

The 'leap' of mHealth: Bridging Access, Linkage, and Engagement for PrEP, HIV and TB

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We have the tools to halt HIV infection and the cure TB

Yet, poor access, limited engagement and/or non-adherence leads to lack of viral suppression and ongoing infection

Innovative behavioral approaches complemented by the 'leap' afforded through mobile health (mHealth) technologies is necessary, but not a holy grail

We will review three exemplars:

- An enhanced case management support intervention for men who have sex with men with a detectable HIV viral load in 4 US cities (HPTN 078);
- LEAP – an escalating, triggered, community health worker mHealth intervention for TB/HIV co-infected patients in South Africa;
- PrEP Care Anywhere – a telemedicine approach to PrEP for men who have sex with men in Baltimore, MD

Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis

Steve Kanters, Jay J H Park, Keith Chan, Maria Eugenia Socias, Nathan Ford, Jamie I Forrest, Kristian Thorlund, Jean B Nachega, Edward J Mills

Summary

Background High adherence to antiretroviral therapy is crucial to the success of HIV treatment. We evaluated comparative effectiveness of adherence interventions with the aim of informing the WHO's global guidance on interventions to increase adherence.

Methods For this systematic review and network meta-analysis, we searched for randomised controlled trials of interventions that aimed to improve adherence to antiretroviral therapy regimens in populations with HIV. We searched Cochrane Central Register of Controlled Trials, Embase, and MEDLINE for reports published up to July 16, 2015, and searched major conference abstracts from Jan 1, 2013, to July 16, 2015. We extracted data from eligible studies for study characteristics, interventions, patients' characteristics at baseline, and outcomes for the study populations of interest. We used network meta-analyses to compare adherence and viral suppression for all study settings (global network) and for studies in low-income and middle-income countries only (LMIC network).

Findings We obtained data from 85 trials with 16271 participants. Short message service (SMS; text message) interventions were superior to standard of care in improving adherence in both the global network (odds ratio [OR] 1.48, 95% credible interval [CrI] 1.00–2.16) and in the LMIC network (1.49, 1.04–2.09). Multiple interventions showed generally superior adherence to single interventions, indicating additive effects. For viral suppression, only cognitive behavioural therapy (1.46, 1.05–2.12) and supporter interventions (1.28, 1.01–1.71) were superior to standard of care in the global network; none of the interventions improved viral response in the LMIC network. For the global network, the time discrepancy (whether the study outcome was measured during or after intervention was withdrawn) was an effect modifier for both adherence to antiretroviral therapy (coefficient estimate –0.43, 95% CrI –0.75 to –0.11) and viral suppression (–0.48; –0.84 to –0.12), suggesting that the effects of interventions wane over time.

Interpretation Several interventions can improve adherence and viral suppression; generally, their estimated effects were modest and waned over time.

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Introduction

The recent scale-up of programmes for antiretroviral therapy has resulted in more than 17 million people receiving treatment worldwide, with most living in low-income and middle-income countries (LMICs).¹ Achievement of the optimum clinical, public health, and social outcomes requires early diagnosis, timely linkage and initiation of antiretroviral therapy, and consistent long-term adherence to antiretroviral therapy.^{2,3} Few interventions consistently improve adherence.⁴ Interventions vary in their intensity and approach and have heterogeneous clinical trial results, making interpretation of their effects challenging. For instance, the use of text messaging (ie, short message service [SMS]) to maintain adherence in low-income settings has been widely promoted; however, not all randomised trials have shown clear improvements.⁵

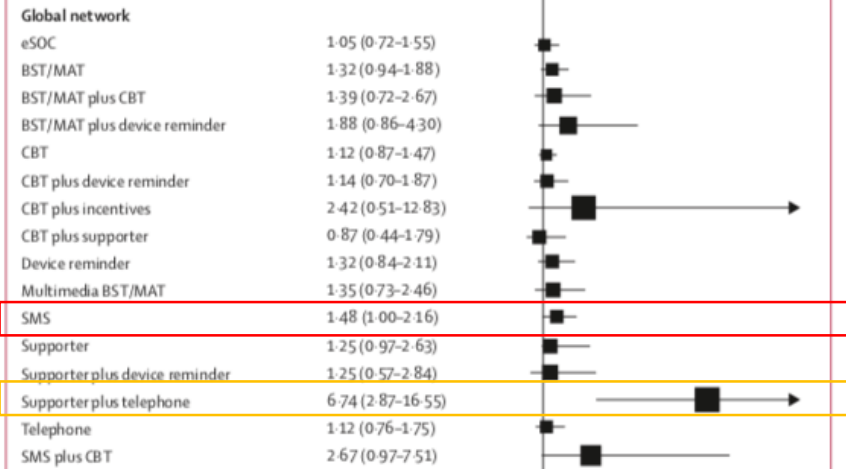
Over the past two decades important progress has been made in meta-analysis and comparative effectiveness, namely, the development of network meta-analysis.^{6,7} Randomised controlled trials, the gold standard of

scientific evidence, tend to use control groups of little clinical interest (eg, an older treatment or placebo). As such, determining the comparative effectiveness of two treatments can be difficult because of the absence of head-to-head evidence. Network meta-analyses allow for the comparison of interventions that have not been compared directly.⁸ Moreover, network meta-analyses simultaneously evaluate all treatment options within a clinical area and so facilitate the evaluation of the complete interventional landscape. As such, these methods naturally lend themselves to the process of evidence synthesis for the purpose of clinical guidelines.

Low adherence has been reported in both high-income countries and LMICs.⁹ Previous work to assess adherence interventions for antiretroviral therapy has been limited to Africa in the case of network meta-analyses¹⁰ and to pairwise comparisons with respect to other reviews.¹¹ Identification of effective interventions is needed for guidance relevant to both high-income countries and LMICs. To inform the latest iteration of the WHO global consolidated guidelines on HIV, we used a network

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See Comment page e5
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Odds ratio relative to SOC (95% CrI)



