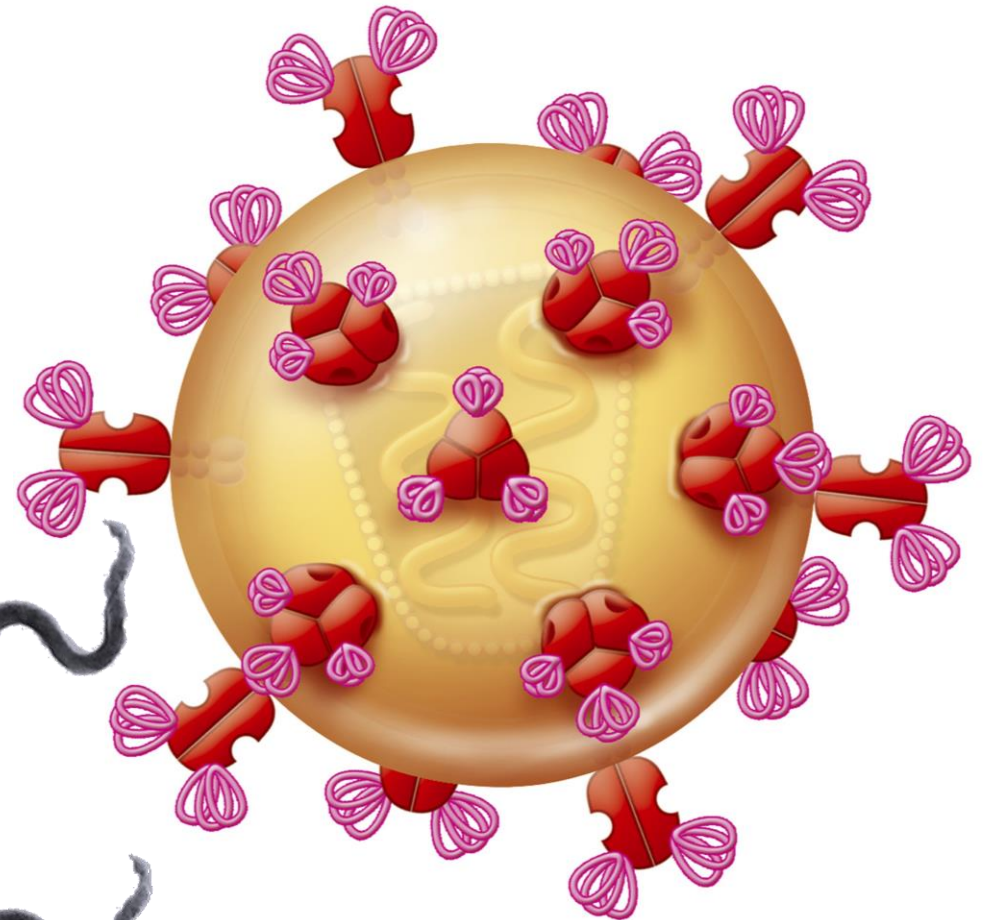


Syndemics:  
intersecting STI and  
HIV epidemics and  
the opportunity to  
improve diagnosis  
and prevention in  
Malawi

Sarah Rutstein

Division of Infectious Diseases



# Outline

Tacking and jibing (aka: how I got here)

Adapting to an evolving epidemic

Syndemics – STIs & HIV

STIs in Malawi – what are we missing?

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Genomics of genital ulcer disease

Integrating HIV prevention and STI services

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Global health is local health



Bailey-Boushay  
House, Seattle  
(2000-2003)

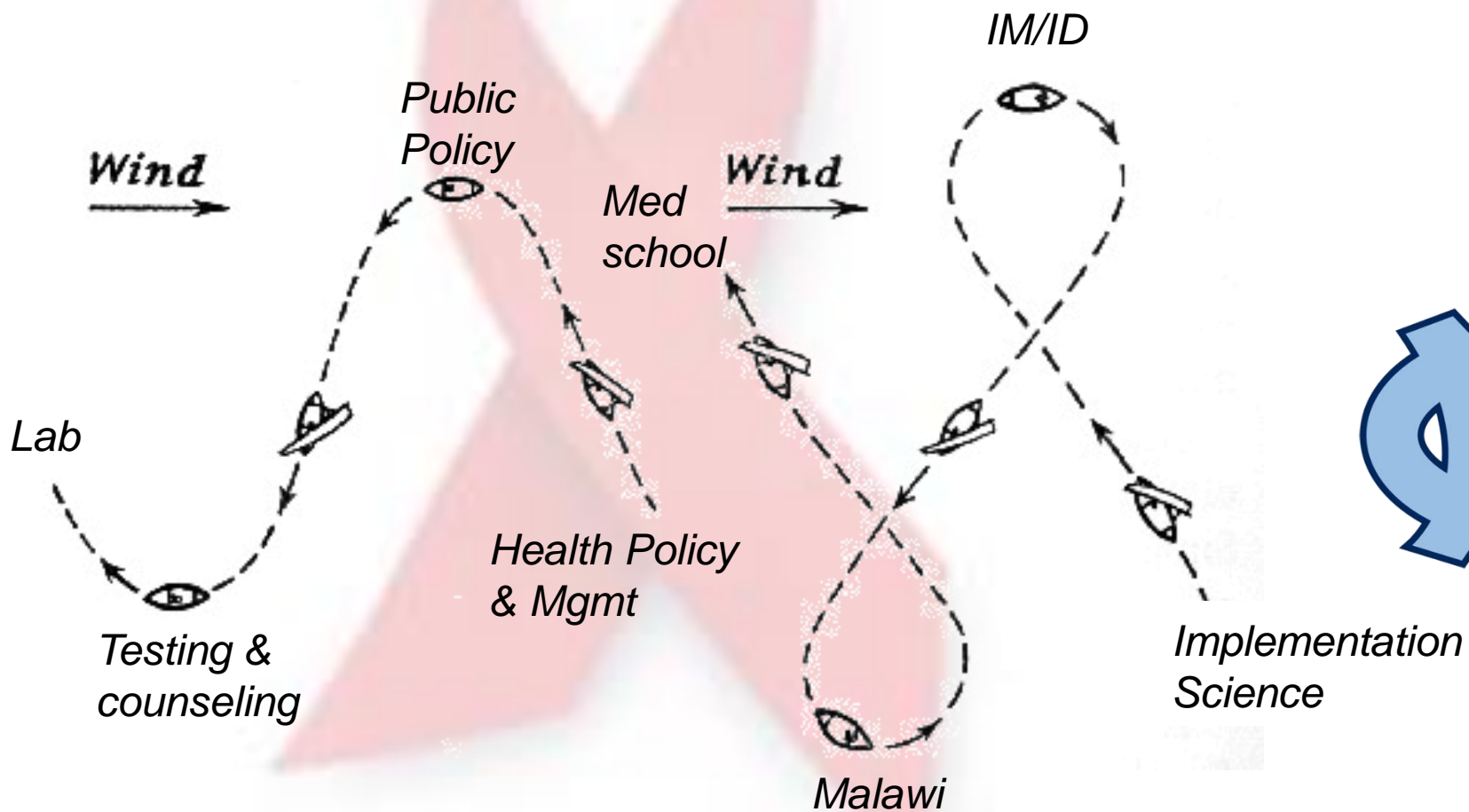




Bailey-Boushay House, Seattle (2000-2003)

