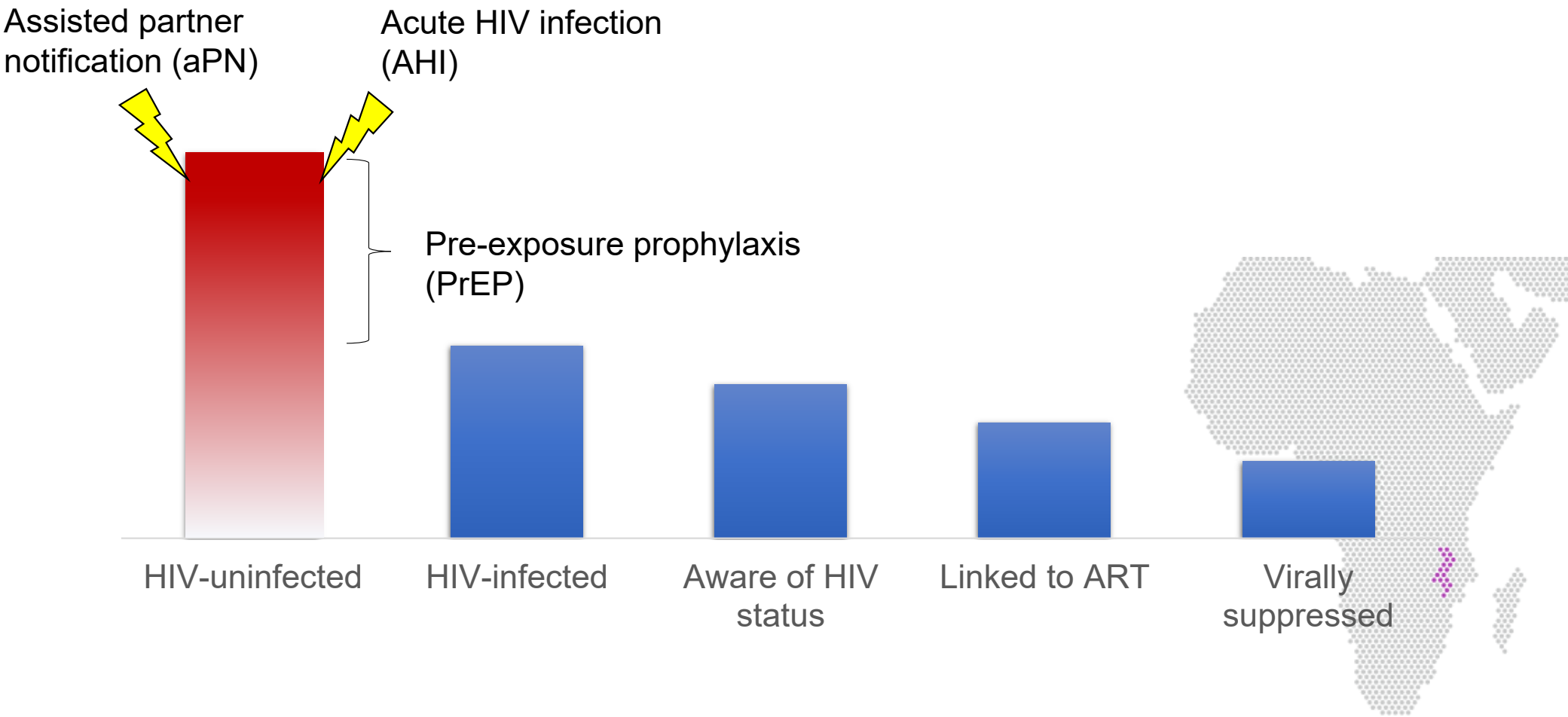
	Individuals who discontinued PrEP (n/N)	Proportion (95% CI)	Weight (%)
≤6 months			
Blackstock et al (2017)[47]	8/21	0·38 (0·17–0·59)	1·59
Blaylock et al (2018)[31]	34/159	0·21 (0·15–0·28)	1·70
Clement et al (2019)[48]	10/84	0·12 (0·05–0·19)	1·69
Doblecki-Lewis et al (2017)[32]	102/173	0·59 (0·52–0·66)	1·69
Fina et al (2019)[49]	38/141	0·27 (0·20–0·34)	1·69
Kagaayi et al (2020)[50]	2491/2536	0·98 (0·98–0·99)	1·71
Kinuthia et al (2020)[21]	1244/2030	0·61 (0·59–0·63)	1·71
Lahuerta et al (2017)[51]	7/72	0·10 (0·03–0·17)	1·70
Lankowski et al (2019)[52]	62/107	0·58 (0·49–0·67)	1·68
Montgomery et al (2016)[53]	15/50	0·30 (0·17–0·43)	1·66
Morgan et al (2018)[33]	65/197	0·33 (0·26–0·40)	1·70
Mugwanya et al (2019)[54]	164/278	0·59 (0·53–0·65)	1·70
Noret et al (2018)[55]	134/1049	0·13 (0·11–0·15)	1·71
O'Byrne et al (2020)[56]	7/21	0·33 (0·13–0·53)	1·60
Reback et al (2019)[57]	70/187	0·37 (0·30–0·44)	1·69
Rolle et al (2019)[58]	147/216	0·68 (0·62–0·74)	1·70
Subtotal (I^2=99·8%, p<0·0001)		**0·41 (0·19–0·64)**	**26·92**



41% (95% CI: 18.8-63.5) of participants discontinued PrEP within the first 6 months

Zhang, Li, Xu, Hu, Rutstein et al, *Lancet HIV*, 2022; Rutstein, Smith, Dalal, Baggaley, Cohen, *Lancet HIV,* 2020

Who needs PrEP (and when)?



PrEP: right place at the right time

An implementation problem…

Implementation science terminology decoder:

The intervention/practice/innovation is THE THING

Effectiveness research looks at whether THE THING works

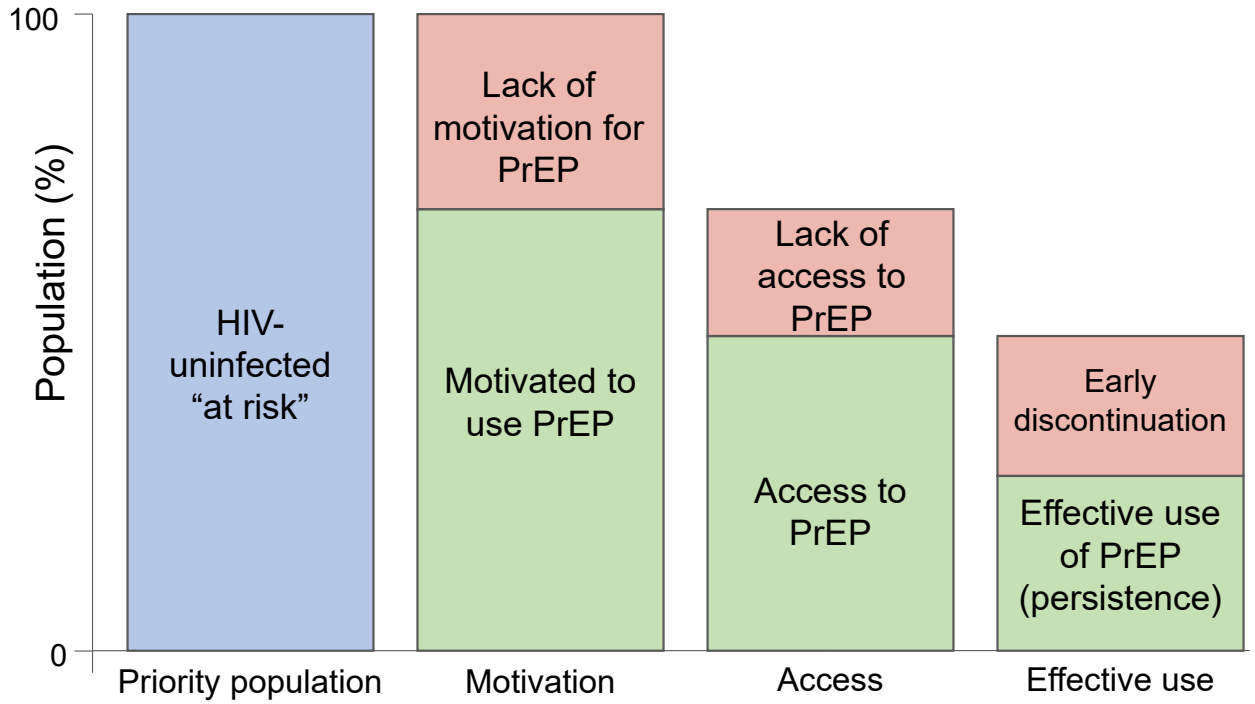
Implementation research looks at how best to help people/places DO THE THING