85 RCTs with 16,271 participants

Note: Excluded studies using real-time adherence monitoring

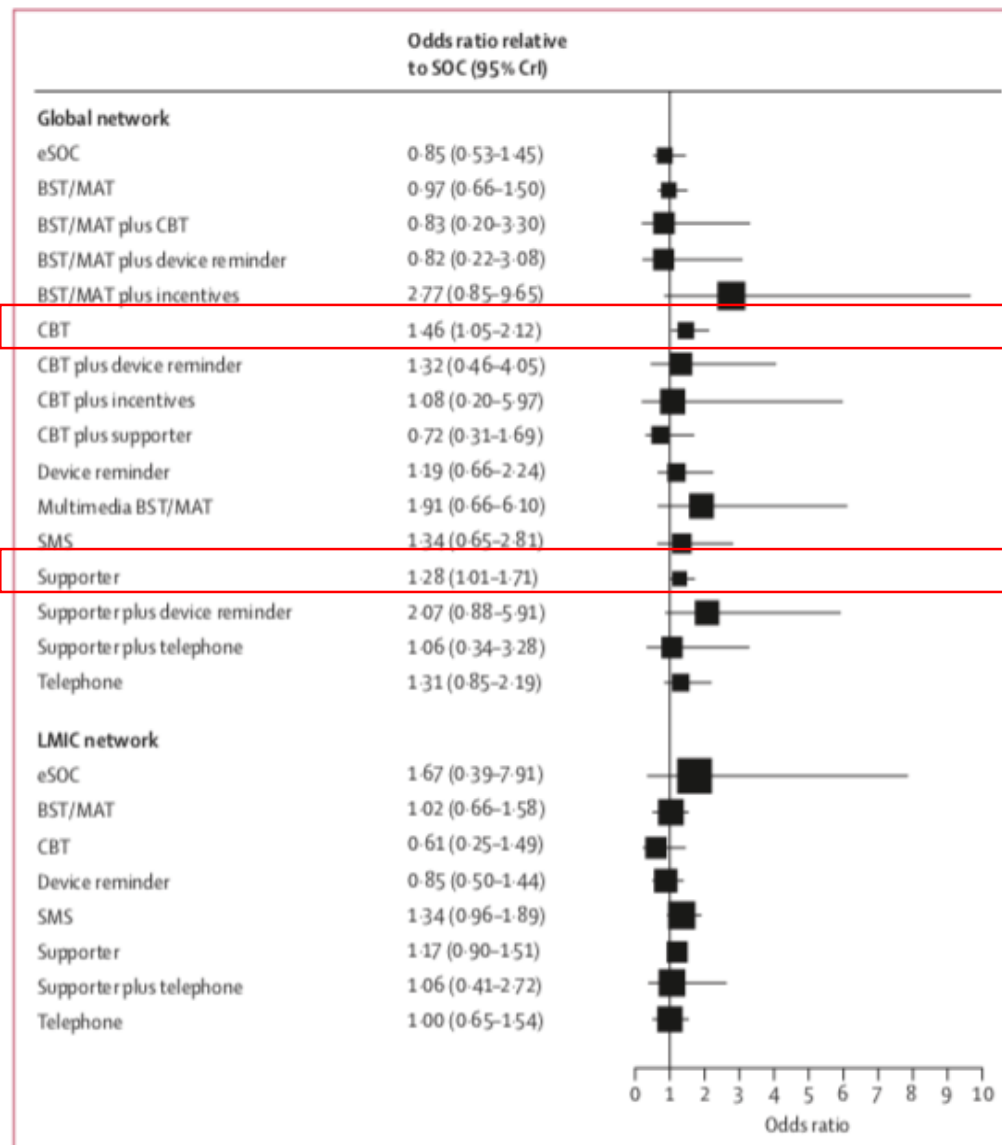


Figure 4: Forest plots for the effect of interventions on viral suppression in the global and LMIC networks
 A random-effects model was used for the global network and a fixed-effects model was used for the LMIC network. SOC=standard of care. 95% CrI=95% credible interval. eSOC=enhanced standard of care. BST/MAT=behavioural skills training or medication adherence training. CBT=cognitive behavioural therapy. SMS=short message services (text messaging). LMIC=lower-income and middle-income countries.



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See Online for appendix

Mobile phone-enabled adherence in HIV/AIDS

The HIV/AIDS epidemic in low-income countries has improved thanks to several technological and anthropological advances in health care.¹ The introduction of laboratory equipment to initially monitor CD4 T-helper cells in 2004 was a technological breakthrough in low-resource settings because many researchers thought that the expensive laboratory infrastructure could not be consistently maintained. Training and access to testing equipment led to widespread uptake. Similarly, the progressive introduction of viral load and resistance testing has shown that even the most complex technological requirements can, with time, be rolled out at a large scale in low-resource settings.² The rapid uptake of mobile phones in low-income settings displays an anthropological advancement, in which the use of mobile phones has surpassed the development of infrastructure for landlines that does not exist. In the early 2000s, mobile phones in low-income settings became ubiquitous for managing banking, education, and health care.³ Mobile devices quickly became a norm for interacting with patients in HIV/AIDS clinics, often via short message service (SMS) and in 2010 the first randomised clinical trial⁴ of cellular devices for monitoring adherence to first-line antiretroviral therapy (ART) in patients living with HIV was published, displaying a modest benefit on self-reported adherence and viral suppression. In this issue of *The Lancet Digital Health*, Robert Gross and colleagues⁵ present the first randomised controlled trial in second-line treatment and fill an important gap in knowledge about the use of SMS in the HIV/AIDS epidemic.

Among the many challenges of monitoring adherence to ART in any setting is how adherence is measured. Self-reported adherence (usually based on 3-day recall), pill counts, and electronic monitoring of medication package opening have all been used to assess adherence but are surrogate outcomes to the medical intention of treatment: to suppress the virus. In the figure, the top panel shows the outcomes of the previously reported SMS trials that measure adherence using these surrogate outcomes. The bottom panel shows the results of the only three trials that have used viral load as an outcome. The uncertainty in interpreting these inconsistent trials was previously ascribed to low statistical power

to detect effects because most patients living with HIV in these settings have high adherence rates, thus, we would expect high reported adherence and viral suppression. The study by Gross and colleagues⁵ is a major contribution in this context because it is the first randomised trial to enrol a population with shown ART challenges in terms of resistance or previous treatment failures and thus is likely to be adequately powered. Although this multicountry study had a small heterogenous population exposed to ART, the findings are statistically definitive that this specific intervention offered no detectable benefit on viral load suppression. We confirmed the findings using Bayesian simulations and found that even with additional thousands of patients, the results would not change (appendix).

The findings of the present study,⁵ that the SMS intervention did not detect a useful treatment effect in the primary outcome, should be considered in terms of whether SMS in general should be used as an adherence support tool or not. The study was well designed and well done. Previous randomised controlled trials investigating SMS interventions have varied slightly in how the SMS is delivered, whether that be one-way or two-way texts (response monitored or not), once daily versus once weekly texts, and the construction of the texts (health questions versus a simple colloquial question—eg, “How are you?”). The mixed findings on

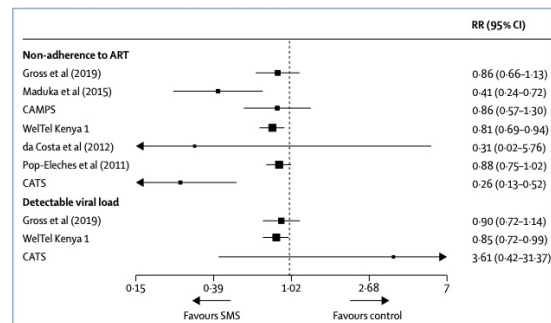


Figure: SMS intervention trials on adherence to ART and detectable viral load
 Previously completed randomised controlled trials of SMS interventions to promote adherence. Outcomes include self-reported adherence (top panel) and detectable viral load, according to reported thresholds (bottom panel). The studies were identified and updated from a systematic literature review⁶ on SMS intervention trials for ART adherence and viral load among patients living with HIV. ART=antiretroviral therapy. CAMPS=Cameron Mobile Phone SMS Trial. CATS=China Through Technology Study. RR=relative risk. SMS=short message service.

Mills, EJ & Lester, RT (2019). Mobile phone enabled adherence in HIV/AIDS. *Lancet Digital Health*, 1(1) PE4-E5

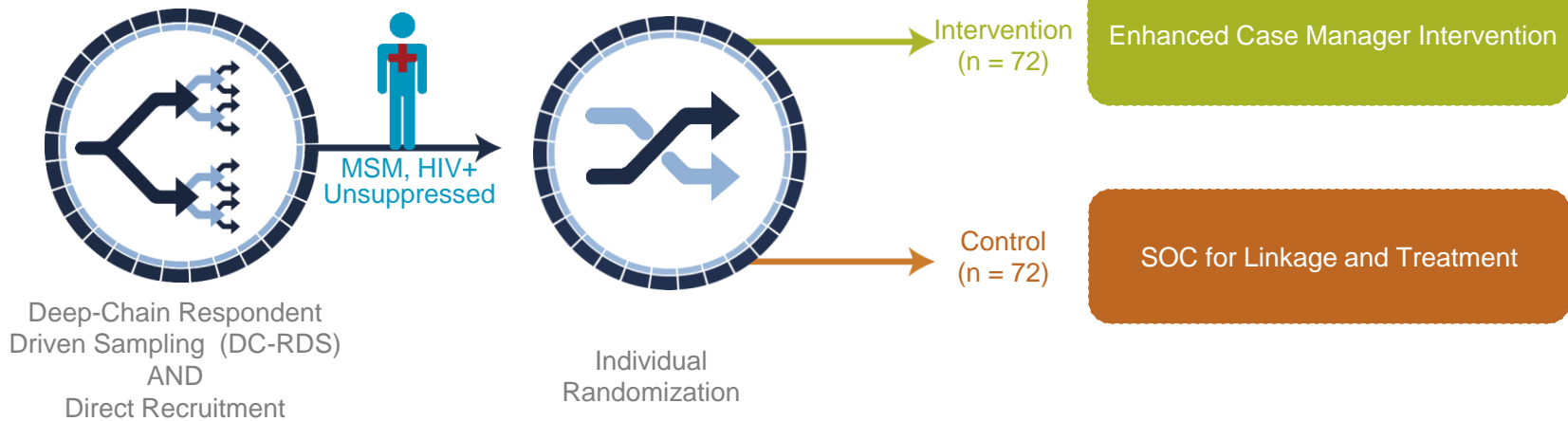
HPTN 078: Primary results of a randomized study to engage men who have sex with men (MSM) living with HIV who are virally unsuppressed in the USA