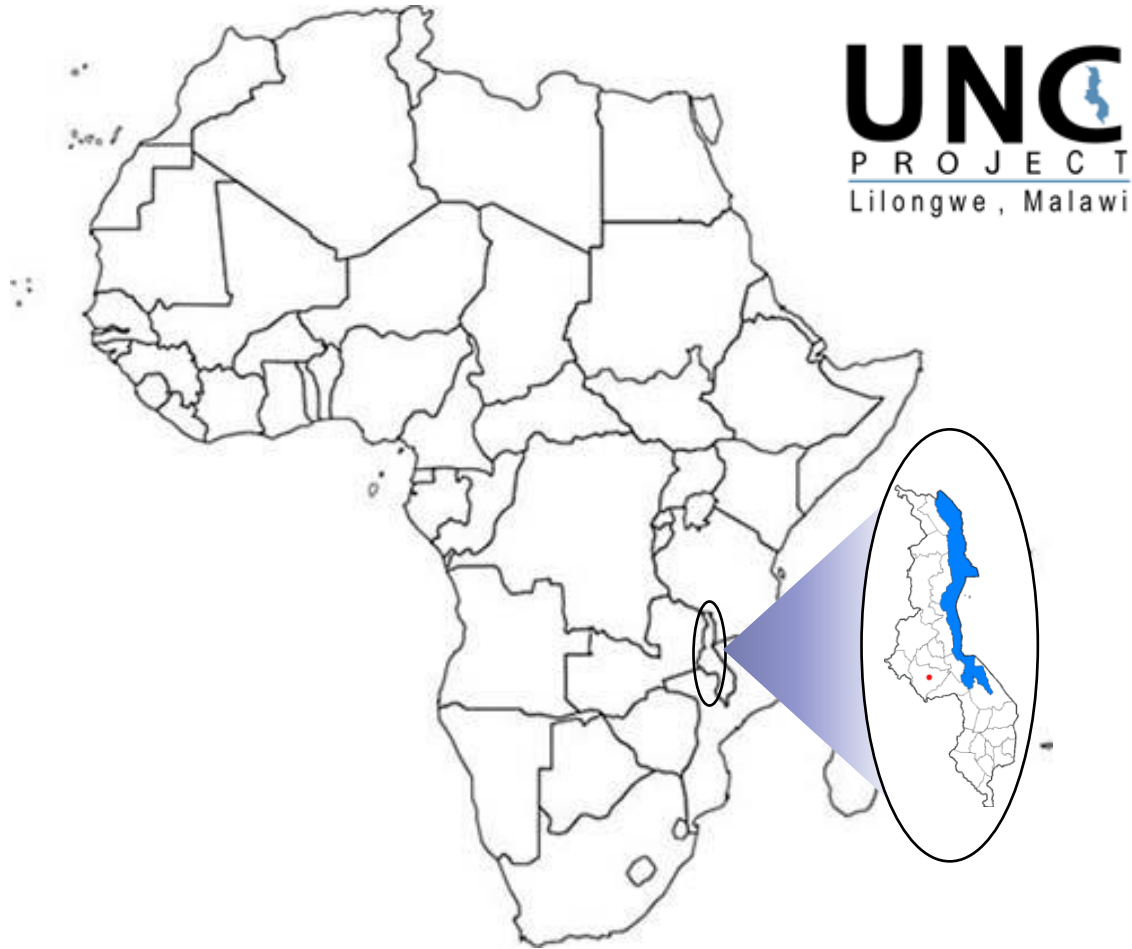


2003-2007

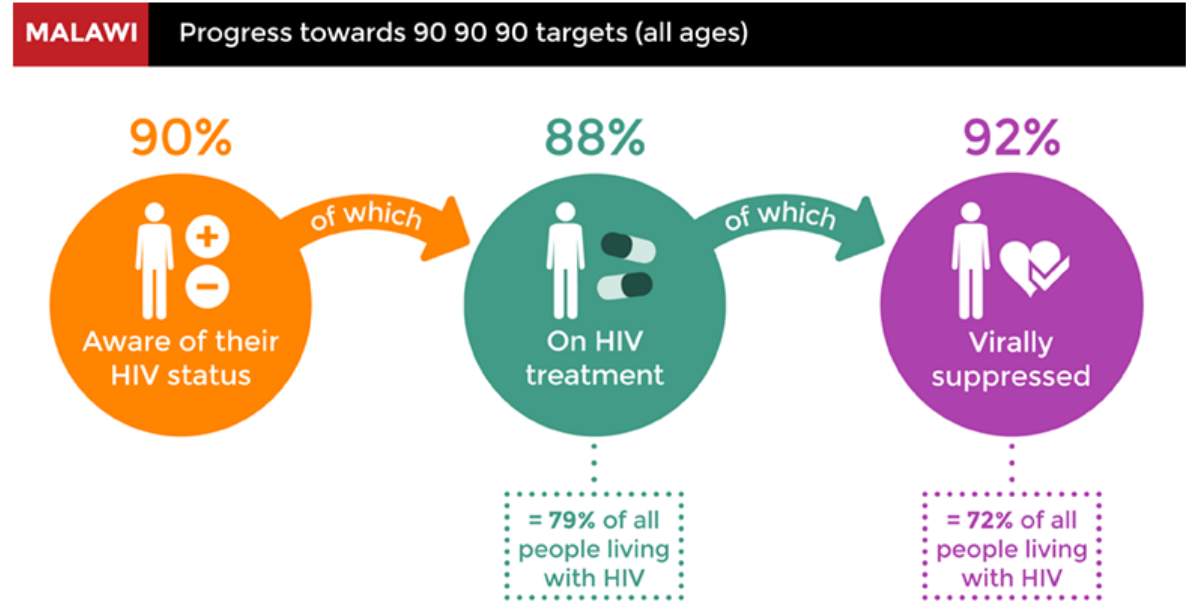
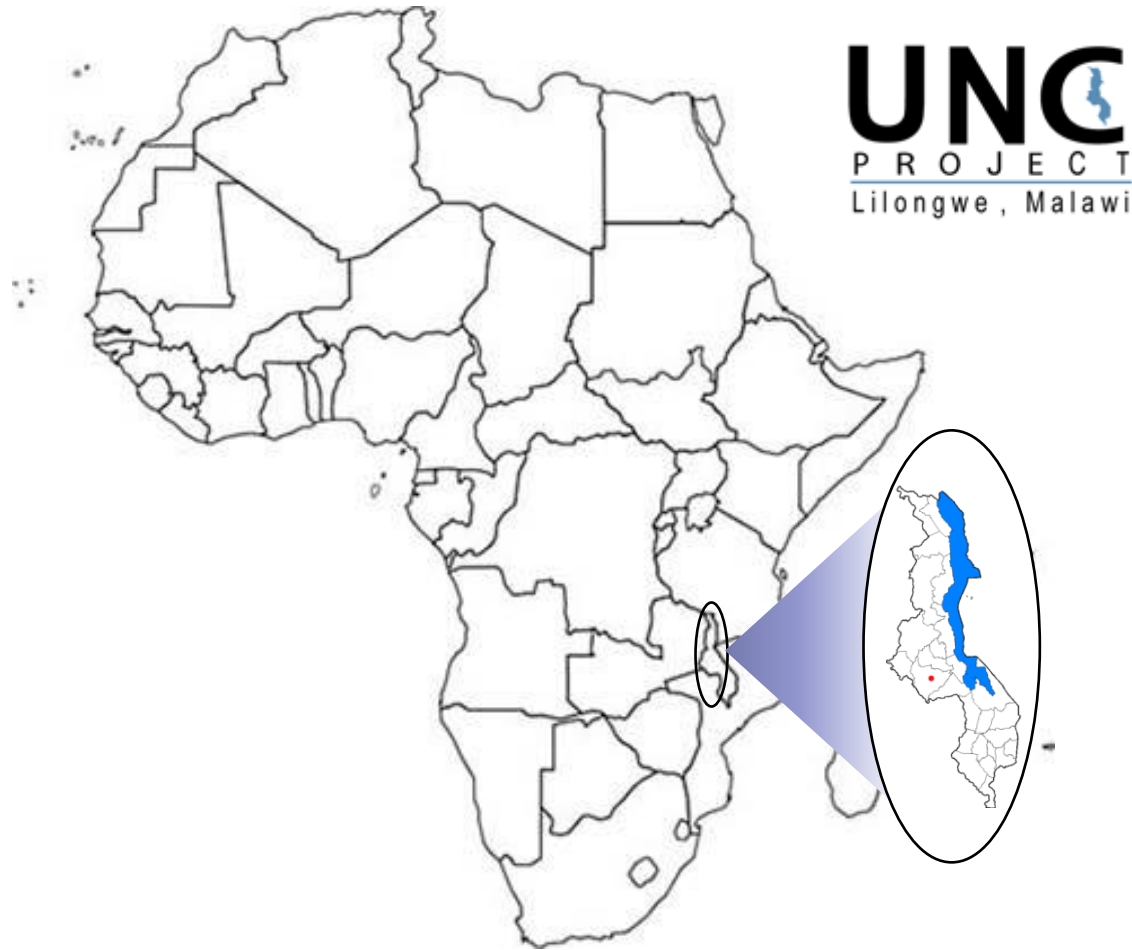