Implementation strategies are the stuff we do to try and help people/places DO THE THING better

Implementation outcomes are how much and how well they do THE THING

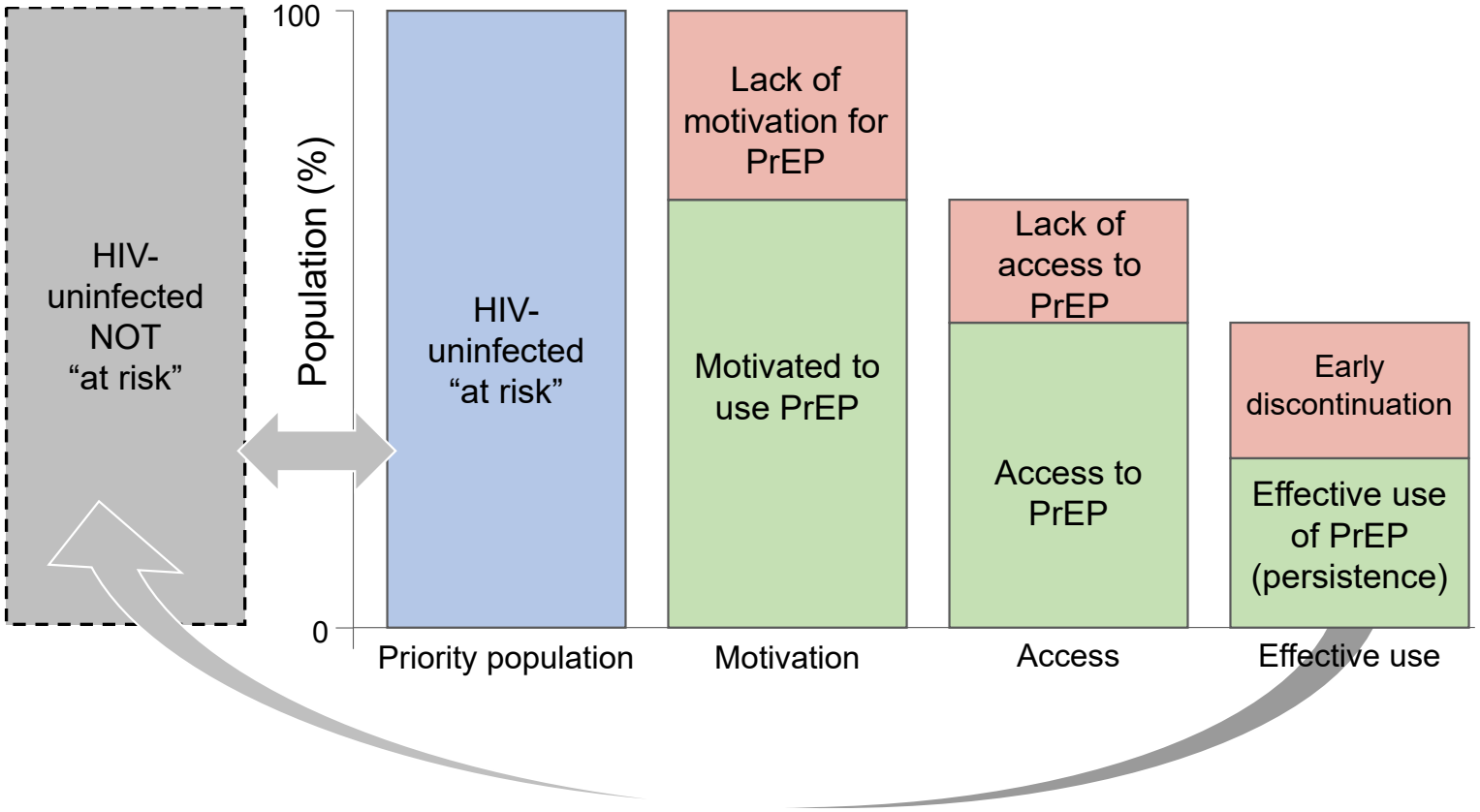
Curran, *Implementation Science Communications*, 2020