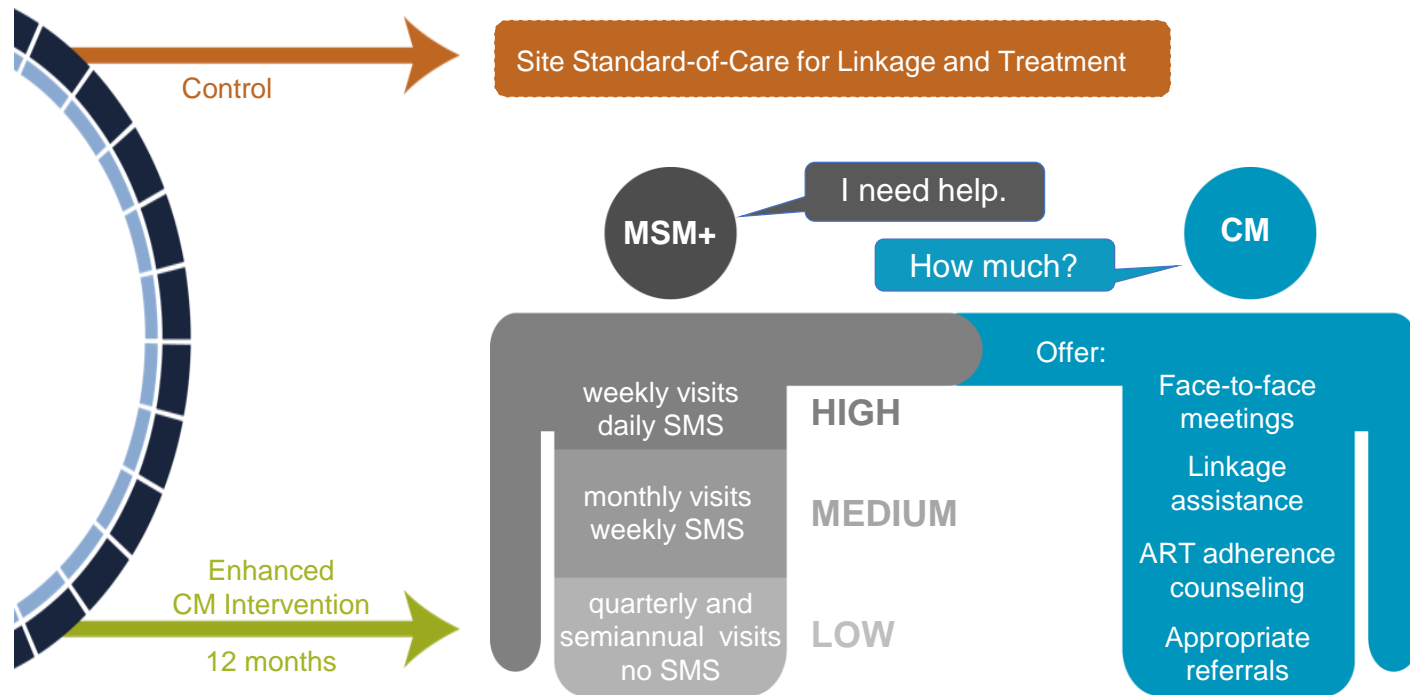
R.H. Remien, T. Gamble, J.E. Farley, Z. Wang, C. del Rio, D.S. Batey, K.H. Mayer, C. Foster, J. Glorioso, W. Graves, K.J. King, S. Shurbaji, I.C. Balán, L. McKinstry, V. Cummings, S.H. Eshleman, M. Stirratt, A. Adeyeye, J.P. Hughes and C. Beyrer for the HPTN 078 study team

Site Investigators of Record: J.E. Farley (Hopkins), C. del Rio (Emory), K.H. Mayer (Harvard) and M. Mugavero (Univ of Alabama Birmingham)

Screened population	Enrolled participants
1305	144
MSM and TGW \geq 16 yo	MSM and TGW HIV+, Unsuppressed
Study Duration: 12 Month Follow-up	

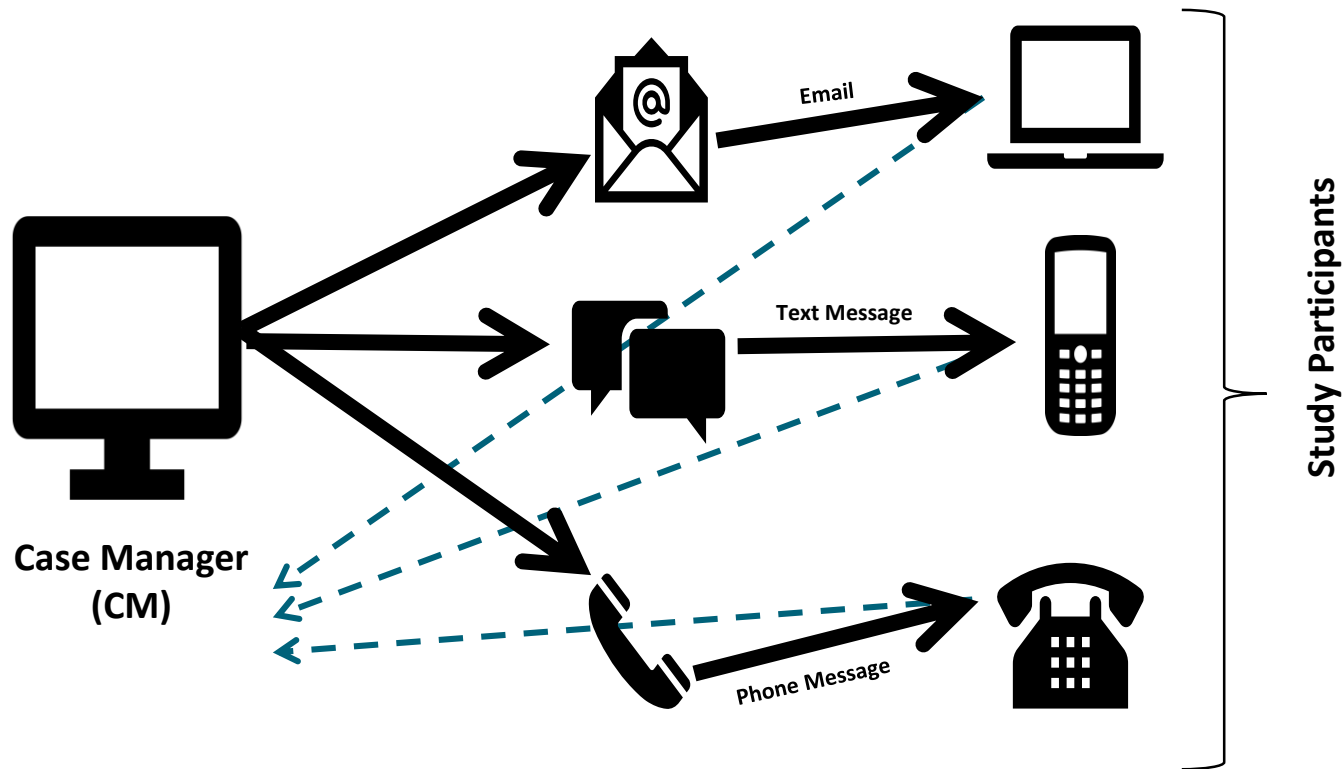
HPTN 078: Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States





The enhanced CM intervention includes patient choice, motivational interviewing and automated phone/email/text messages

Technology Enhanced Adherence Support



Participants had multiple choices – method, frequency, time of day, etc.