2009 -

# Malawi's HIV epidemic



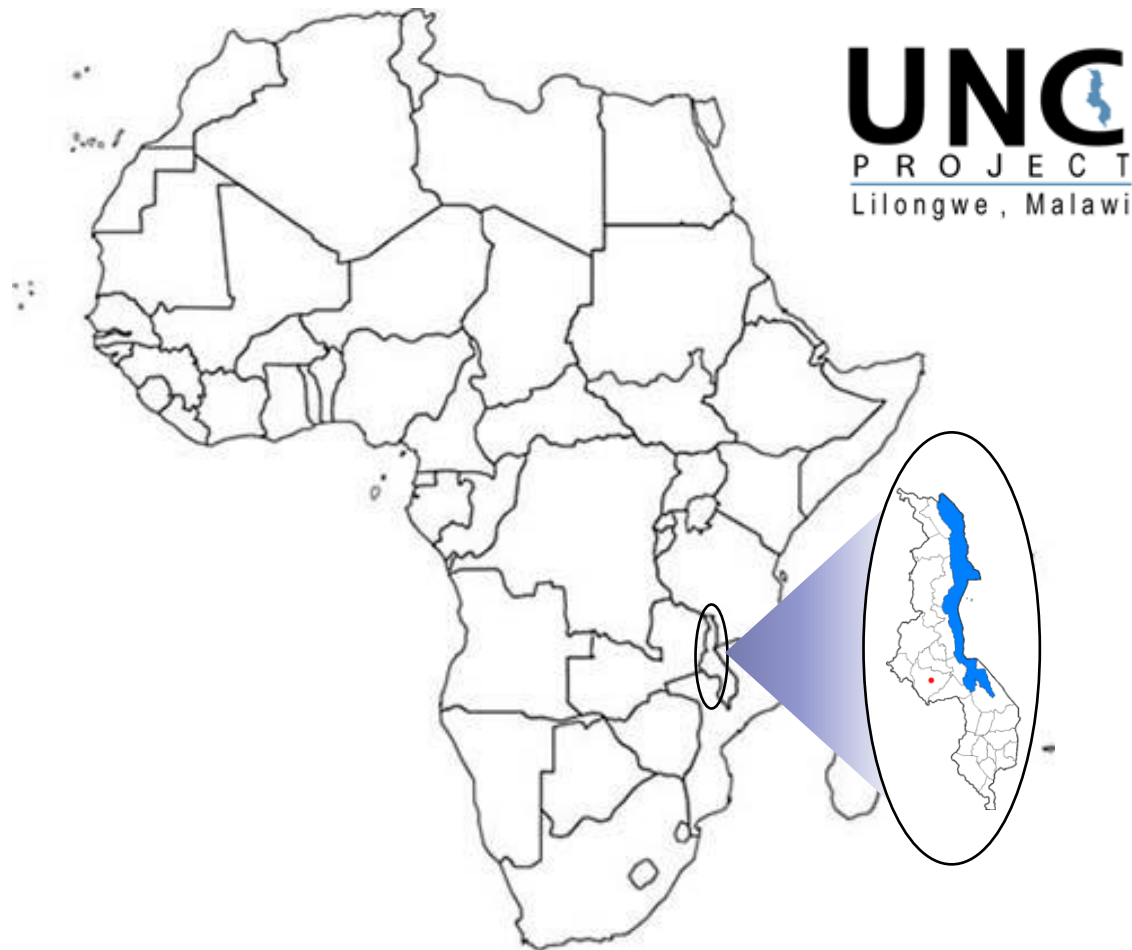
# Malawi's HIV epidemic



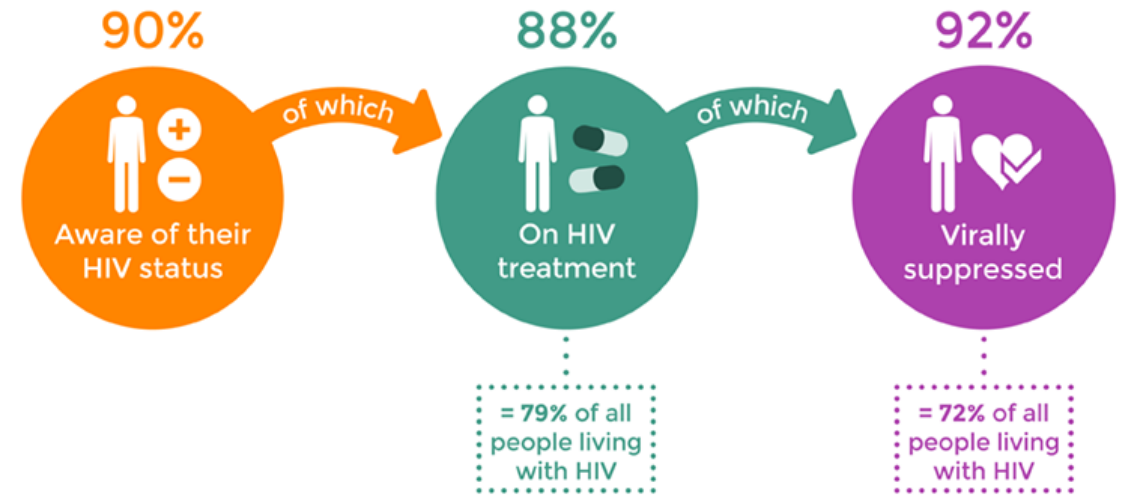
Source: UNAIDS Data 2020



# Malawi's HIV epidemic

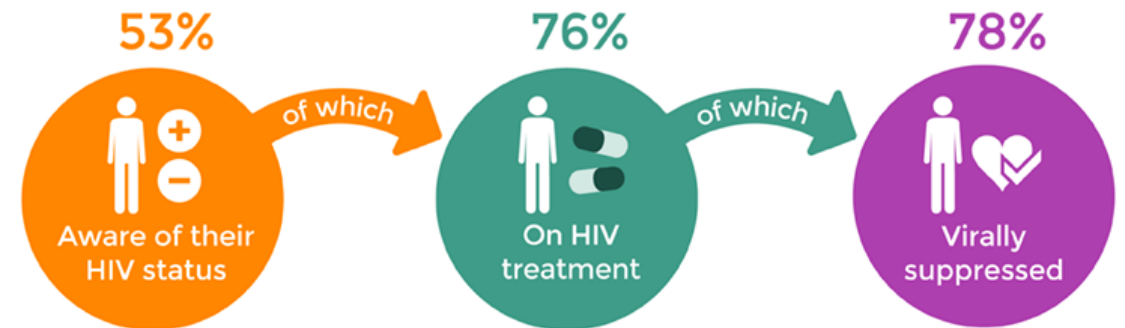


## MALAWI Progress towards 90 90 90 targets (all ages)



Source: UNAIDS Data 2020

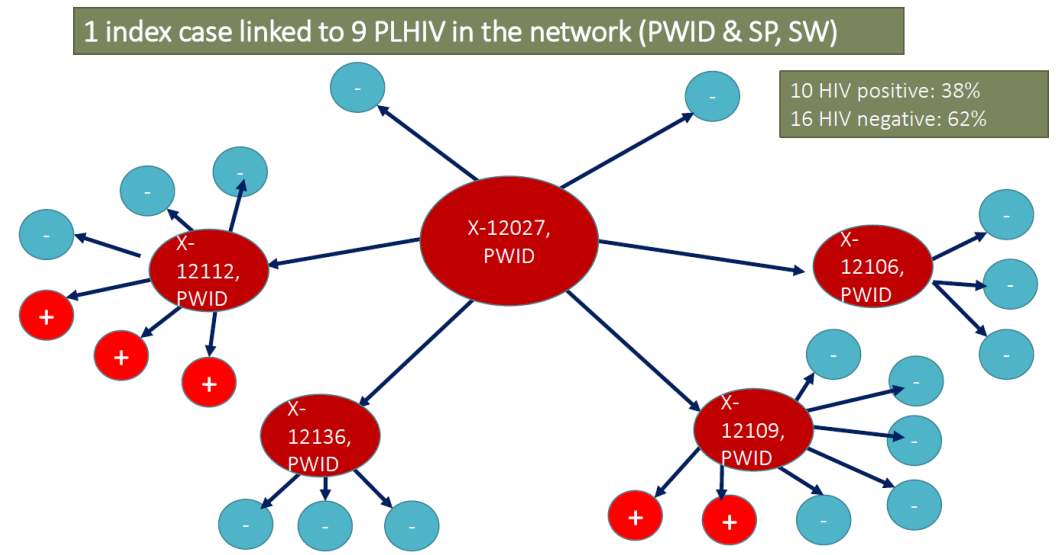
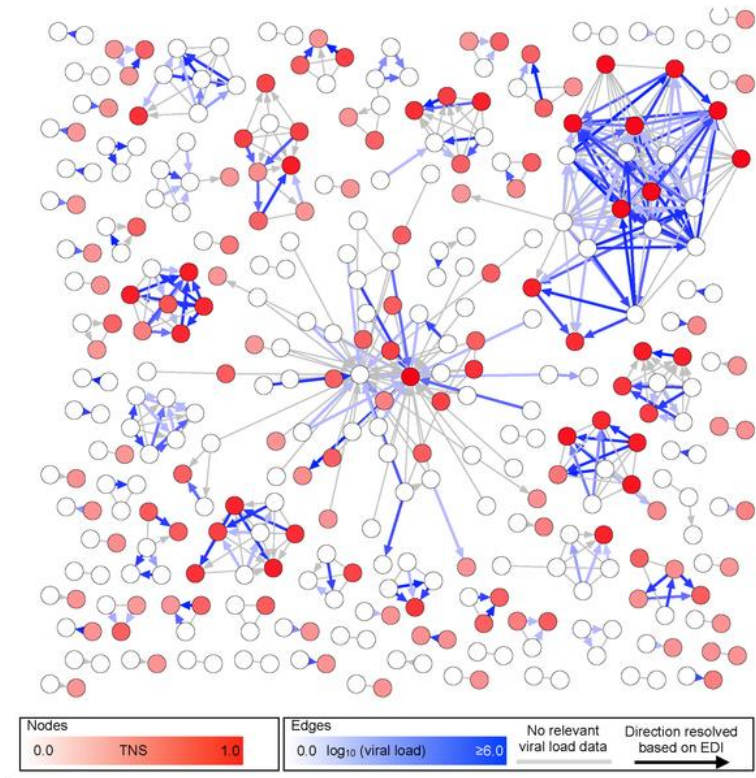
## MALAWI Progress towards 90/90/90 targets among 15-24 year olds for 2020



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

# Finding, testing, and linking the “unaware”

Targeted testing to high-risk social and sexual networks



# Adapting case finding and prevention to local context: what works

Assisted partner notification (APN)

Tracing and offering testing to named sexual partners of newly diagnosed (or persons with high viral loads)

Social network recruitment

Using clinic- (or community-) based “seeds” to recruit persons in their sexual or social networks for HIV testing

Acute HIV infection (AHI) screening

Early and brief phase of infection with high viral loads, disproportionate role in new infections

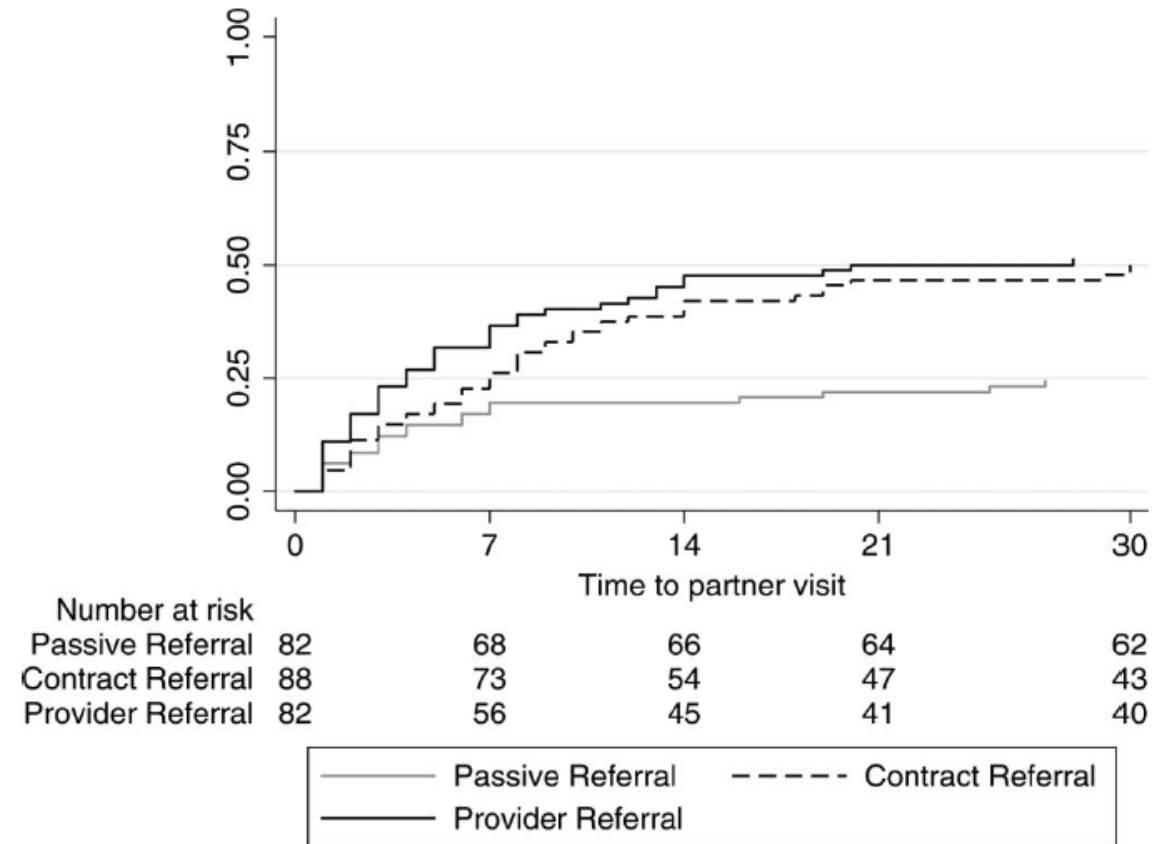
# Provider or contract notification 2x as effective as passive