A unifying HIV prevention cascade

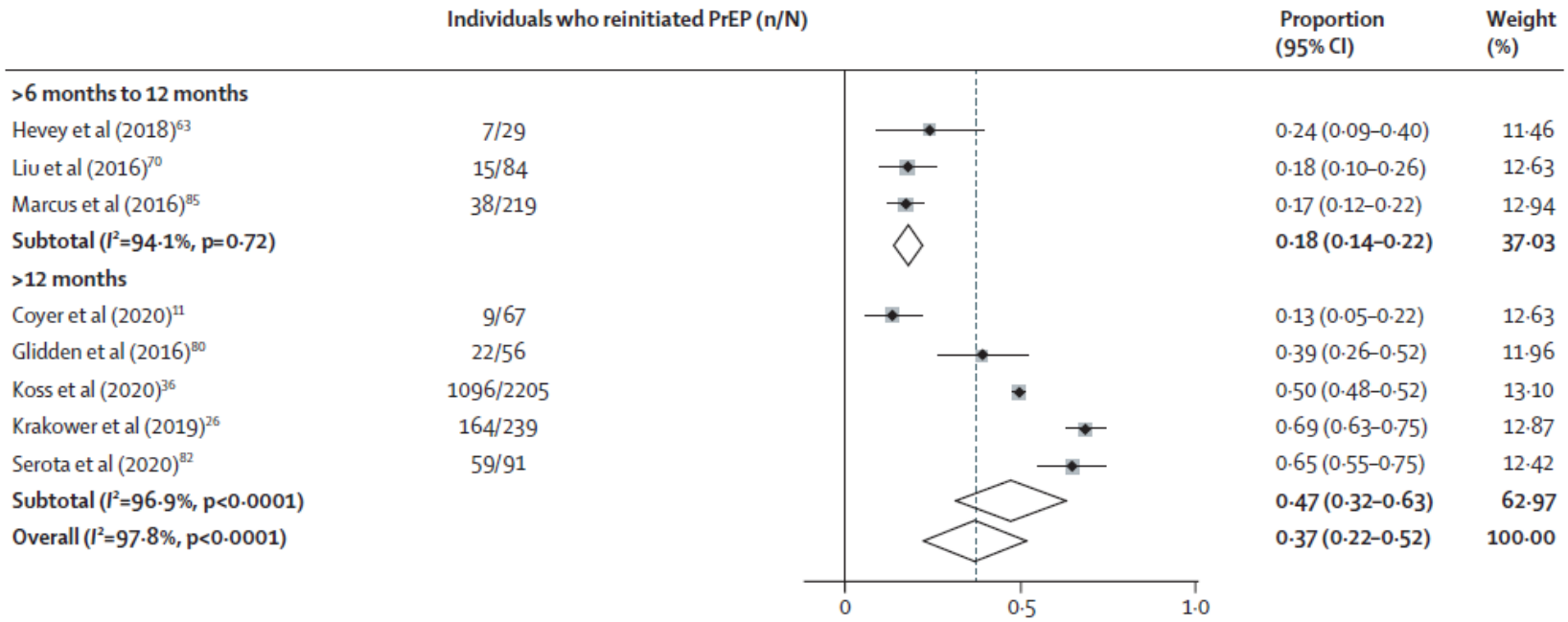


Schaefer et al, *Lancet HIV*, 2019

A unifying HIV prevention cascade



Nearly half of persons who stopped PrEP, restarted within 1 year

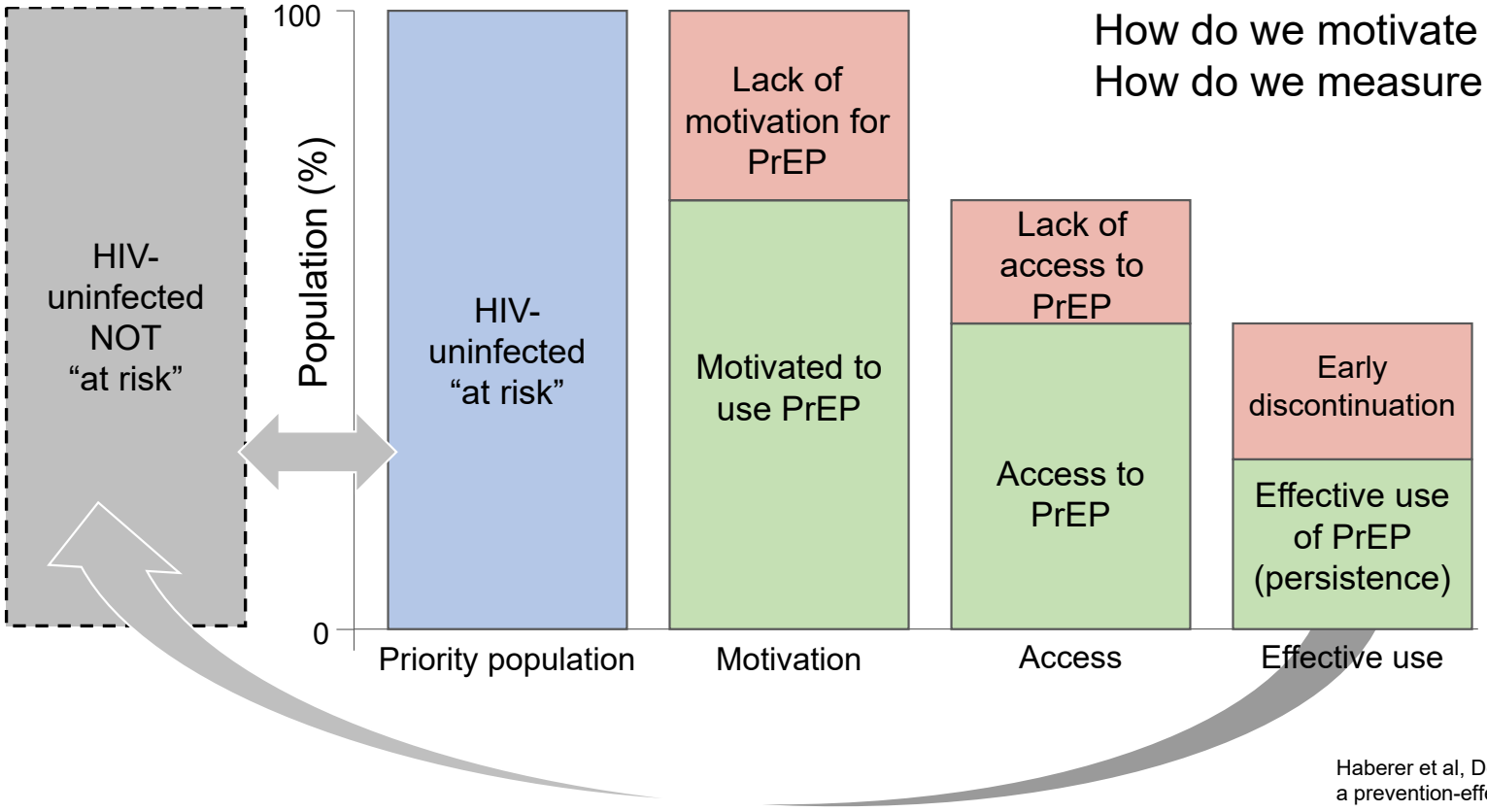


	Individuals who reinitiated PrEP (n/N)	Proportion (95% CI)	Weight (%)
>6 months to 12 months			
Hevey et al (2018)[63]	7/29	0·24 (0·09–0·40)	11·46
Liu et al (2016)[70]	15/84	0·18 (0·10–0·26)	12·63
Marcus et al (2016)[85]	38/219	0·17 (0·12–0·22)	12·94
Subtotal (I^2=94·1%, p=0·72)		**0·18 (0·14–0·22)**	**37·03**
>12 months			
Coyer et al (2020)[11]	9/67	0·13 (0·05–0·22)	12·63
Glidden et al (2016)[80]	22/56	0·39 (0·26–0·52)	11·96
Koss et al (2020)[36]	1096/2205	0·50 (0·48–0·52)	13·10
Krakower et al (2019)[26]	164/239	0·69 (0·63–0·75)	12·87
Serota et al (2020)[82]	59/91	0·65 (0·55–0·75)	12·42
Subtotal (I^2=96·9%, p<0·0001)		**0·47 (0·32–0·63)**	**62·97**
Overall (I^2=97·8%, p<0·0001)		**0·37 (0·22–0·52)**	**100·00**

Among those who discontinued, 47.3% (95% CI: 31.5 - 63.2) restarted within 1 year

Zhang, Li, Xu, Hu, Rutstein et al, *Lancet HIV*, 2022

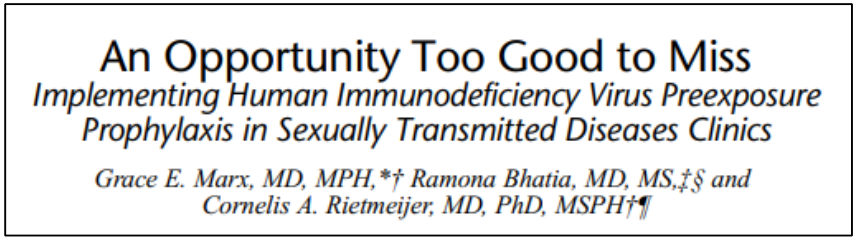
A unifying HIV prevention cascade



Who is "at risk"?
How do we motivate and provide access?
How do we measure "effective" PrEP use?

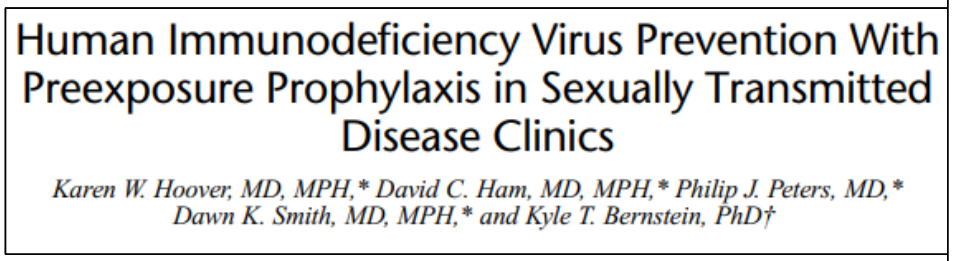
Haberer et al, Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm, *AIDS* 2015

Integrating services – PrEP & STI clinics



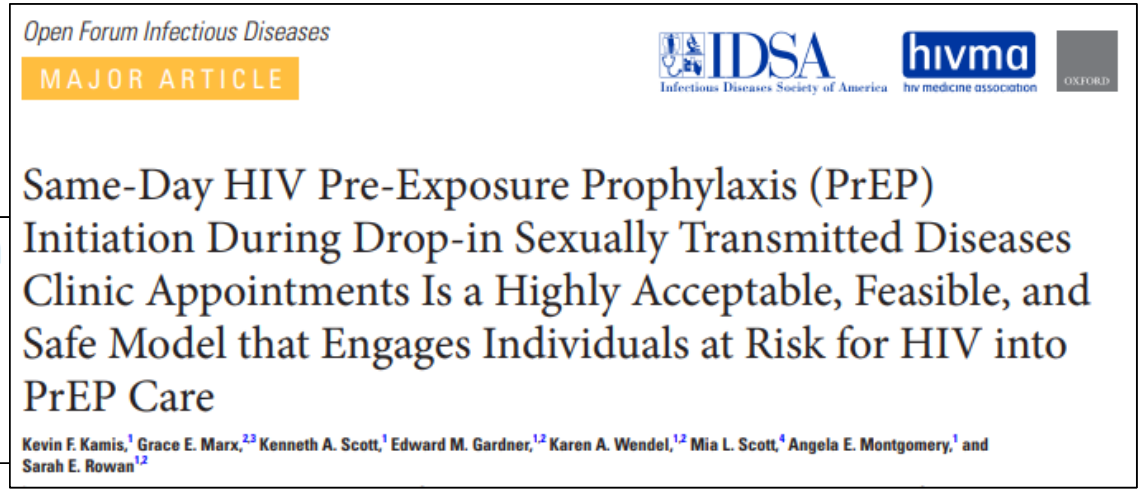
An Opportunity Too Good to Miss
Implementing Human Immunodeficiency Virus Preexposure Prophylaxis in Sexually Transmitted Diseases Clinics

Grace E. Marx, MD, MPH,† Ramona Bhatia, MD, MS,‡§ and Cornelis A. Rietmeijer, MD, PhD, MSPH†¶*