Socio-demographics (Who We Found)

	DC-RDS (N=721)	Direct Recruitment (N=584)	Overall N=1305	Enrolled N=144
	N (%)	N (%)	N (%)	N (%)
Age (Median, IQR)	41 (30, 52)	41 (30, 52)	41 (30, 52)	39 (29, 49)
Gender (self-reported)				
Male	695 (96)	545 (93)	1240 (95)	139 (97)
Transgender Female	17 (2)	29 (5)	46 (4)	3 (2)
Race				
Black	448 (62)	457 (78)	905 (69)	121 (84)
White	179 (25)	84 (14)	263 (20)	19 (13)
Other	99 (13)	56 (8)	165 (11)	4 (3)
Education				
Less than high-school diploma	92 (13)	100 (17)	192 (15)	15 (10)
Beyond high-school	629 (87)	484 (83)	1113 (85)	129 (90)
Income				
Low Income (<\$20,000)	476 (66)	409 (70)	885 (68)	93 (65)

Most screened & enrolled were Black, educated and poor

Socio-demographics

	Enrolled N=144	CM Arm N=72	SOC Arm N=72
	N (%)	N (%)	N (%)
Age (Median, IQR)	39 (29, 49)	39 (29, 49)	39 (29, 49)
Gender (self-reported)			
Male	139 (97)	71 (99)	68 (94)
Transgender Female	3 (2)	1 (1)	3 (4)
Race			
Black	121 (84)	62 (86)	59 (82)
White	19 (13)	9 (13)	10 (14)
Other	4 (3)	1 (1)	3 (4)
LatinX	10 (7)	3 (4)	7 (10)
Education			
Less than high-school diploma	15 (10)	7 (10)	8 (11)
Beyond high-school	129 (90)	65 (90)	64 (89)
Income			
Low Income (<\$20,000)	93 (65)	48 (67)	45 (63)
Not employed	97 (67)	48 (67)	49 (68)

Majority had access to health care, high rates of HCV and syphilis

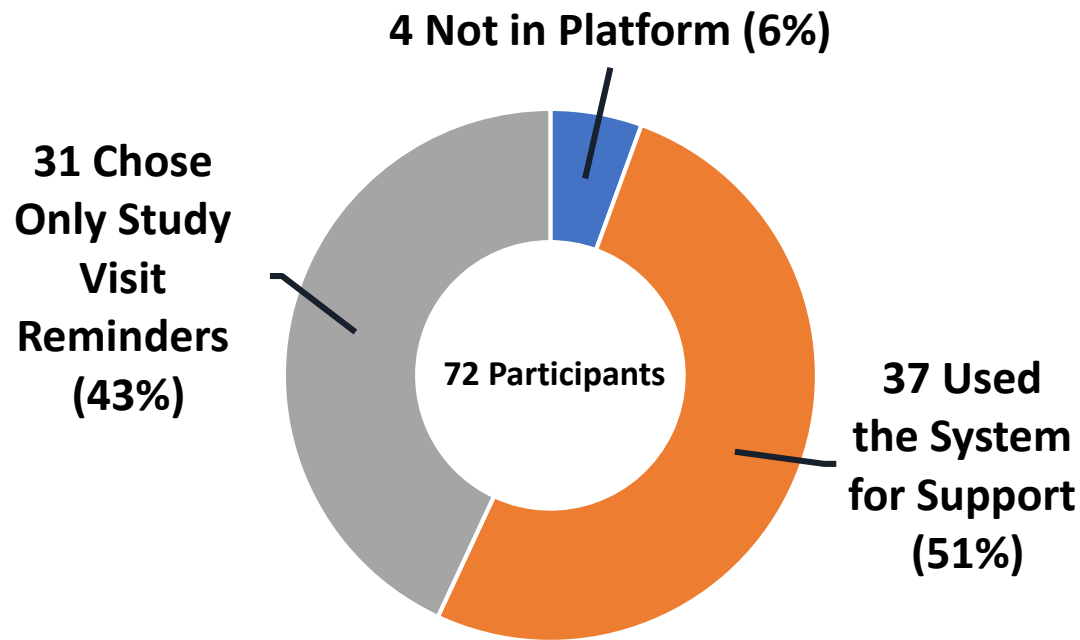
Viral Suppression (<200) by Arm and Visit

	Overall	CM Arm	SOC Arm
Month 3	41 (28%)	20 (28%)	21 (29%)
Month 6	52 (36%)	26 (36%)	26 (36%)
Month 9	56 (39%)	28 (39%)	28 (39%)
Month 12	68 (48%)	30 (42%)	38 (54%)

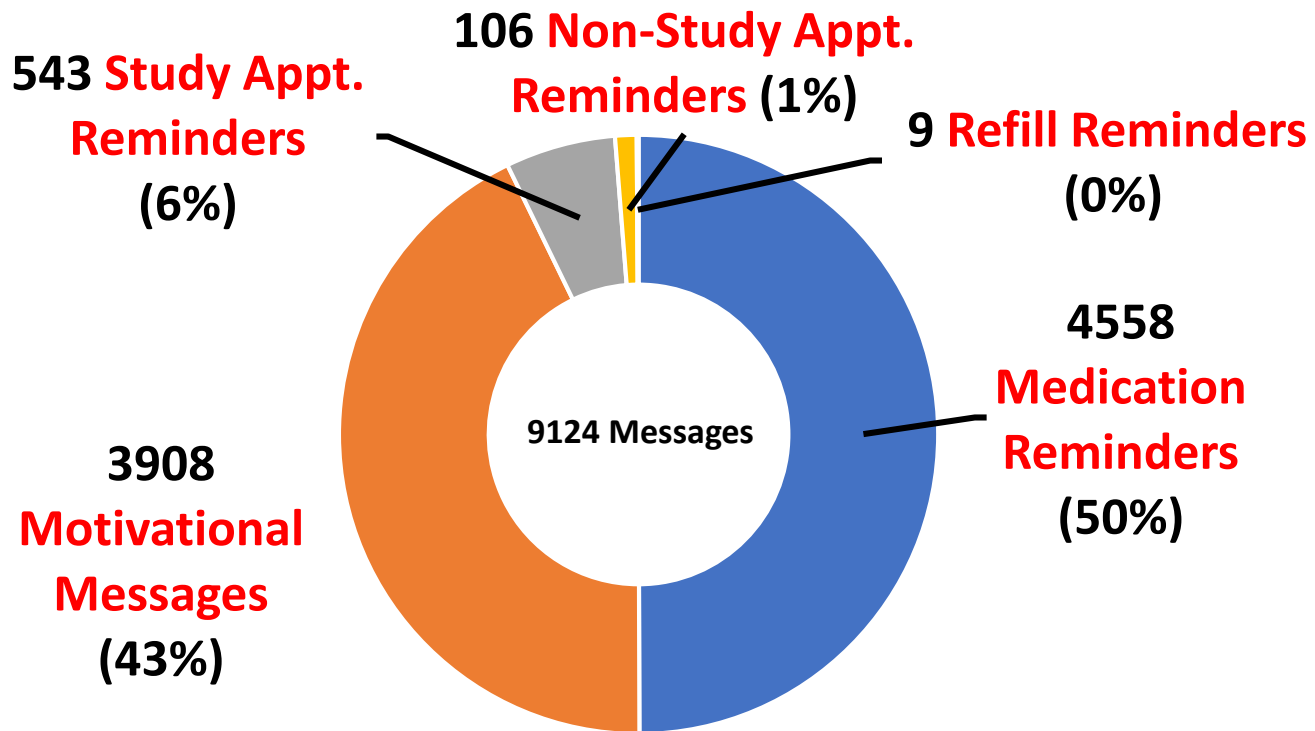
At baseline, the median viral load was 19,459 copies/mL, and at Month 12, 48% were virally suppressed, with no difference between the CM and SOC arms (OR = 0.615 [p = 0.1526, 95% CI = 0.315, 1.197]).