Enrolled 245 index patients

302 names sexual partners (252 with locator information)

Active notification arms 2x as likely to have returning partners

107 HIV Testing & Counseling  
67/107 (64%) were HIV-infected  
54/67 (81%) newly diagnosed

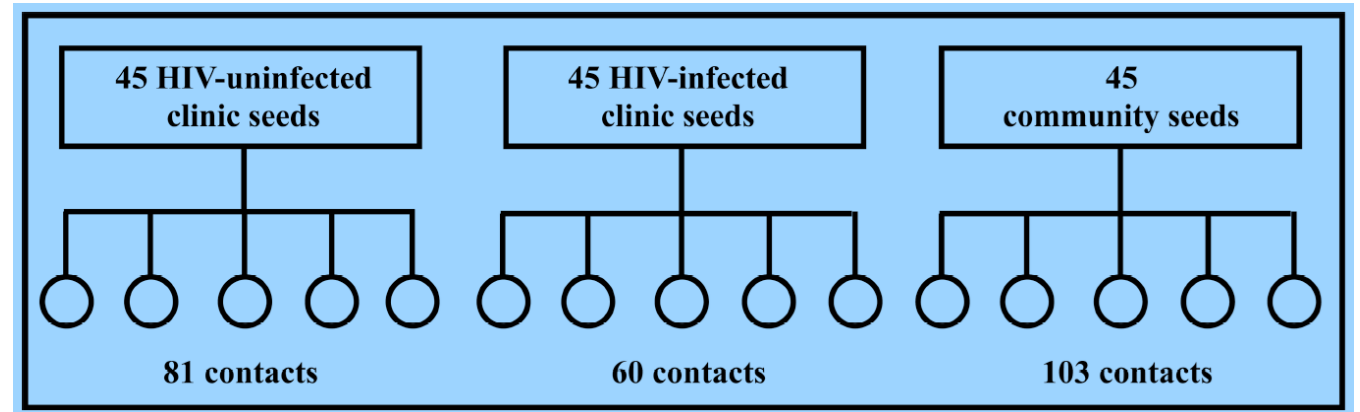


**FIGURE 1.** Shows the cumulative proportion of partners of partners presenting for testing for each method of partner notification. Time to partner visit is the number of days following the index patient enrollment visit.

# Social contacts from STI clinic effective “seeds” for identifying new HIV

Contacts of HIV-infected clinic seeds > HIV prevalence than contacts of community seeds

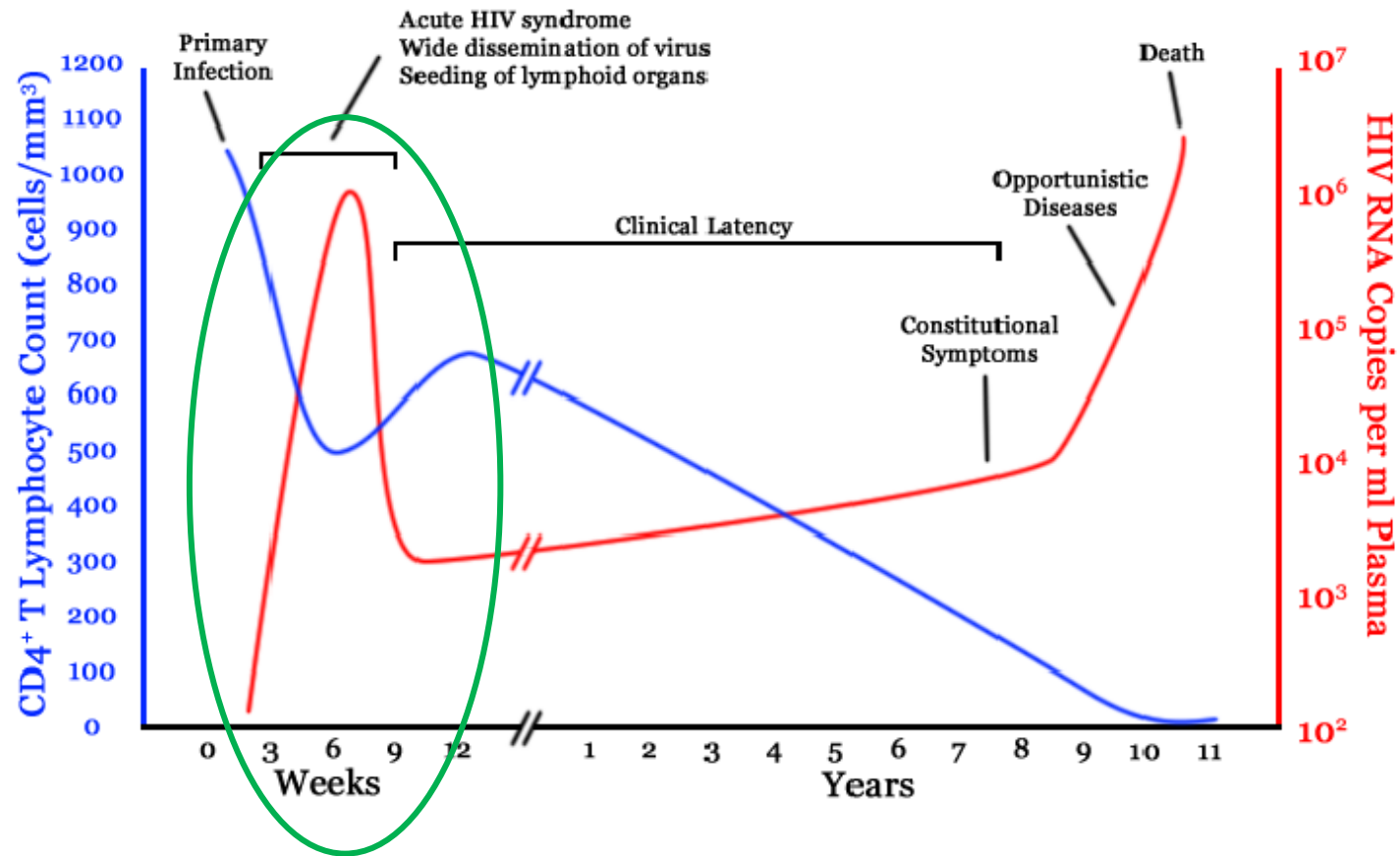
NNT(test): 8-10 clinic seeds



Social contact recruitment in a generalized epidemic among persons with biological evidence of risk – newly diagnosed HIV and/or STI

30% of contacts of persons with AHI had HIV

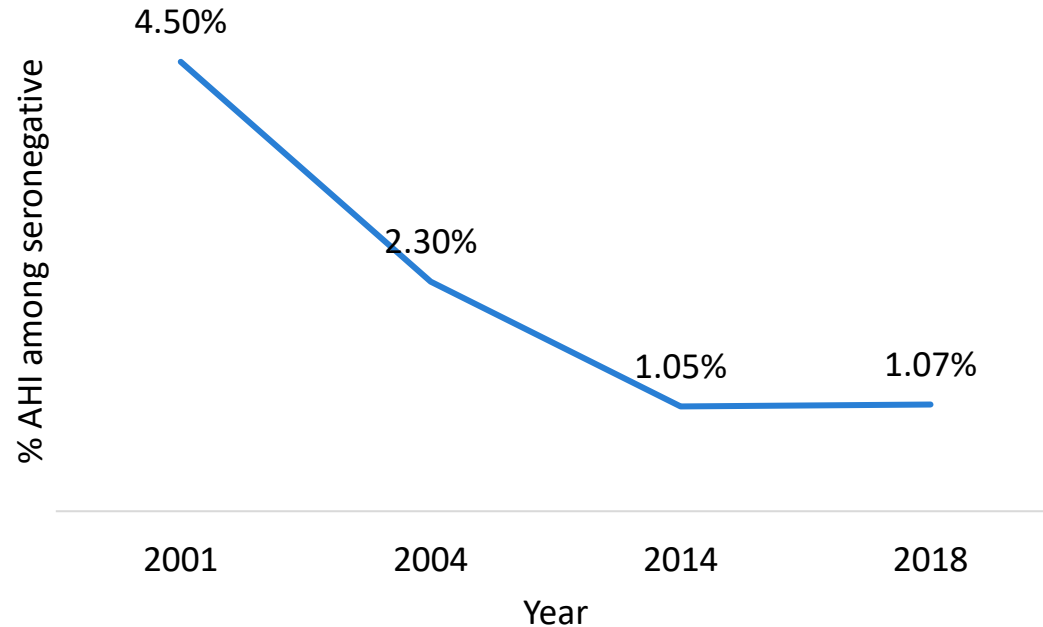
# Acute HIV infection (AHI)