Human Immunodeficiency Virus Prevention With Preexposure Prophylaxis in Sexually Transmitted Disease Clinics

Karen W. Hoover, MD, MPH, David C. Ham, MD, MPH,* Philip J. Peters, MD,* Dawn K. Smith, MD, MPH,* and Kyle T. Bernstein, PhD†*



Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Same-Day HIV Pre-Exposure Prophylaxis (PrEP) Initiation During Drop-in Sexually Transmitted Diseases Clinic Appointments Is a Highly Acceptable, Feasible, and Safe Model that Engages Individuals at Risk for HIV into PrEP Care

Kevin F. Kamis,[1] Grace E. Marx,[2,3] Kenneth A. Scott,[1] Edward M. Gardner,[1,2] Karen A. Wendel,[1,2] Mia L. Scott,[4] Angela E. Montgomery,[1] and Sarah E. Rowan[1,2]

Current PrEP screening uses epidemiologic/self-reported risk profiling

In high HIV incidence settings, incident STI → objective indicator of HIV risk

Logical (and efficient?) extension of existing sexual health services

Integrating PrEP and STI services in Malawi: the ePrEP study

Examine the acceptability, feasibility, and effectiveness of enhanced PrEP implementation strategy into an STI clinic in Lilongwe, Malawi

"Enhanced PrEP" → use of aPN, AHI screening, etiologic STI testing, and co-located services (STI + PrEP)

ePrEP patient participant groups

Group 1: Primary index participants initiating PrEP

Group 2: Named sexual partners

N≈200

Group 3: PrEP eligible patients declining PrEP initiation

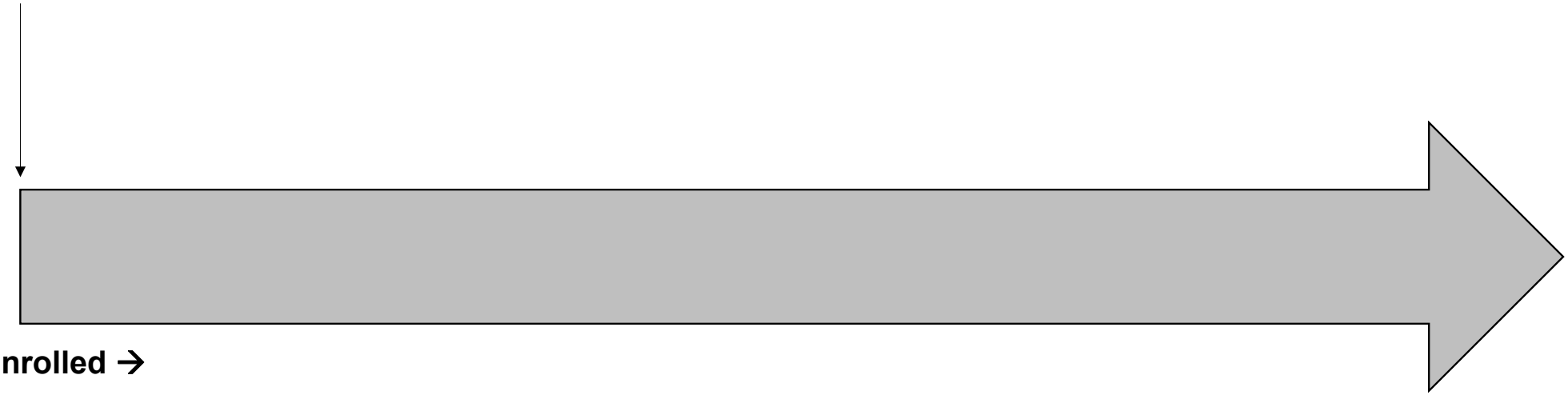
N≈50

Followed for 6-months

"Effectiveness" outcome: persistent PrEP use

Cohort timeline

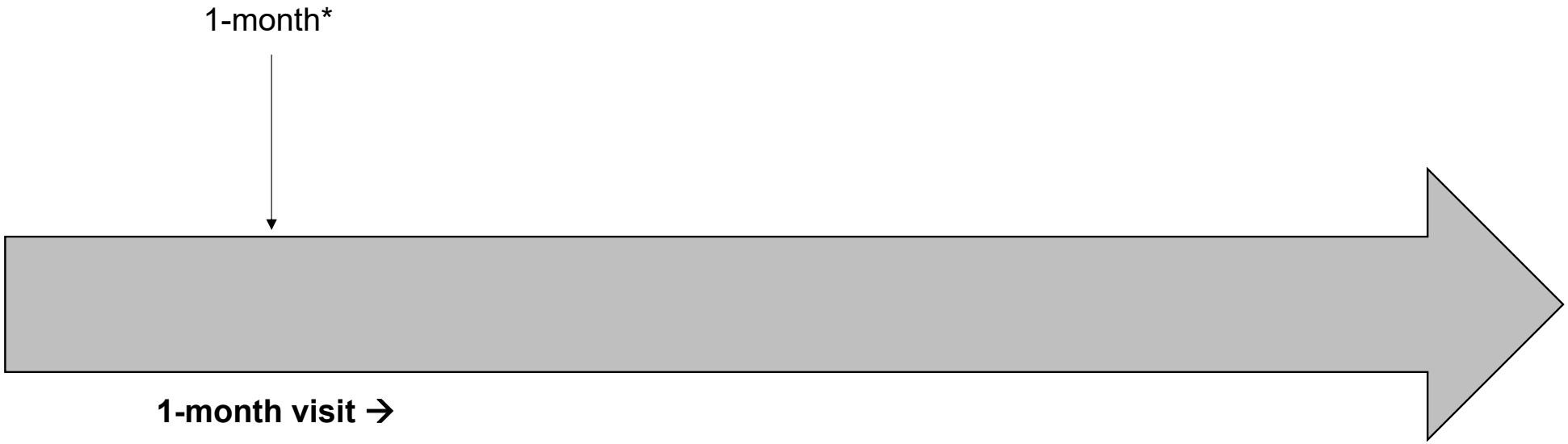
Presents to STI clinic for syndromic management, confirmed HIV seronegative