91% were retained at Month 12

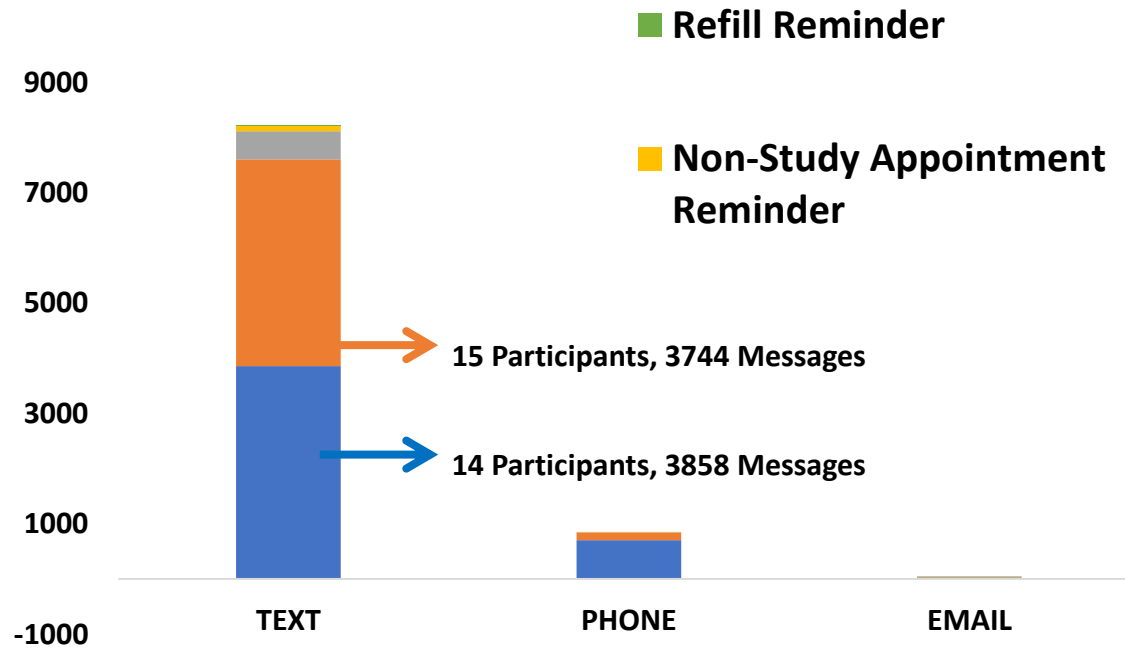
About half of the cohort used the system for support



Motivational messages and medication reminders were chosen most often



Participants primarily chose text messages



Why Didn't the CM Intervention Show a Difference? Potential Reasons

- SOC provided similar level/type of support; the CM intervention was not distinct enough from SOC
- Participants did not want or perceive a need for the CM intervention
- There was a gap between the availability of the VL data and the CM sessions
- More medically-focused counselors are required
- The CM intervention could not overcome structural barriers (e.g., stigma, racism, insensitive care)
- The CM intervention components were not the right ones, nor sufficient to overcome participant challenges
- Other reasons

Successfully built a web-based communication system

- This system could easily be adapted for real world implementation

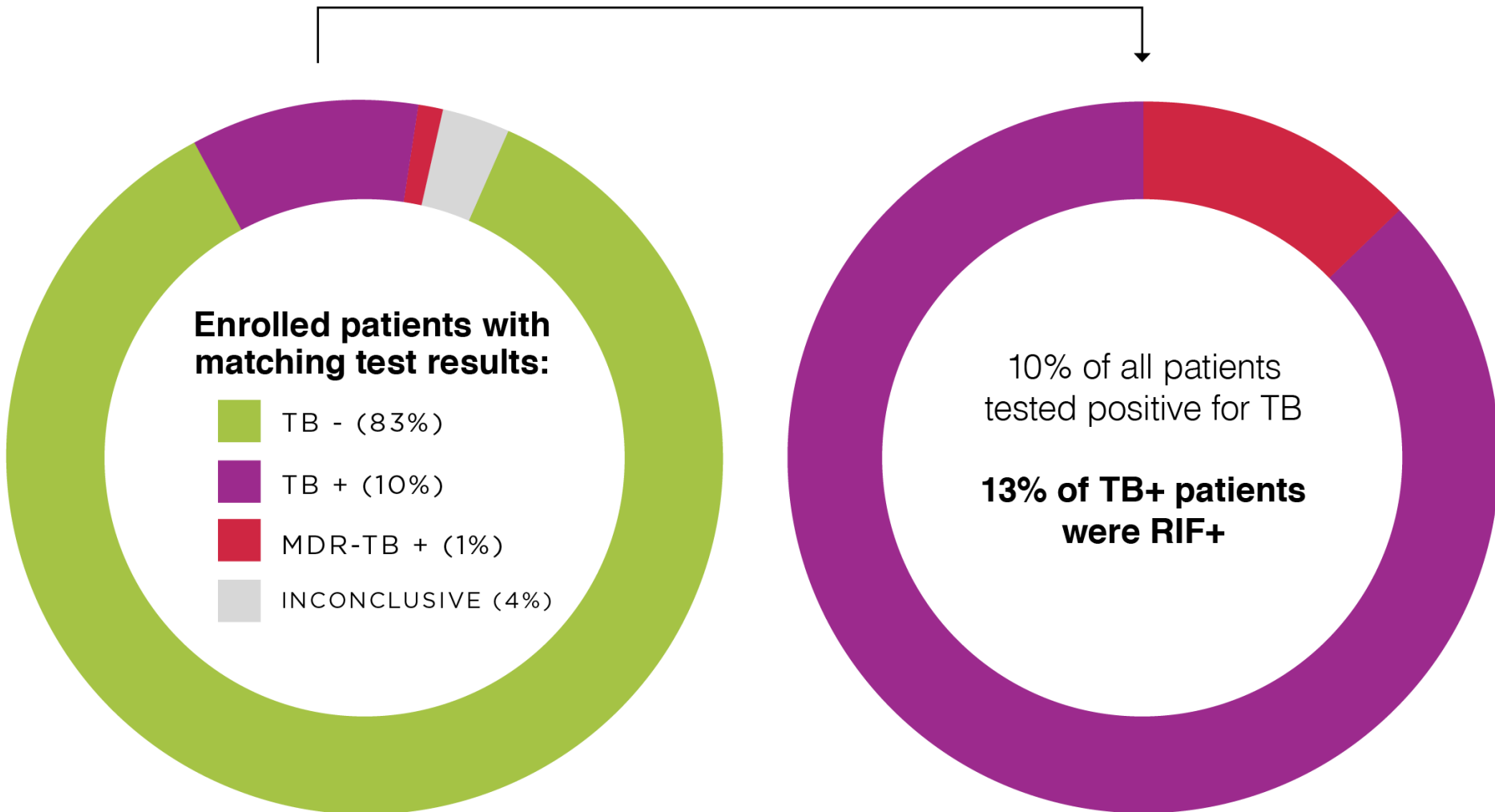
More choices resulted in higher participation, for some patients

- Not everyone wanted, nor felt they needed this level of support

Still, 43% chose not to use the system for support

- Due to lack of access, personal preference, real and perceived need, fear of HIV status exposure
- This type of technological support may not be the best option to help all HIV-positive patients achieve and maintain viral suppression.