# Frequently detected AHI at STI clinic

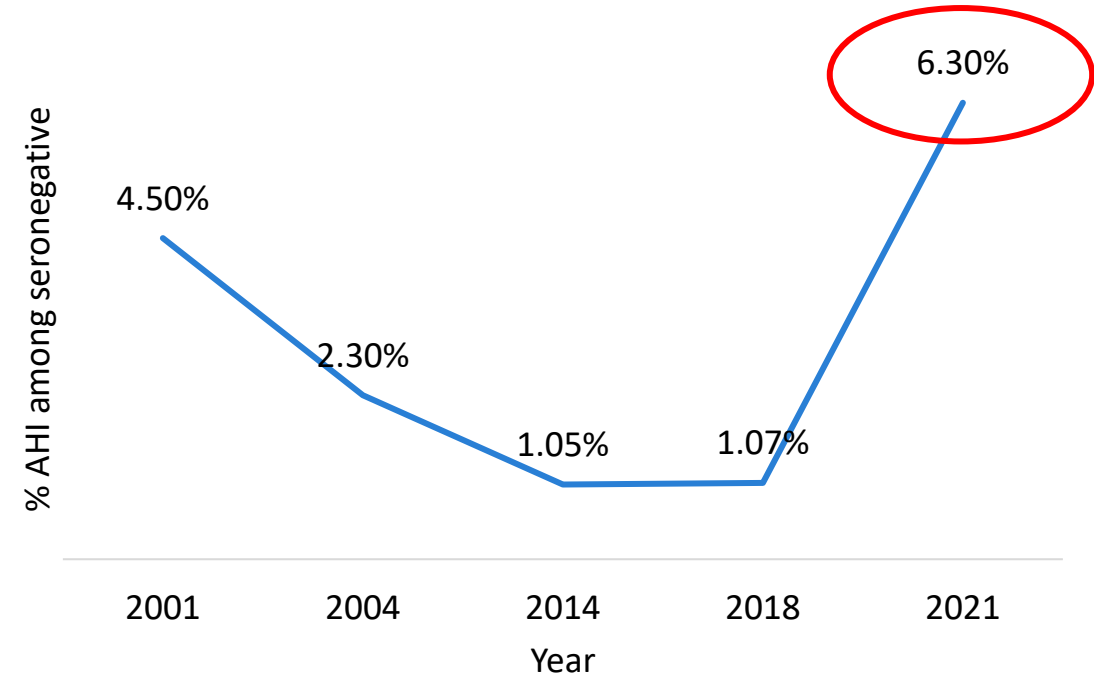
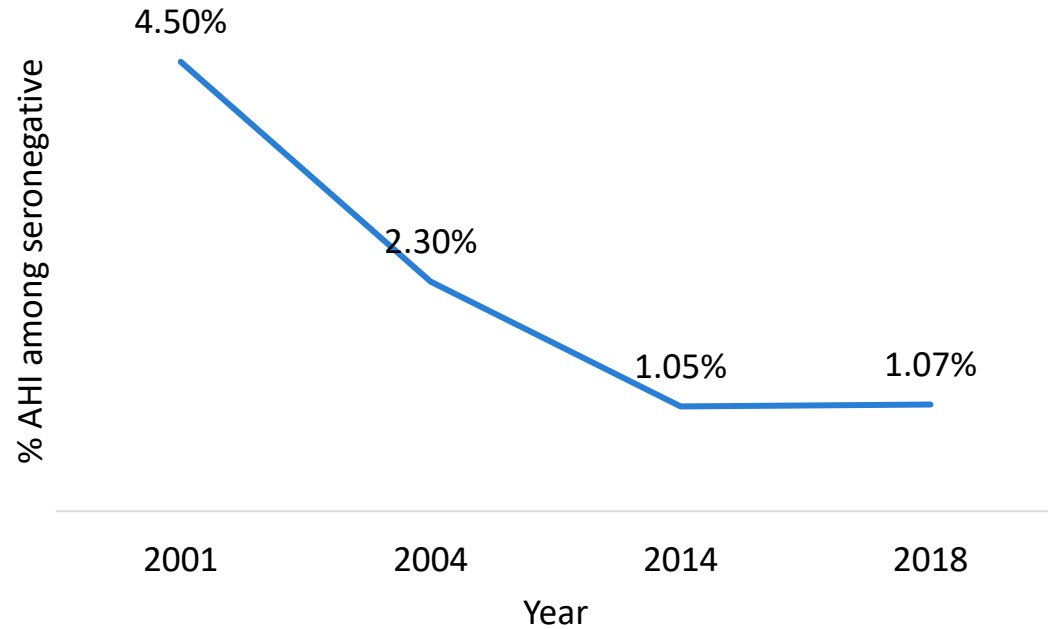


Griffin Bell



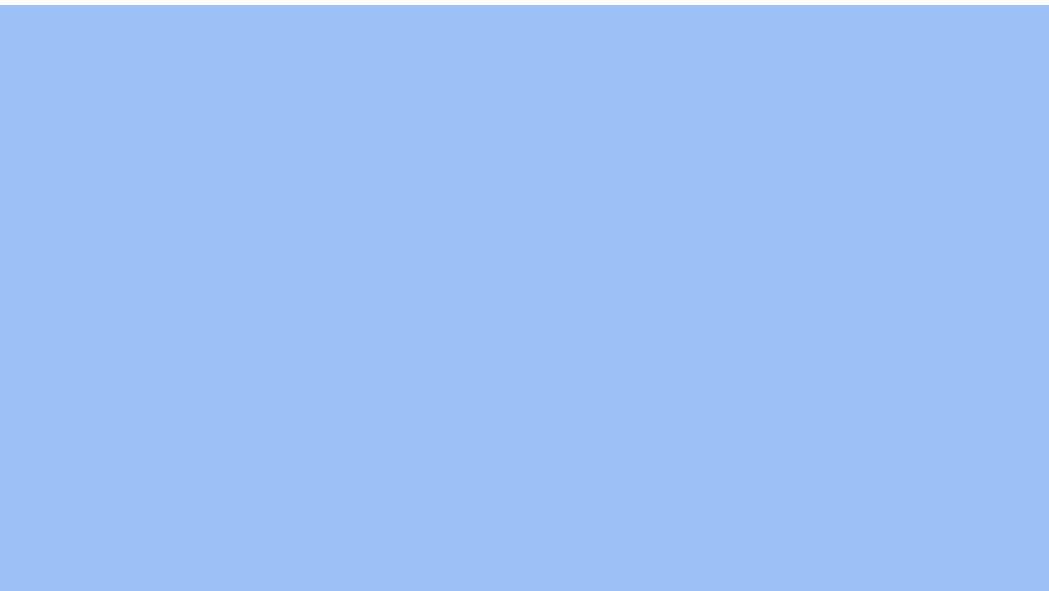
AHI Risk Score:	Points
Discordant rapid antibody tests:	4
Fever, body ache, >1 partner:	1 (each)
Diarrhea, GUD :	2 (each)

# Frequently detected AHI at STI clinic



Highly selected patient population  
(stay tuned)



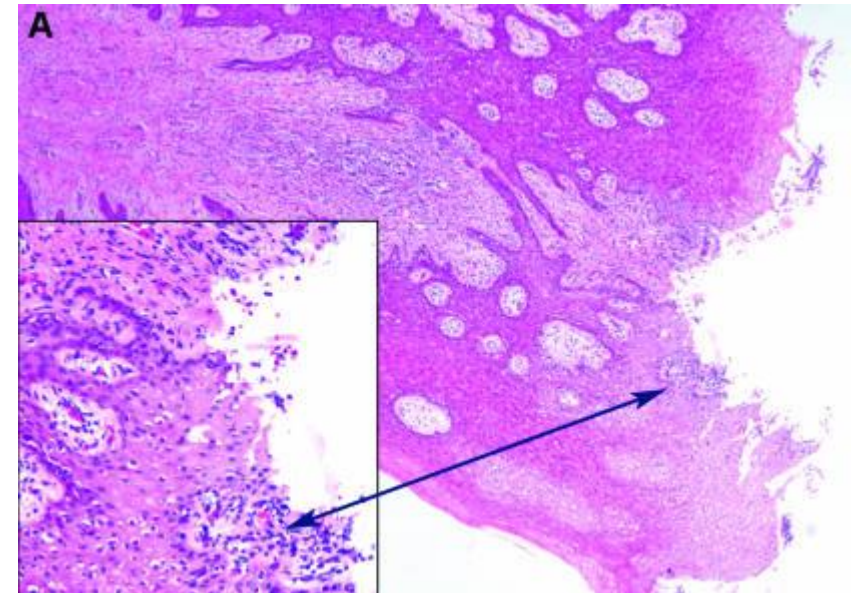


# Syndemic bacterial STI/HIV: stronger together

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



# Epidemiological synergy

...so if we treat STIs, can we control HIV??

Study (author, year)	Intervention	Study design	Primary outcome	Study population (region)	Results
Celum et al 2010	Suppressive acyclovir to	RCT	HIV transmission	Serodiscordant heterosexual, SSA	No effect on HIV transmission <b>73% reduction in genital ulcers</b> due to HSV-2 tx group
Celum et al, 2008	Suppressive acyclovir to reduce HIV-1 acquisition	RCT	HIV acquisition	HIV-negative women and MSM, SSA, Peru, USA	No reduction in HIV-1 acquisition <b>47% decrease in incidence of genital ulcers</b> in tx group
Grosskurth et al, 1995	Establishment of STD reference clinic, staff training,	RCT	HIV/STI incidence	Adults (aged 15-54), Tanzania	- <b>Reduced HIV incidence</b> (RR: 0.58, CI 0.42, 0.79) - STD prevalence consistently lower in intervention group, but not statistically significant - <b>Symptomatic urethritis (men) reduced</b> in intervention vs comparison (RR: 0.49, CI, 0.09, 2.55)
Wawer et al, 1999	Intensive STD control via home-based mass antibiotic treatment	RCT	HIV-1 incidence	Adults in Rakai, Uganda	- no difference in HIV-1 incidence - <b>reduced syphilis</b> (RR: 0.8, CI 0.71, 0.89) and <b>trichomoniasis</b> (RR 0.59, CI 0.38, 0.91) in intervention group
Kamali et al, 2003	Information/education +/- improved management of STIs vs standard	Community-randomized study	HIV-1 incidence	Adults, Uganda	- no difference in HIV incidence - <b>lower HSV2 incidence</b> in intervention - no difference in incidence of chlamydia between groups
Kaul et al, 2004	Monthly antibiotic prophylaxis (azithromycin)	RCT	HIV-1 incidence	Female sex workers, Nairobi, Kenya	- no difference in HIV-1 incidence - <b>reduced incidence of gonorrhea, Chlamydia trachomatis, and Trichomonas vaginalis</b>
Ghys, et al, 2001	Once monthly STD test/ tx or intensive strategy with examination regardless of symptoms	RCT	HIV-1 seroconversion	Female sex workers, Cote d'Ivoire	- no difference in HIV seroconversion, chlamydia, or genital ulcers rate between arms - <b>decrease in N. gonorrhoeae</b> (14 to 5%, p<0.005) and <b>T. vaginalis</b> (24 to 11%, p<0.001)
Gregson et al, 2007	Community-based peer education, condoms, and STI tx and counseling services	Cluster RCT	Feasibility and HIV-1 incidence	Adults, Zimbabwe	- <b>reduced HIV-1 incidence and increased cessation of STI symptoms</b> among males in the intervention communities who attended program meetings
Watson-Jones et al., 2008	Suppressive acyclovir treatment	RCT	HIV incidence	Female sex workers, Tanzania	- no between group difference in HIV-1 incidence or genital ulceration at 1.5 year follow-up

CI: confidence interval; MSM: men who have sex with men; RR: rate ratio; SSA: sub-Saharan Africa; USA: United States of America



# Enter Treatment as Prevention

Research (and research dollars) shifted away from STIs as a strategy for HIV control

ART effectively interrupts transmission even in setting of concomitant STI (despite detectable virus in genital tracts)

Despite 1 million incident *curable* STIs occur worldwide each day, little progress in diagnostics or prevention strategies

# STI burden and diagnosis in Malawi

15% of  
Women

## Sexually transmitted infections (STIs) and symptoms

Respondents who have ever had sex are asked whether they had an STI or symptoms of an STI (a bad-smelling, abnormal discharge from the vagina/penis, a genital sore, or an ulcer) in the 12 months before the survey.