Enrolled →

AHI screening
STI testing
Behavioral survey
Named sexual partners

Cohort timeline

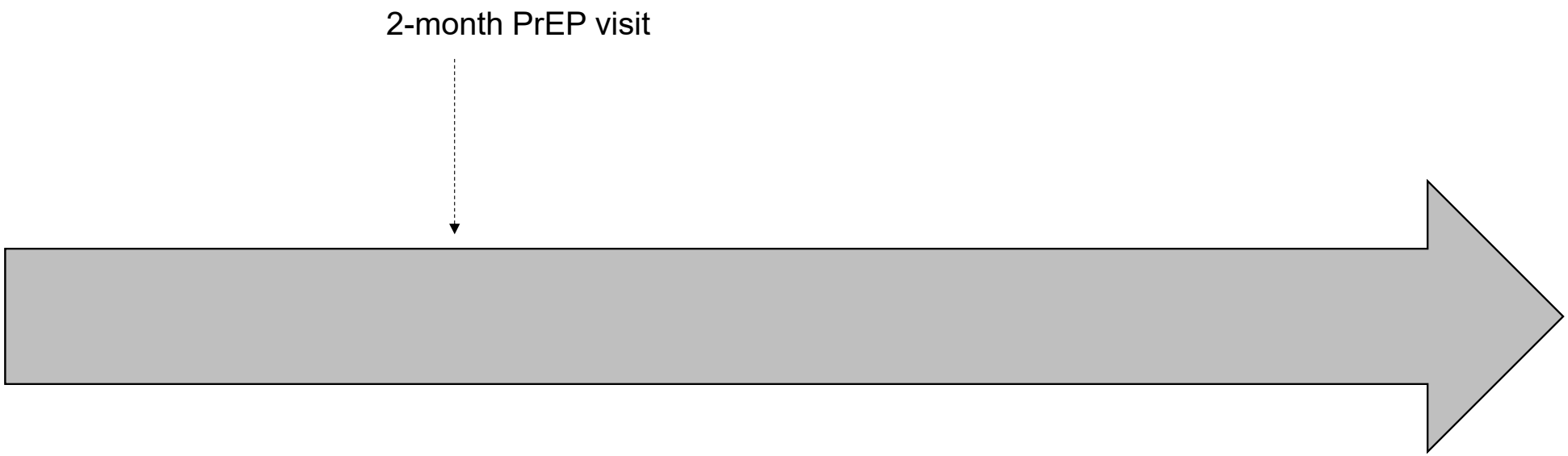


1-month visit →

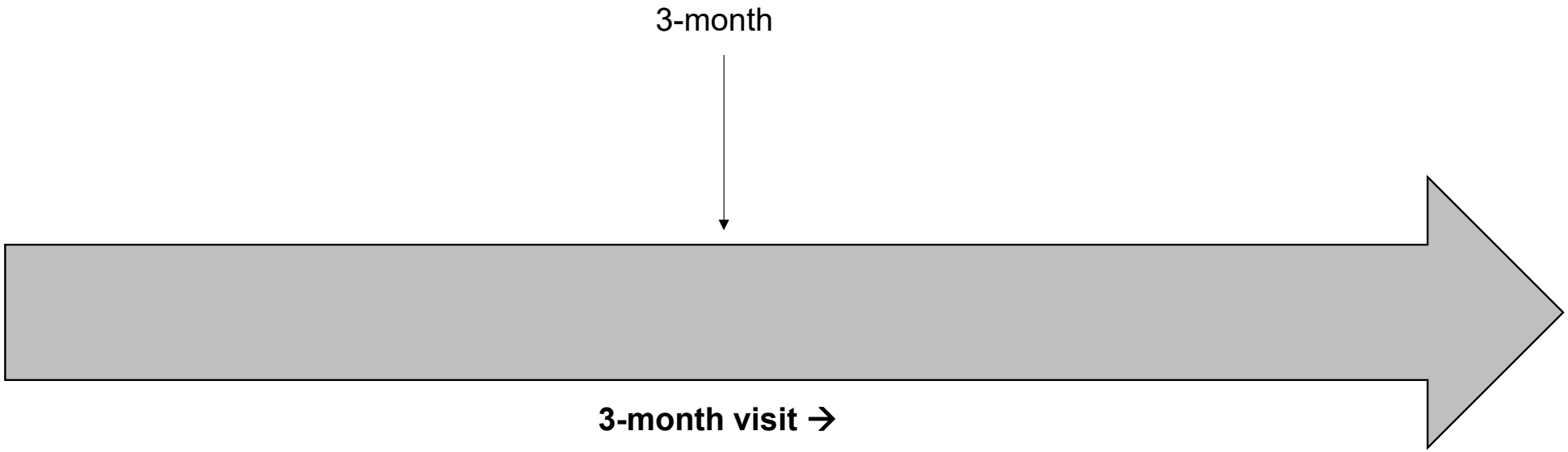
HIV antibody test
PrEP use, side effects
Behavioral survey

*only if initiated PrEP at enrollment (Group 1 and 2)

Cohort timeline



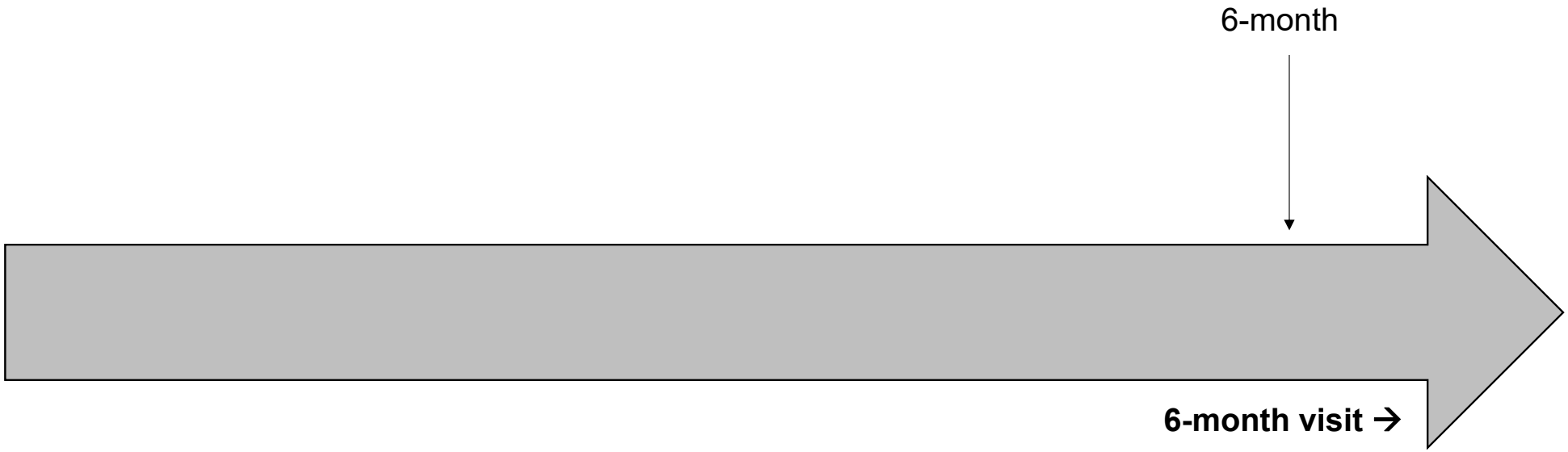
Cohort timeline



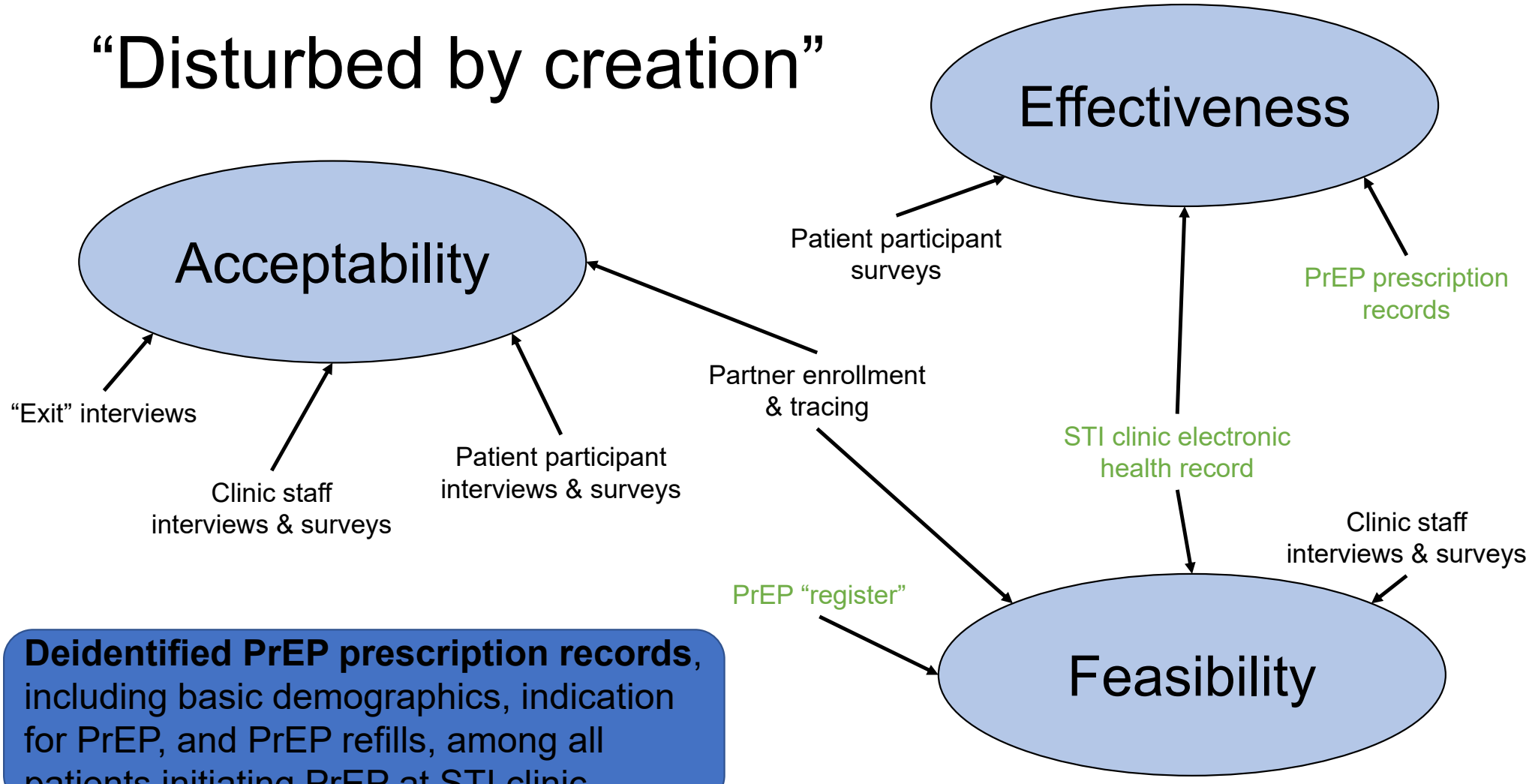
3-month visit →

HIV antibody test
STI testing
PrEP use, side effects
Behavioral survey

Cohort timeline



“Disturbed by creation”