A convenience sample of 6,341 patients with suspected TB were enrolled. Of the 631 positive TB sputum specimens, 41 (6.5%) were found to be rifampin-resistant (RR-TB)



Enrollment → RR-TB Treatment Initiation 3 days, 21 hours, 17 minutes

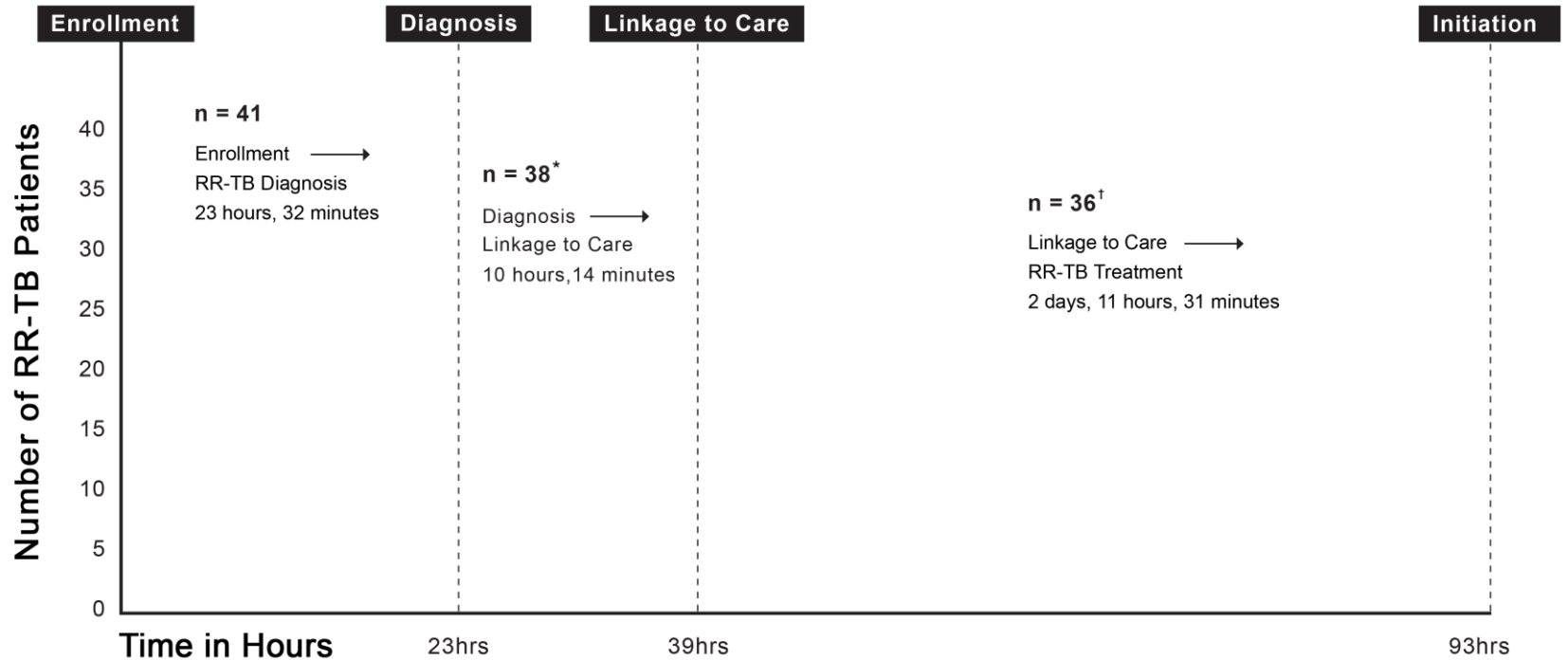


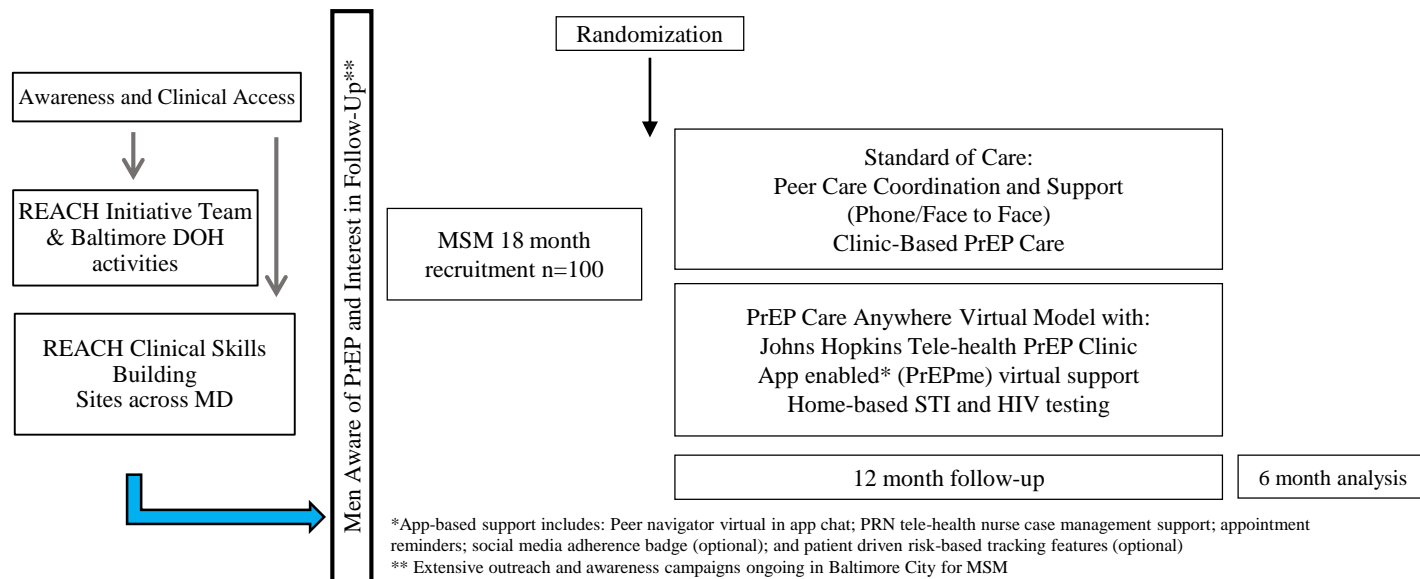
Figure 2 miLINC RR-TB Care Cascade in South Africa

5/41 patients lost to follow-up
 *3 lost after RR-TB diagnosis, †2 between diagnosis and linkage to care

PrEP Care Anywhere

Multi-Component Intervention

PrEP Care Anywhere: Study Overview



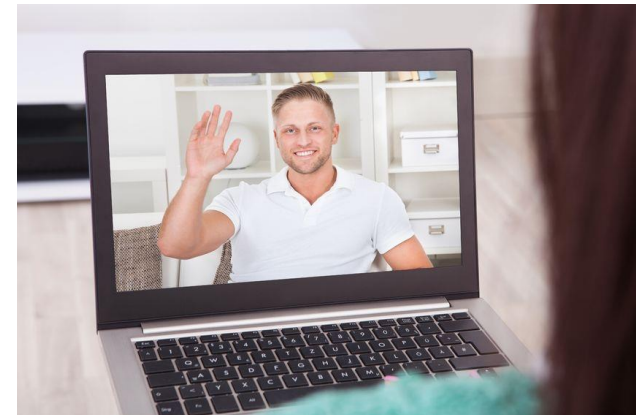
Study Objectives

Primary Interventional Linkage Objectives for MSM:

- To evaluate retention in prevention services in standard of care PrEP visits versus PrEP Care Anywhere Telemedicine visits

Primary Outcome Measures

- Retention at 12 months



PrEP Care Anywhere Arm

At Home Testing:

- HIV; GC / CT; Syphilis



Face to face visit (intake)

- All patients

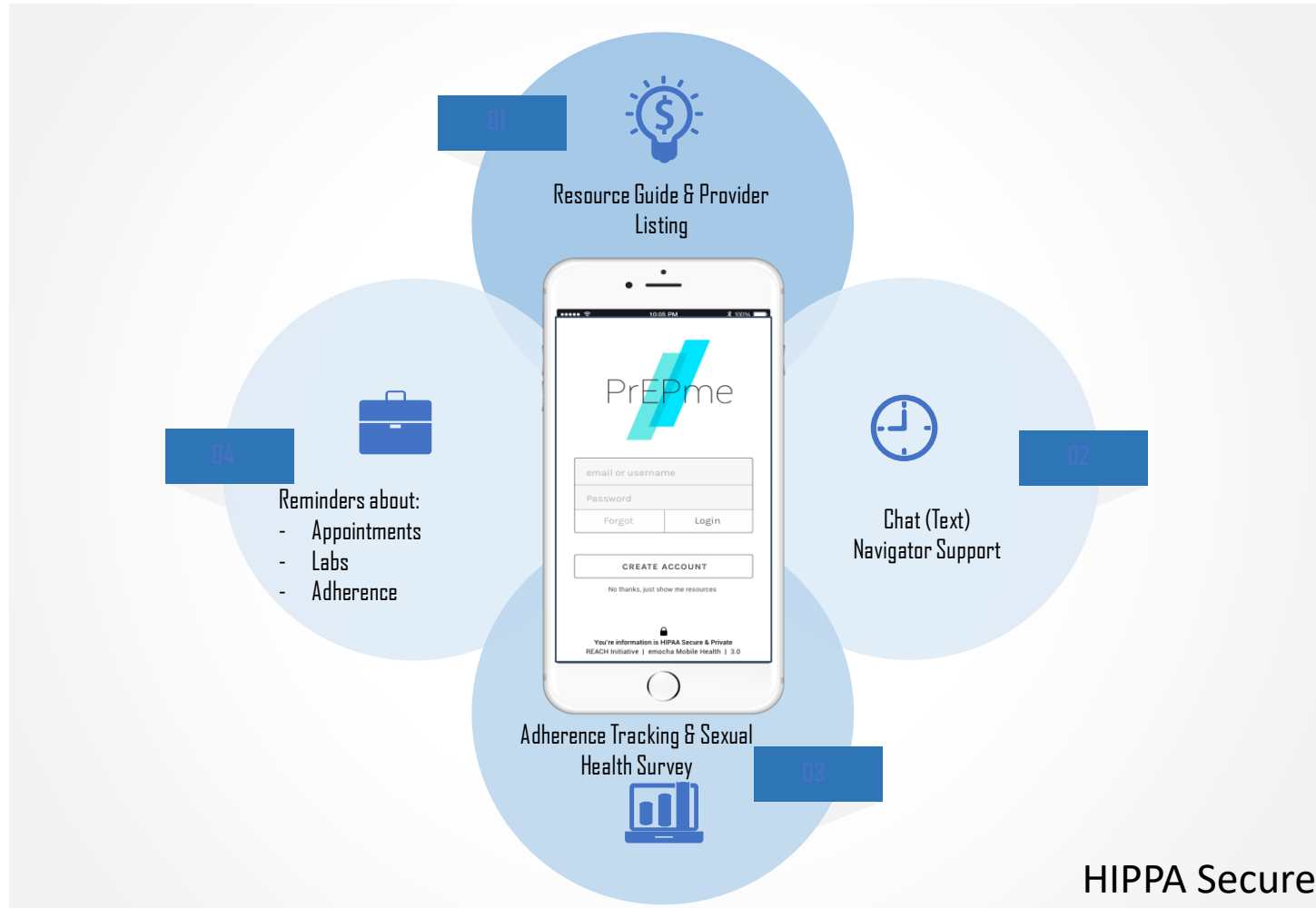
Telemedicine PrEP Visit:

- Evaluation of labs
- Adherence
- PrEPme dashboard
- Virtual Case management
- PrEP refills
- PRN face to face visits

Standard of Care:

- Face to face follow-up

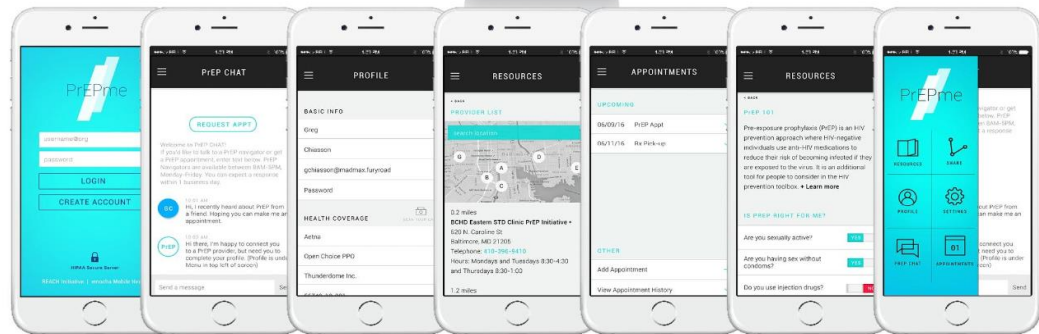
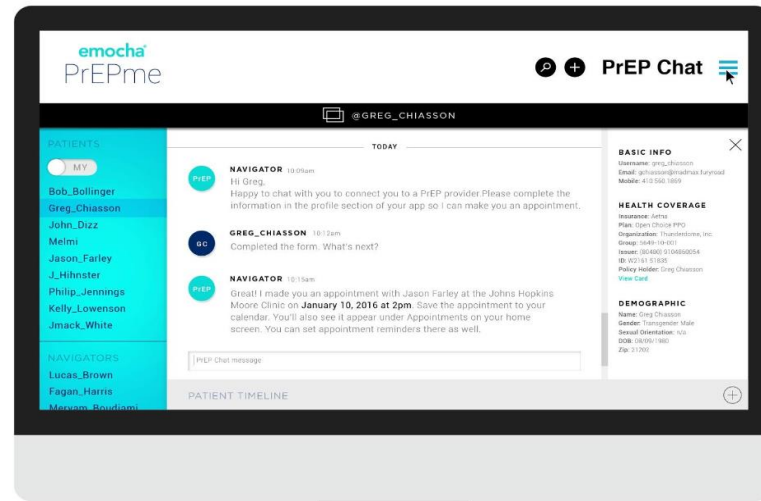
PrEPme Current Functionality: PrEP User View