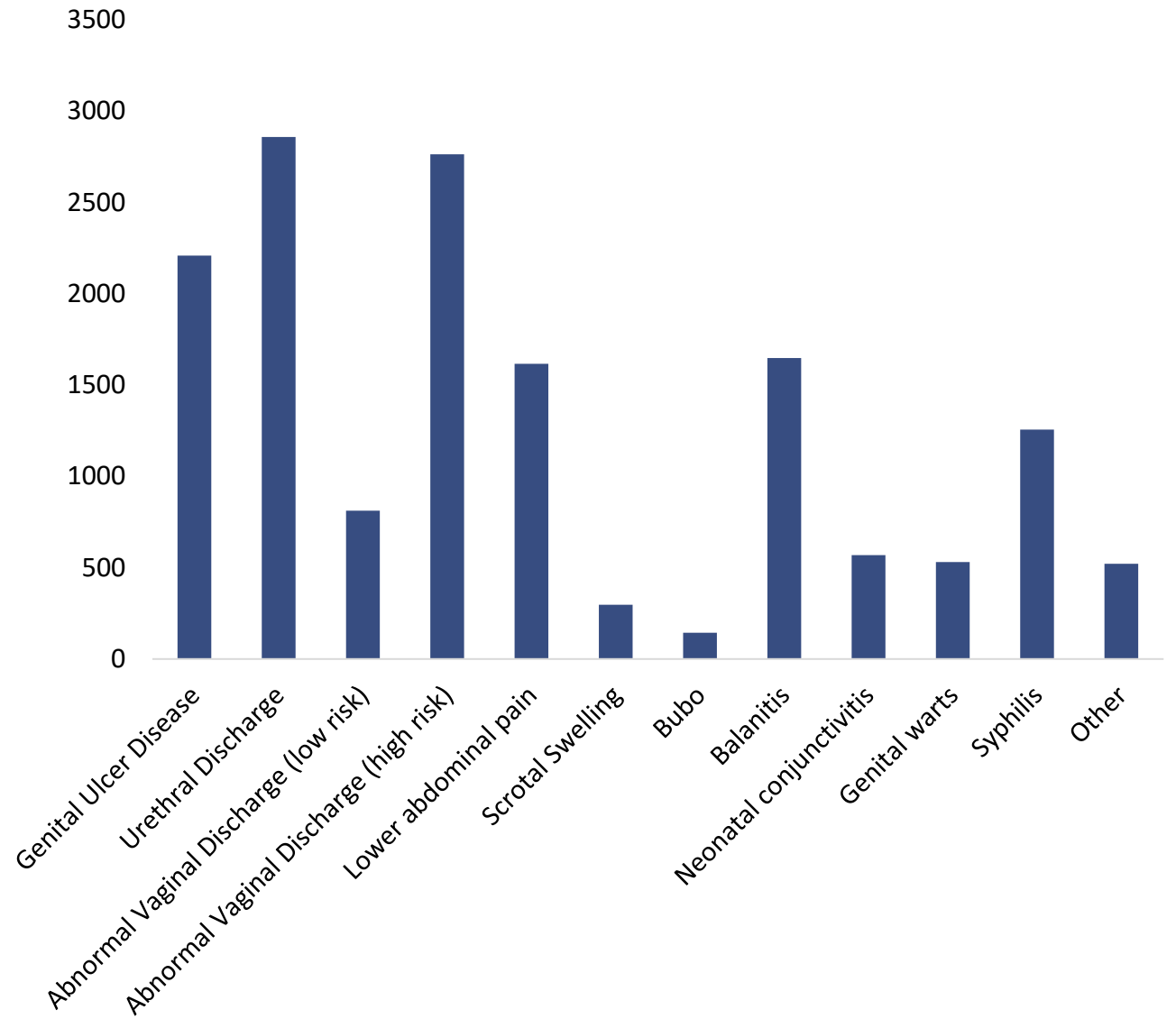
**Sample:** Women and men age 15-49

10% of  
Men

Percentage of women and men age 15-49 reporting an STI or symptoms of an STI in the past 12 months who sought advice or treatment from:



STIs at  
Bwaila clinic  
(2017)  
(n=15,223)



# Syndromic Management

Implemented in early 1990s

Relies on subjective assessment of symptoms



Majority of curable STIs are asymptomatic and thus missed, *particularly among women*

→ implications for fertility, partner tracing/testing/treatment

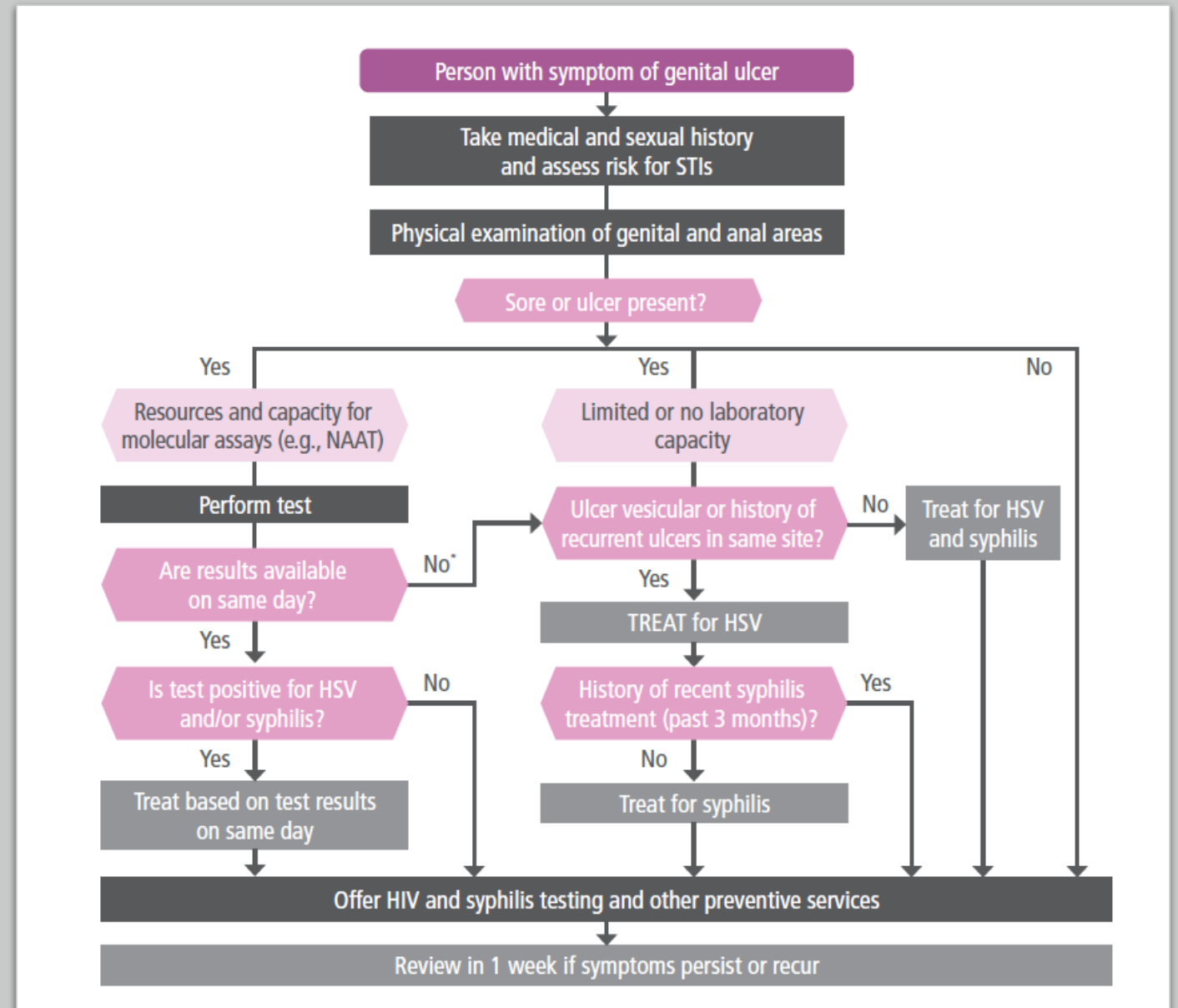
Poor sensitivity (10-20%) as well as high false positive (up to 80% for some syndromes) → under and over treatment

→ antimicrobial resistance



# Syndromic Management: an update

Revised (June 2021) WHO guidelines recommend management using quality-assured molecular assays, if available



# Genomics of genital ulcer disease (G-GUD)

UNC CFAR-funded Development Award (2020)

Known enhanced risk of HIV transmission and acquisition

Most diagnosed as syphilis, herpes simplex virus, chancroid, lymphogranuloma venereum (LGV), or granuloma inguinale BUT nearly 1/3 have no identifiable infectious etiology

*Understanding of etiology and epidemiology outdated and incomplete*

# G-GUD: study design

Prospective observational cohort study

Consecutively enrolled persons  $\geq 18$  with moist, non-healing ulcer

Excluded persons with recent (30d) antibiotic use

Stratified by HIV sero-status and sex

Collected swab (ulcer and unaffected skin) and blood at baseline  
and then swabbed non-healing ulcers at 2-week follow-up

**Main Objective:** To examine the infectious etiology and clinical outcomes of GUD, as well as contemporaneous sexual risk behaviors, among persons with HIV (acute, recent, or chronic) or persons at high risk for HIV-infection in Malawi.