Deidentified PrEP prescription records, including basic demographics, indication for PrEP, and PrEP refills, among all patients initiating PrEP at STI clinic

Embracing integrated services

It is like when you want to kill birds, you set a trap where the birds gather, and you can easily trap them. So, at STI clinics is where the people who are at risk of getting HIV are found and they need to be prevented from HIV from there. – *provider participant*

PrEP is best provided at the STI clinic because that is where people who suffer STIs are found…[PrEP] is not supposed to be provided in the community because people treat the symptoms with traditional medicine but there can be no one to diagnose the STIs there…the STI clinic is ideal because everyone who goes there has a problem…all of us who go there are STI patients so there is no stigma. – *patient participant*

ePrEP by the numbers (March – Dec 2022)

Characteristic	Index participants n=175 (%)
Sex	
Male	110 (63)
Age	
15-24	70 (40)
25-34	78 (45)
>34	27 (15)
Marital status	
Never married	65 (37)
Married	56 (32)
Other	54 (31)
Additional HIV risk factor	
Buy/sell sex	72 (41)
HIV+ partner	19 (11)
Older partner	51 (29)
Primary partner (last month)	93 (53)
Aware of 1° partner HIV status	56 (32)

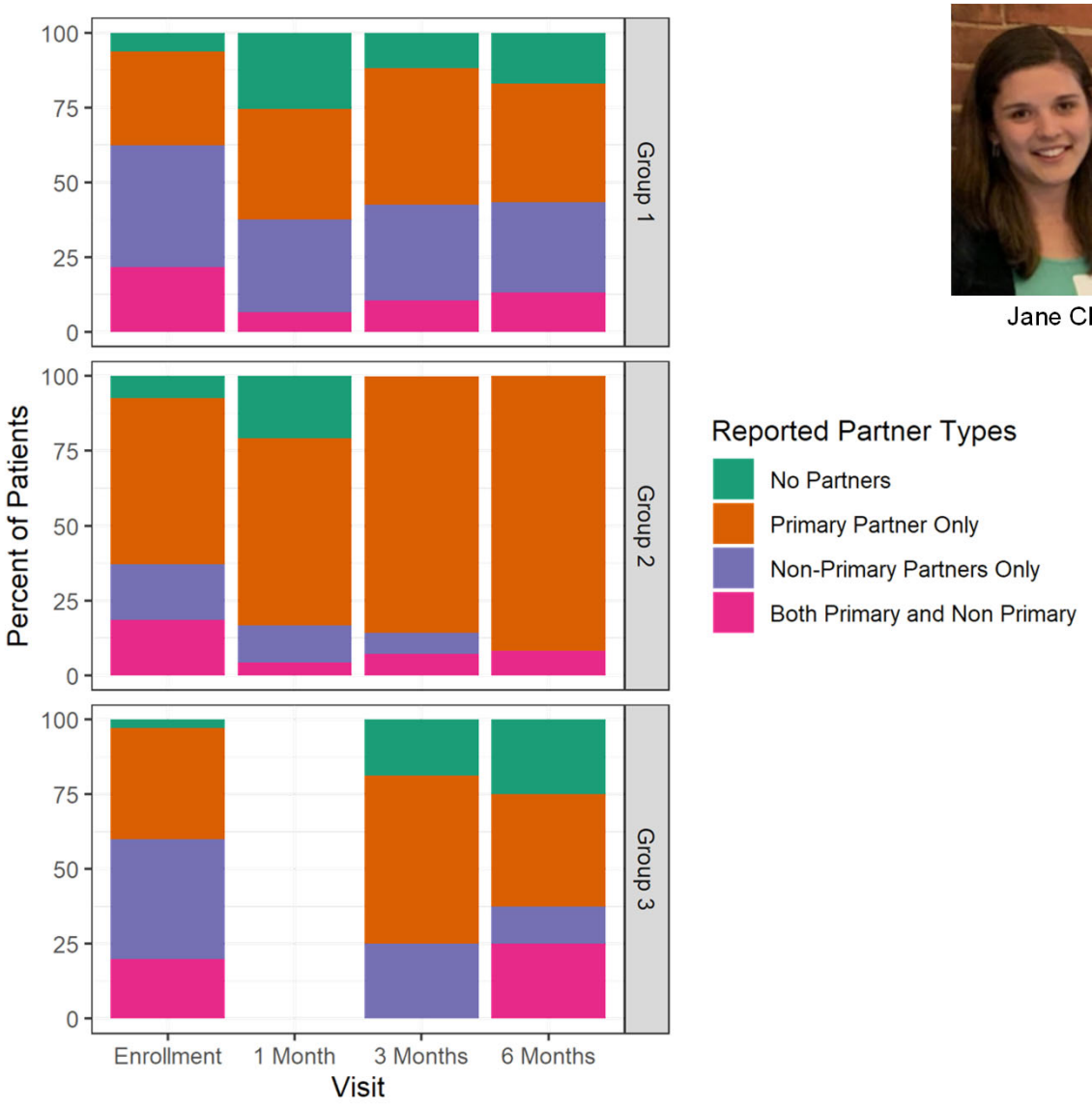
PrEP refusers: n=37

Screened partners: 58
Enrolled partners: 27
- Previously HIV+: 16 (3 no ART)
- Newly diagnosed with HIV: 4
- Not interested in PrEP: 5
- Not interested in *study:* 2
- Other ineligibility: 4

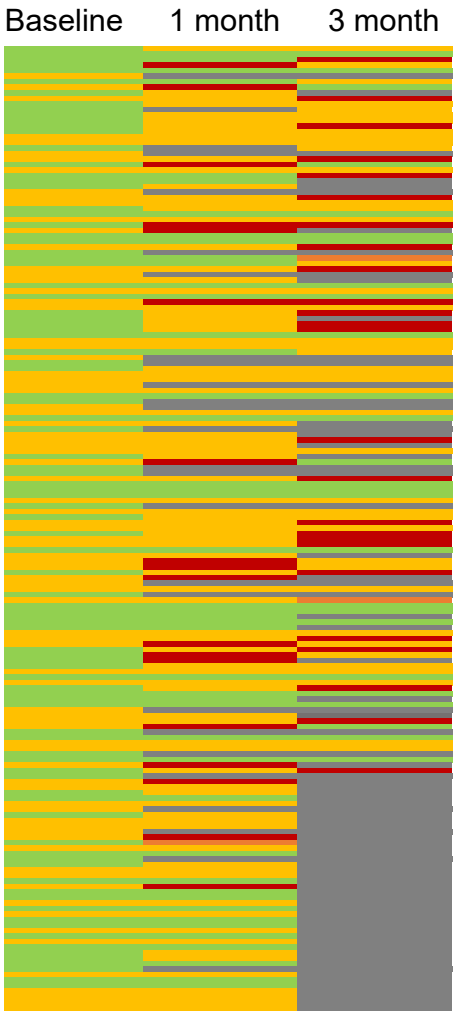
Edward Jere; Esther Mathiya; Mercy Tsidya

Claire Pedersen

Partner type switching



Jane Chen



Complex partner switching

175 index participants

No primary partner
Same primary partner
Unknown primary partner
New primary partner
No visit

Risk aligned PrEP: beyond detectable drug levels

Unique longitudinal insight into fluctuations of risk, perceived risk, and PrEP use among understudied population

Frequent discontinuations and “restarts”

aPN may help extend PrEP reach (and could influence persistence)

Poor daily oral PrEP adherence likely addressed with long-acting injectable PrEP, but…

- Who needs AHI screening for injections?
- How do we bridge gaps in PrEP use or intentional stops/starts?