PrEPme Current Functionality: PrEP Navigator View

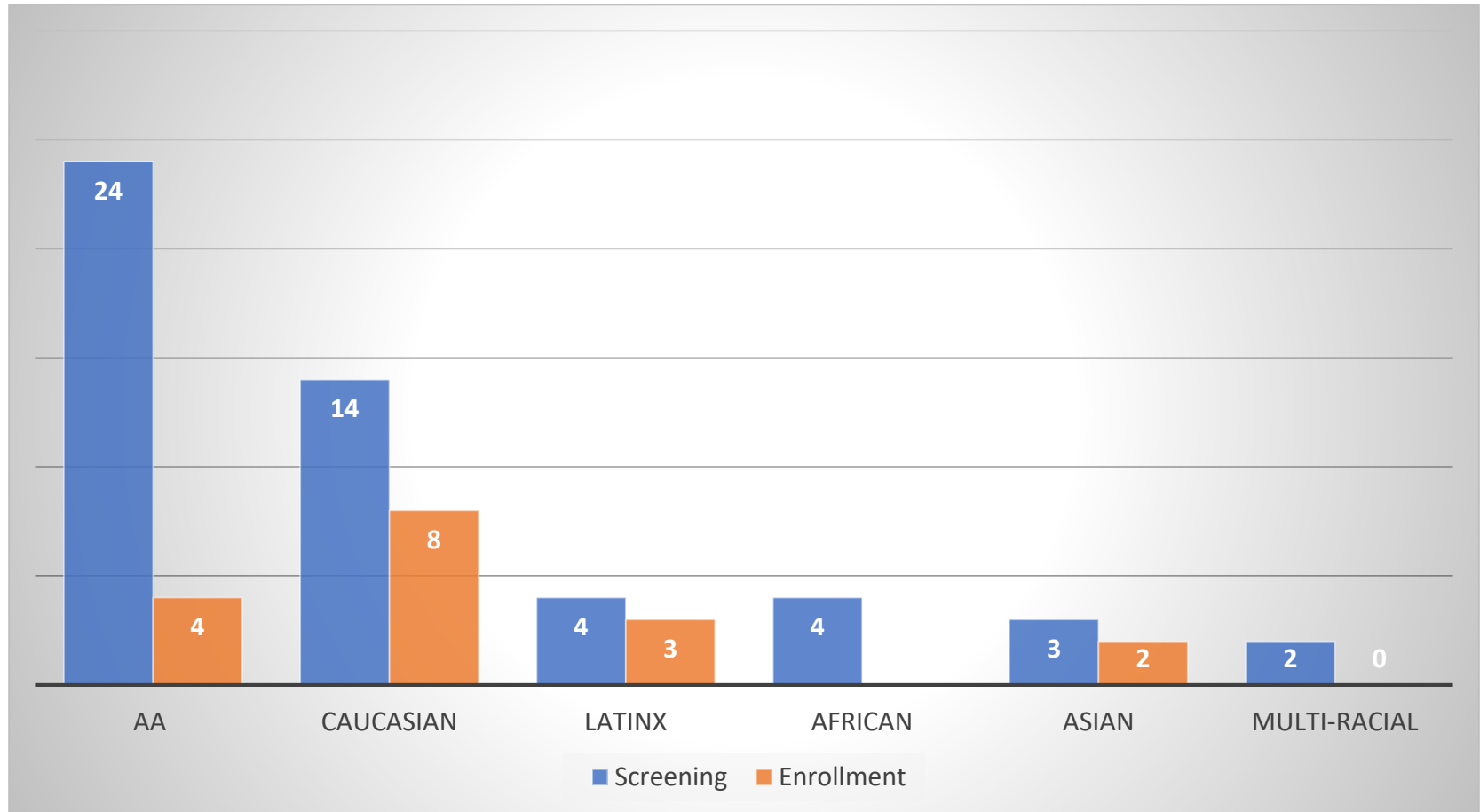
Navigators Options:

- Tracking client interactions
- Sending group messages
- Reviewing insurance and demographic details
- Chatting with clients in secure fashion
- Reassigning navigators
- Appointment reminders
- Assisting with appointment scheduling
- Reviewing progress in linkage cascade



<https://drive.google.com/file/d/0B0qeU5EEiq-LT2MxVINGaUpTT28/view?usp=sharing>

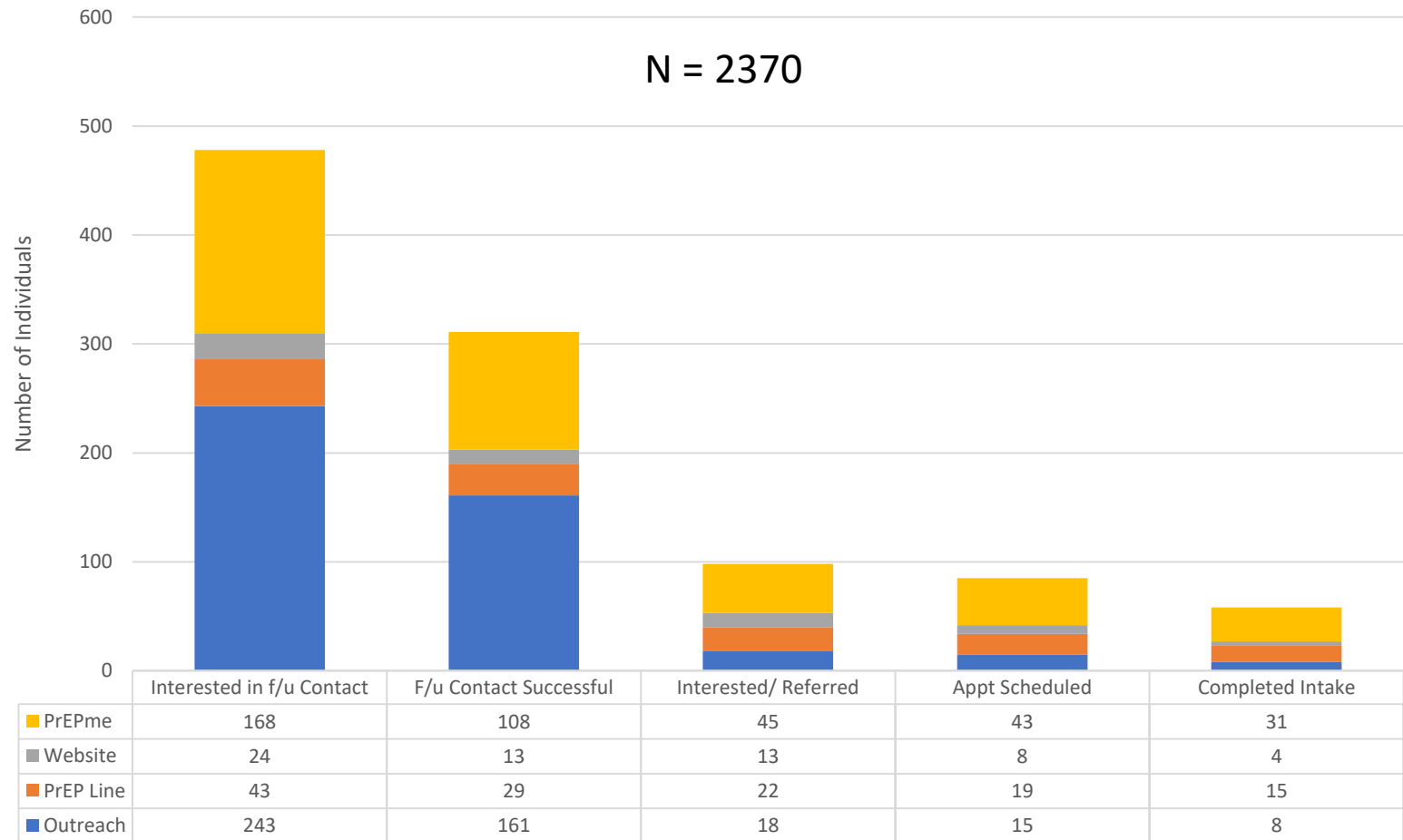
Screening N = 68 / Enrollment N = 17



Findings to date:

- Recruitment challenges for African American men
- Of the 17 enrolled to date, those randomized to standard of care were disappointed to the point of study withdrawal
 - Necessitating forfeiting of the randomized design and obtaining approval from sponsor for prospective cohort
- PrEPme highly utilized for linkage to care activities only, but both staff and participants prefer “out of app” communication after linkage
 - Barriers identified:
 - Extra log in step
 - Lack of immediate response from staff, generally in a few hours

Peer CHW PrEP Care Cascade, Baltimore, MD between March 2016 and March 2019



Thank you

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- Michael Stirratt, PhD
- Adeola Adeyeye. MD
- Jim P. Hughes. PhD
- Chris Beyrer, MD, MPH

- Case managers & participants!