# G-GUD preliminary results: HIV

Enrolled 50 adults (31 males, 19 females)

18 HIV-seropositive (11 previously known positive, 7 new)

32 HIV-seronegative

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Enrolled 50 adults (31 males, 19 females)

18 HIV-seropositive (11 previously known positive, 7 new)

32 HIV-seronegative

2 with acute HIV → 2/32 (6.3%) of seronegative patients

# G-GUD preliminary results: demographics

	HIV +, n (%)	HIV-*, n (%)
Age (median, IQR)	26.5 (22.5, 32)	26.5 (24, 41)
Marital status		
Never married	0	8 (25)
Married	13 (72)	18 (56)
Separated/divorced	4 (22)	6 (19)
Widowed	1 (6)	0
Education		
None	4 (22)	6 (19)
Primary (some or all)	8 (45)	20 (62)
Secondary (some or all)	6 (33)	6 (19)
Electricity at home (yes)	5 (28)	10 (31)
Travel in past 30 days**	2 (11)	2 (6)

\*includes persons with AHI

\*\* 2 HIV+ persons reported traveling to southern Malawi, and 2 HIV- reported traveling to northern Malawi

# G-GUD preliminary results: sexual behaviors

	HIV +, n (%)	HIV-*, n (%)
Contraception (asked of female participants)		
None	4 (44)	3 (33)
Implant	2 (22)	5 (56)
Injection/IUD/condom	3 (33)	0
On ART (among previous positives)	10 (90)	
Partners in past week (mean)	1.1	0.65
Partners in past month	3	5.3
Condom at last sex (yes)	3 (17)	2 (6)
Alcohol or drug use before last sex (yes)	6 (33)	6 (19)
Sexual partner with sore or blister in past month	8 (50)	8 (28)
Known HIV-infected partner in past month	7 (44)	2 (7)
Days of ulcer symptoms (median, IQR)	7 (7,14)	12 (7, 21)
Had sex since noticed ulcer	7 (39)	12 (38)
Ever exchanged sex for goods or money (yes)	12 (67)	15 (47)
History of similar ulcers	2 (11)	2 (6)

# G-GUD preliminary results: 2-week follow-up

45/50 retained for 2-week follow-up

Most (59%) did not have any partners in intervening weeks

16 (36%) had 1 partner, 1 (2%) had 3 partners, and 1 (2%) had 10

13 (29%) reported symptoms were improving

31 (71%) reported symptoms had resolved

2 (5%) reported new ulcers since enrollment visit



# G-GUD next steps

Serology: HSV, syphilis (RPR → titer, TPPA),

PCRs (genital swabs): herpes simplex virus-type 2, *Haemophilus ducreyi*, *Chlamydia trachomatis*, *T. pallidum*, *Schistosoma*, *T. vaginalis*, and other bacteria associated with GUD

Genomic analyses: 16S and ITS sequencing using DNA extraction

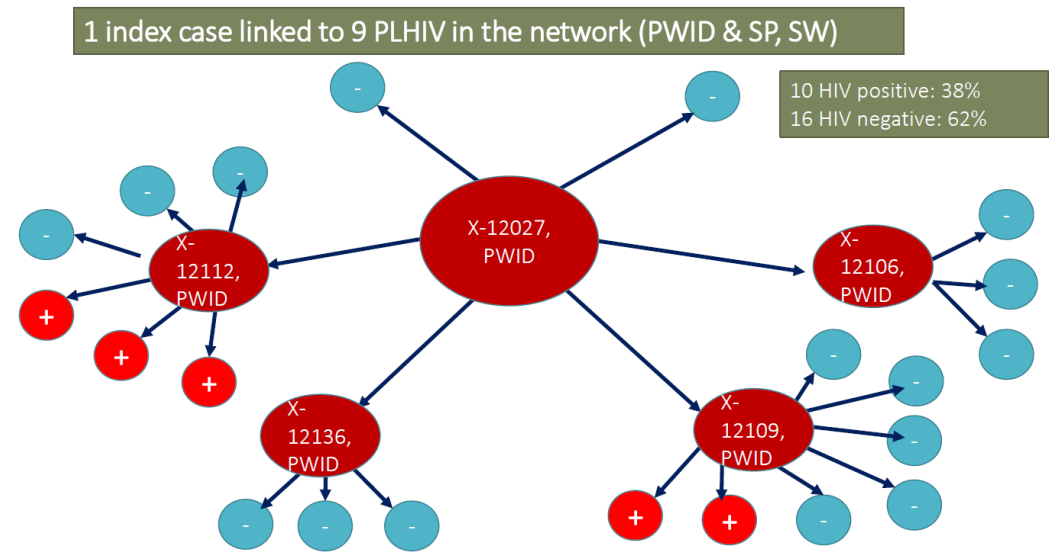
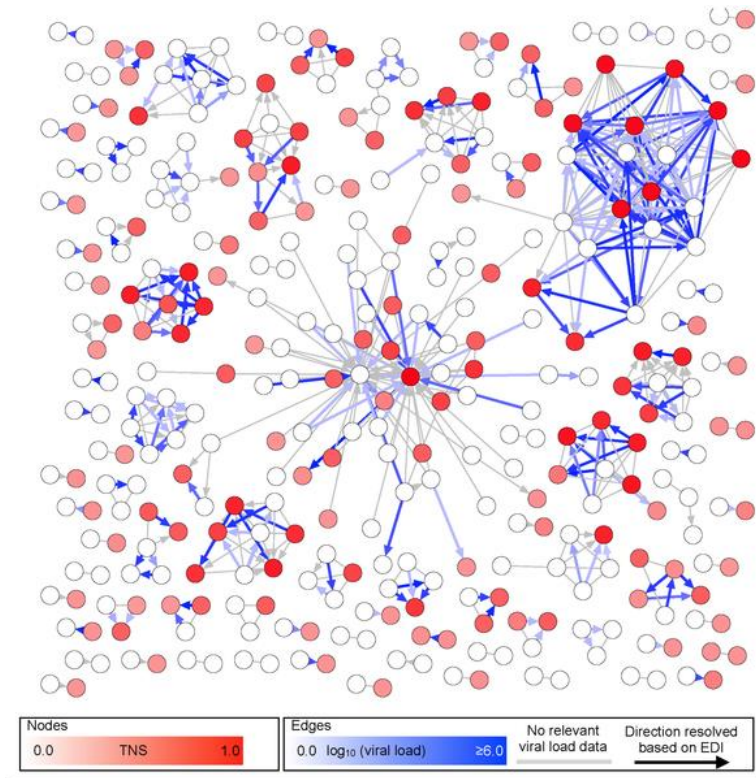
Photo examination

STIs & HIV →  
not just *what*  
we are missing  
but *who* we are  
missing

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# Finding, testing, and linking the “unaware” ... to HIV prevention



# Integrating services: one-stop-shops

## We know:

STI services are a good place to screen for AHI

People who seek STI services, even if HIV negative, may also have high-risk sexual partners (at risk for or infected with HIV)

## We don't know:

How best to integrate PrEP into STI care

Whether using APN effectively identifies other HIV-negative persons who could benefit from PrEP

# Logical extension of STI services - PrEP

Daily oral PrEP reduces HIV acquisition risk by >90%\*

Current PrEP screening uses epidemiologic/self-reported risk profiling

Incident STIs are an objective marker of unprotected sex and in high HIV prevalence settings like Malawi, a reasonable proxy for HIV risk

\*if taken consistently

# Logical extension of STI services - PrEP

Incorporating PrEP with STI care an efficient leveraging of existing infrastructure

High rates of incident STIs on PrEP (>30%), often asymptomatic, reinforces importance of etiologic STI testing + PrEP care...and may motivate retention?

Increasing evidence that incidence of “classical” STIs increases (even after controlling for testing frequency) after PrEP initiation