Funding Opportunity Title

Innovative Models for Delivering PrEP and STI Services to Stop HIV in the United States (R61/R33 Clinical Trial Optional)

PrEP in rural North Carolina

Kate Muessig

Disparities of PrEP in the Southern US

Accounts for >50% of new HIV, but 33% of PrEP users

STI	NC National ranking (2019)
HIV	6th
Chlamydia	6th
Gonorrhea	9th
Syphilis	15th

Uptake disparities among young sexual and gender minority (YSGM) men of color, particularly in rural counties

STI/HIV syndemics track along demographics and geography, with high burden among rural YSGM

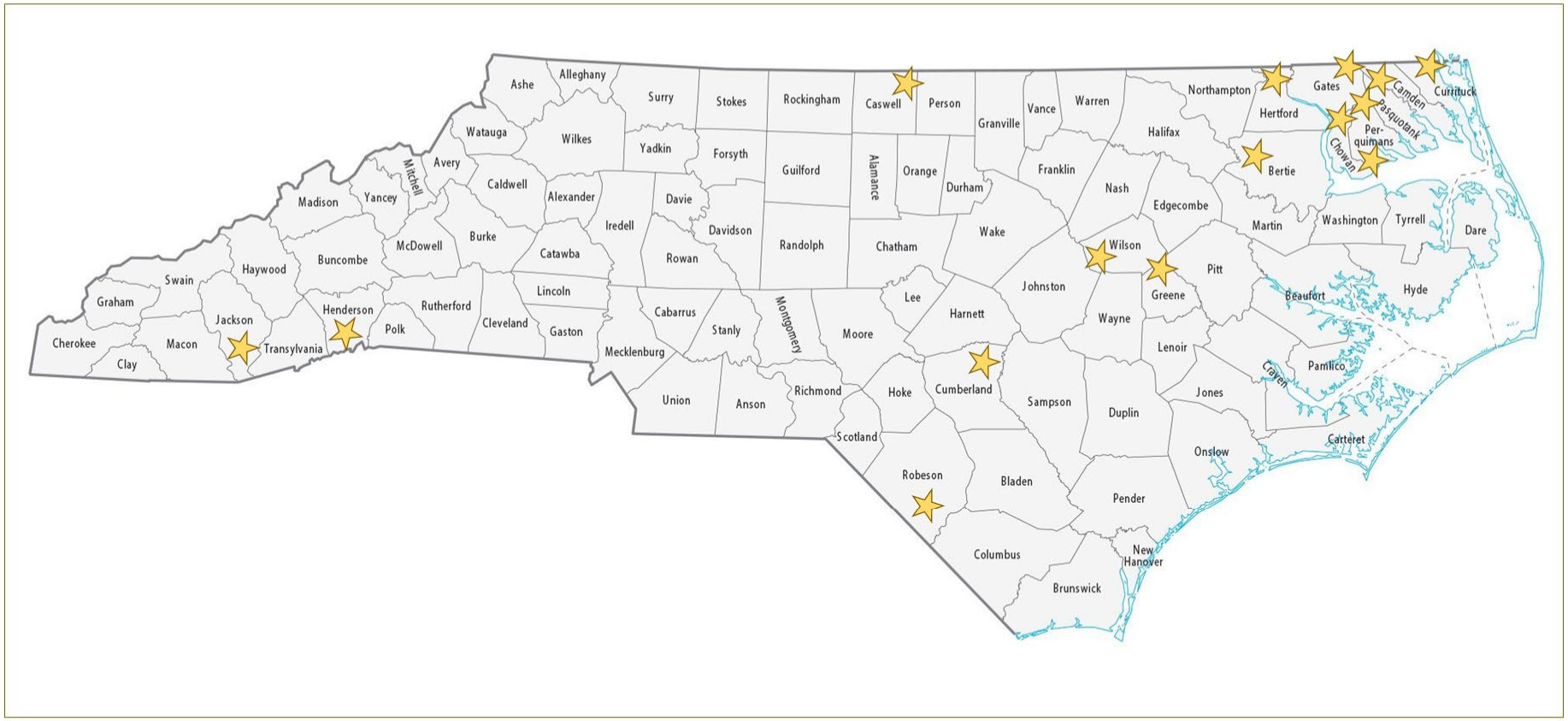
Supporting Tailored And Responsive PrEP in Rural North Carolina – STARR NC

"... support the development of effective strategies for expanding the provision of HIV PrEP for people at increased risk but currently lacking these services by leveraging existing STI programs."