APN may bolster PrEP recruitment to high-risk persons not accessing STI services

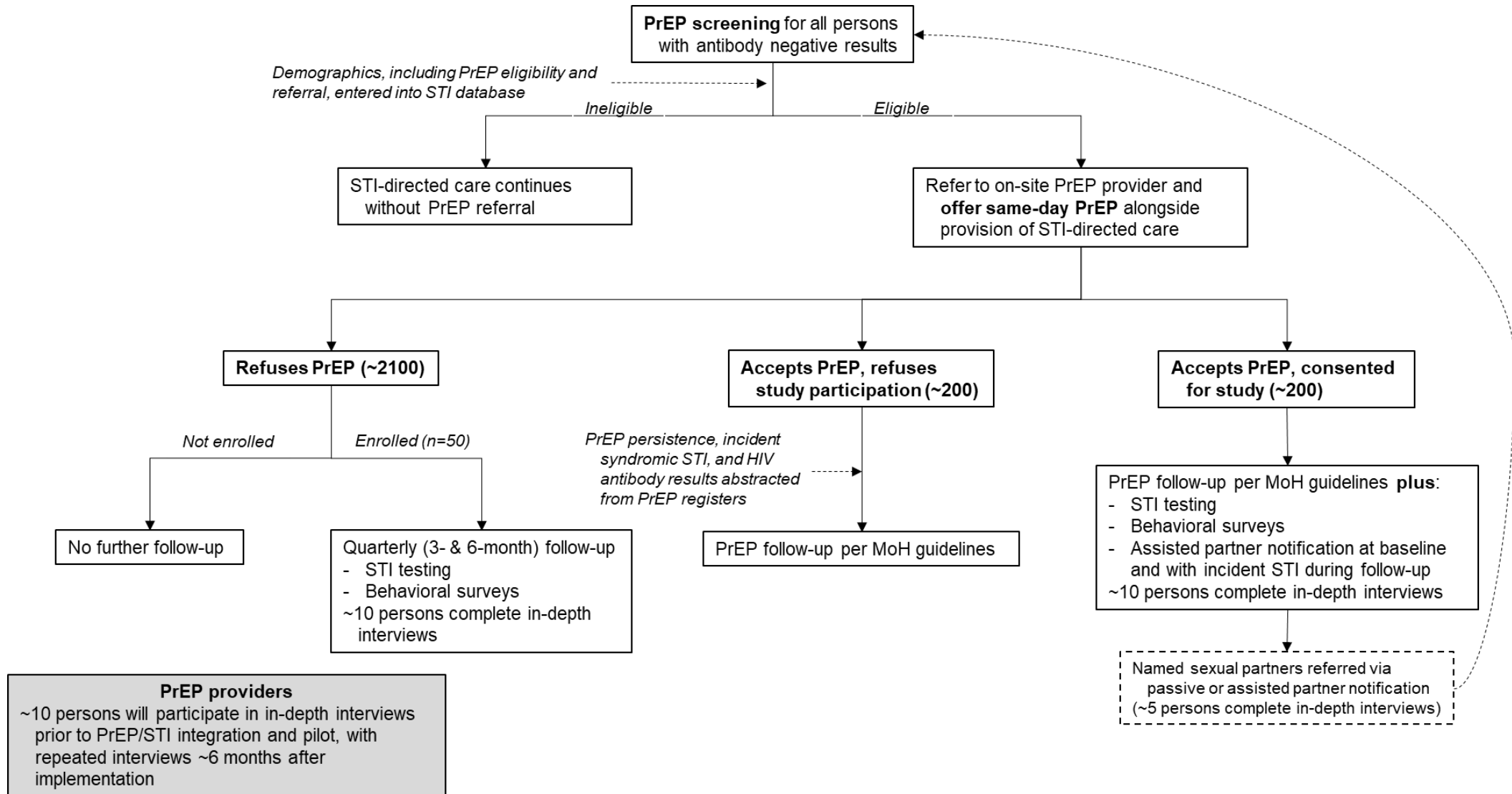
# Enhanced Integrated PrEP: a pilot

Funded through Physician Science Training Program (PSTP), DoM

Pilot study enrolling PrEP users from Lilongwe-STI clinic and using APN to identify/recruit PrEP-eligible partners and etiologic STI testing, regardless of symptoms

**Primary objective:** To examine the feasibility, acceptability, and effectiveness (PrEP uptake and persistence) of integrating an enhanced PrEP implementation strategy into an STI clinic (Bwaila STI) in Lilongwe, Malawi.

# Enhanced Integrated PrEP: study design





# Enhanced Integrated PrEP: study population

**1) Potential PrEP users (including index and named sexual partners)**

**2) PrEP providers**

*STI clinic patient (“potential PrEP user”):*

- i. ≥15 years of age.
- ii. Eligible for PrEP according to Malawi PrEP guidelines
- iii. Presenting for care at STI clinic (primary presentation or referral from partner based on STI or HIV exposure)
- iv. Able to consent for study participation and willing to provide locator information for follow-up tracing

*PrEP provider:*

- i. ≥18 years of age.
- ii. Duties relevant to integration or provision of PrEP and/or aPN at STI clinic

## Schedule of Events

Evaluation	Baseline	Month		
		1	3	6
PrEP eligibility screen	X			
Rapid HIV antibody tests	X	X	X	X
Syndromic STI assessment <sup>1</sup>	X	X	X	X
PrEP risk assessment, adherence assessment and counseling	X	X	X	X
Behavioral survey	X	X	X	X
HIV RNA testing	X			
STI testing (urine/blood) <sup>2</sup>	X		X	X
Sexual partner elicitation <sup>3</sup>	X	X	X	X
In-depth interviews <sup>4</sup>	X			

<sup>1</sup>if indicated based on clinical symptoms; <sup>2</sup> *Neisseria gonorrhoea* and *Chlamydia trachomatis* via GeneXpert, syphilis (RPR), Hepatitis B at baseline only, if symptoms detected/reported at 1-month or interim study visit, participants may have etiologic testing completed; <sup>3</sup> at baseline (all) and then if incident STI detected; <sup>4</sup> In-depth interviews with PrEP users  
PrEP: pre-exposure prophylaxis; RPR: rapid plasma reagin; STI: sexually transmitted infection

# Outcomes

- 1) *Feasibility and acceptability of integrating enhanced PrEP delivery into existing STI clinic services among PrEP users and providers.*
  - Number and proportion of STI clinic patients eligible for PrEP
  - Number and proportion of potentially eligible PrEP users referred for PrEP
  - Acceptability and feasibility assessed using modified validated measures among PrEP providers
  - In-depth interviews will further contextualize survey responses, referral rates, and patient uptake, identifying potential barriers and facilitators to integration of enhanced PrEP within STI clinics, and preferences for PrEP delivery and follow-up

# Outcomes

- 1) *Feasibility and acceptability of integrating enhanced PrEP delivery into existing STI clinic services among PrEP users and providers.*
- 2) *PrEP uptake and PrEP persistence when enhanced PrEP delivery is integrated into existing STI clinics*
- 3) *Feasibility, acceptability, and preferences for enhanced PrEP recruitment via assisted partner notification among PrEP users and providers.*
- 4) *PrEP uptake and PrEP persistence among referred sexual partners*
- 5) *Feasibility and acceptability of incorporating etiologic STI testing with PrEP among PrEP users and providers*
- 6) *Potential clinical utility of incorporating etiologic STI testing with PrEP care at an STI clinic*

Sometimes an opportunity presents itself...

**Funding Opportunity Title**

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

# Sweet Home North Carolina



## Disparities of PrEP in the Southern US

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

STI	NC National ranking (2019)
HIV	6 <sup>th</sup>
Chlamydia	6 <sup>th</sup>
Gonorrhea	9 <sup>th</sup>
Syphilis	15 <sup>th</sup>

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

# Meet me where I am: study design

Multilevel intervention linking PrEP and STI services, addressing barriers at policy, clinic, provider, and user levels

Partnering with local health department STI clinics

Fig 1. Rate of newly diagnosed HIV by county of residence, 2019

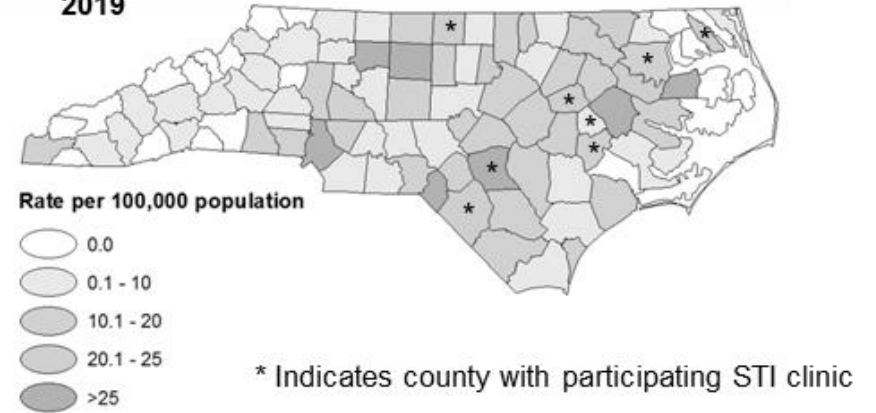
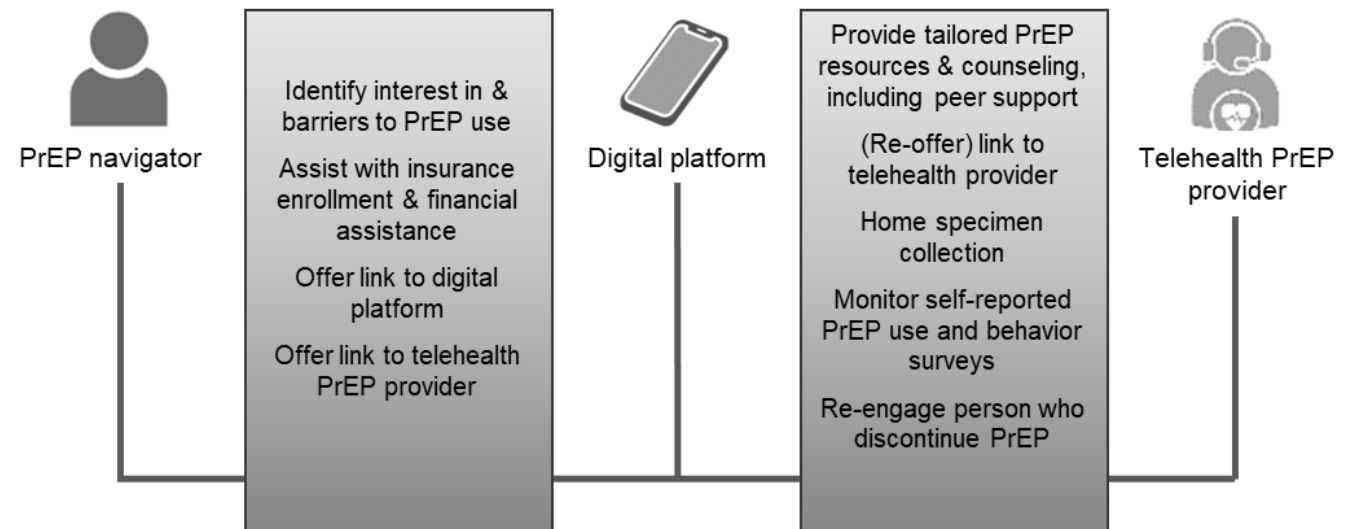
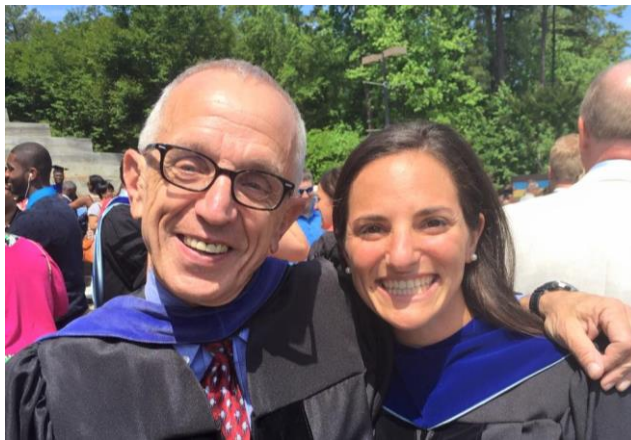


Fig 2: HMP app screenshots



Figure 3: Multilevel Intervention





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UNC Project-Malawi

UNC ID

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OGHE/Global Health Scholars



# Questions

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