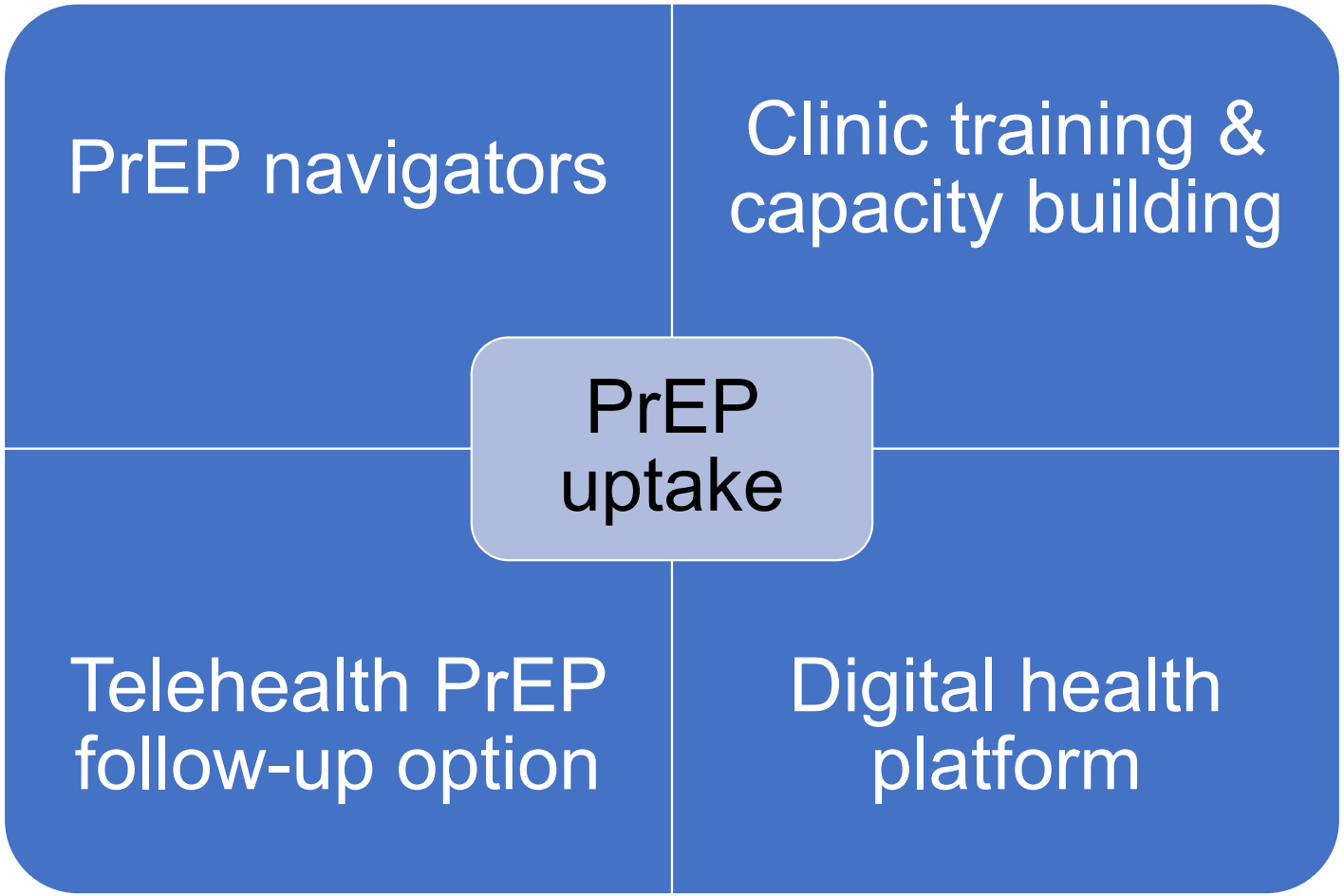
Three-year "formative" (R61) phase

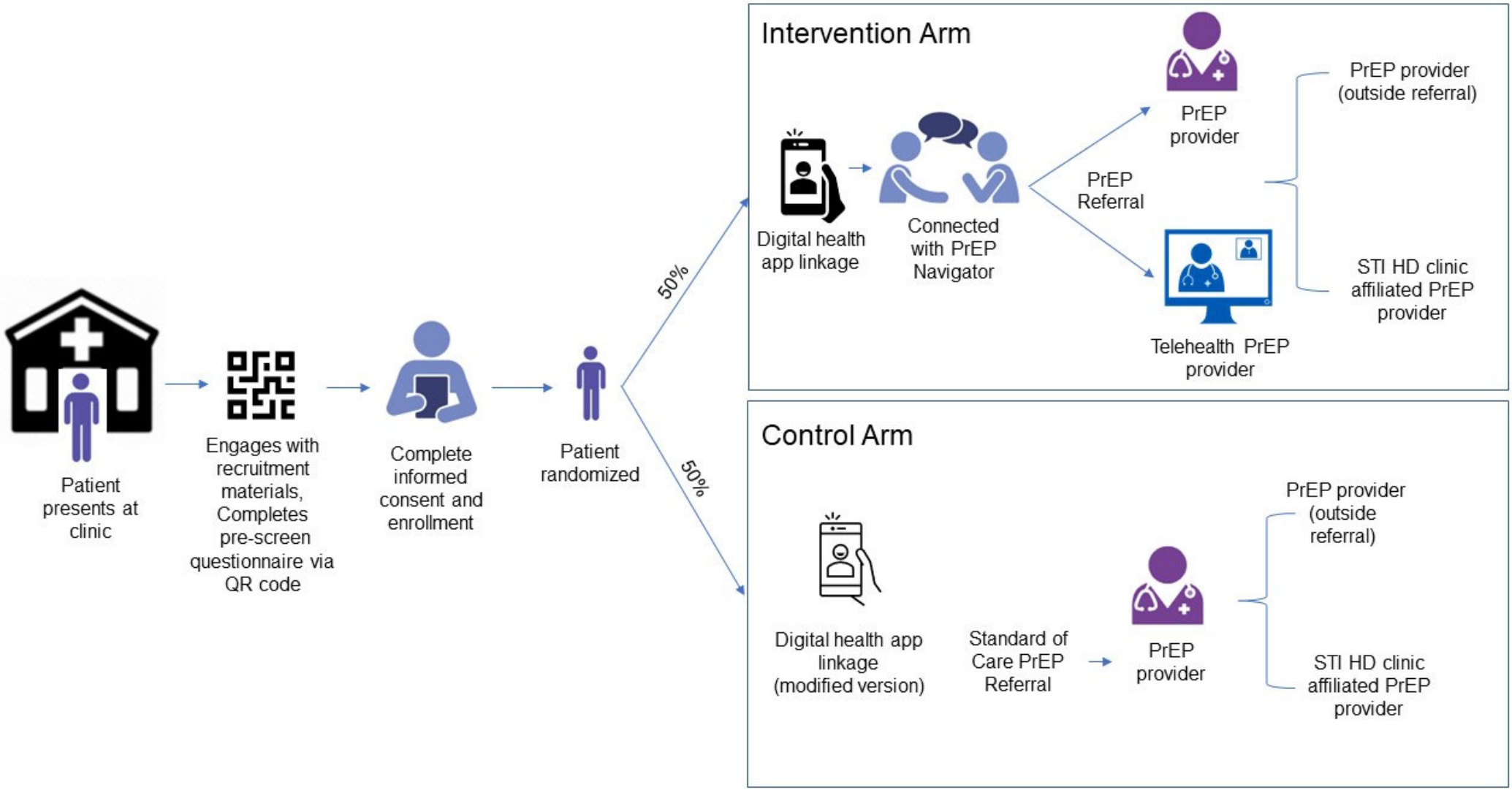
- Randomized clinical trial
- Primary outcome: PrEP uptake within 3 months of STI clinic visit

Additional two-year "implementation trial" (R33) phase based on meeting milestones


Ashe
Alleghany
Surry
Stokes
Rockingham
Caswell
Person
Granville
Vance
Warren
Northampton
Gates
Camden
Currituck
Watauga
Wilkes
Yadkin
Forsyth
Guilford
Alamance
Orange
Durham
Halifax
Hertford
Pasquotank
Perquimans
Chowan
Avery
Mitchell
Caldwell
Alexander
Davie
Davidson
Randolph
Chatham
Wake
Franklin
Nash
Edgecombe
Bertie
Martin
Washington
Tyrrell
Dare
Madison
Yancey
Iredell
Rowan
Wilson
Pitt
Greene
Beaufort
Hyde
Buncombe
McDowell
Burke
Catawba
Swain
Haywood
Graham
Jackson
Henderson
Rutherford
Polk
Cleveland
Lincoln
Gaston
Cabarrus
Stanly
Montgomery
Moore
Lee
Harnett
Johnston
Wayne
Lenoir
Pamlico
Craven
Cherokee
Macon
Clay
Transylvania
Mecklenburg
Union
Anson
Richmond
Hoke
Cumberland
Sampson
Duplin
Jones
Carteret
Onslow
Scotland
Robeson
Bladen
Pender
Columbus
New Hanover
Brunswick

Multilevel intervention




Intervention Arm
Control Arm
Patient presents at clinic
Engages with recruitment materials, Completes pre-screen questionnaire via QR code
Complete informed consent and enrollment
Patient randomized
50%
50%
Digital health app linkage
Connected with PrEP Navigator
PrEP Referral
PrEP provider
Telehealth PrEP provider
PrEP provider (outside referral)
STI HD clinic affiliated PrEP provider
Digital health app linkage (modified version)
Standard of Care PrEP Referral
PrEP provider
PrEP provider (outside referral)
STI HD clinic affiliated PrEP provider

Clinic training & capacity building

On-site trainings to orient staff to PrEP prescribing

NC AETC
University of North Carolina at Chapel Hill
AIDS Training and Education Center

Telehealth option for PrEP

- Facilitated by PrEP navigator
- Convenient, discrete, secure
- Continuity of care beyond study
- Some clinics may opt to offer PrEP providers on-site

Image from: https://www.statnews.com/2020/08/17/telehealth-new-choreography-anywhere-care/

Digital health platform: HealthMpowerment (HMP)

Fig 2: HMP app screenshots

PrEP navigator roles

PrEP navigator

- Identify interest in & barriers to PrEP use
- Assist with insurance enrollment & financial assistance
- Offer link to digital platform
- Offer link to telehealth PrEP provider

Digital platform

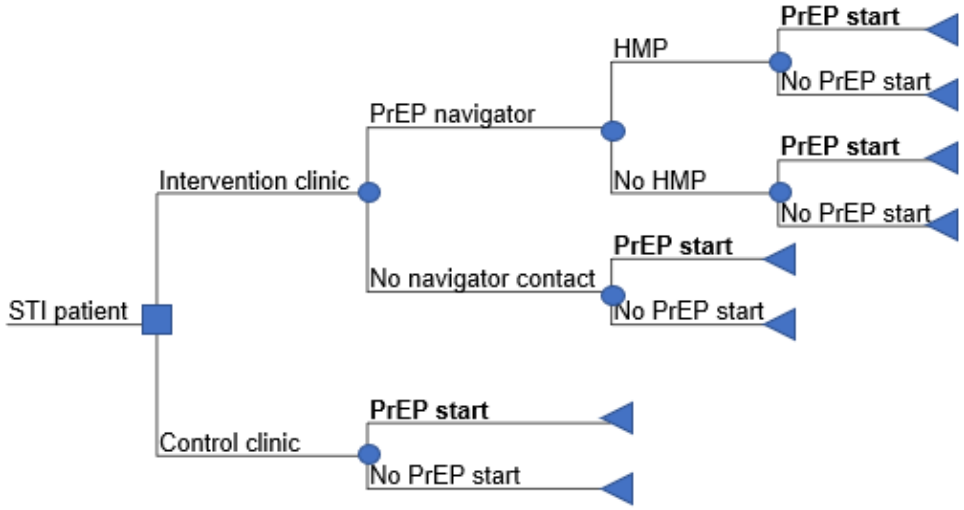
- Provide tailored PrEP resources & counseling, including peer support
- (Re-offer) link to telehealth provider
- Monitor self-reported PrEP use and behavior surveys
- Re-engage person who discontinue PrEP

Telehealth PrEP provider

Sounds great! What'll it cost?

Costing embedded into trial

Decision analysis from health system perspective



Outcomes:

- incremental cost per person started on PrEP
- Budget impact (1- & 3-years)

Implementing HIV prevention services: right place, right time.

Leveraging existing infrastructure and targeting resource-intensive interventions to improve *effective use of PrEP:*

- …in urban public STI clinics in Malawi
- …in rural health department STI clinics in NC

Adapting metrics and outcomes to accommodate fluctuating HIV prevention needs

- …support continuous/protective use while on PrEP
- …and bringing folks back to PrEP when they are at risk

Thank you!

Questions? srutstein@unc.edu