Ongoing Dynamic Choice to Address HIV Treatment Interruption in Malawi (CHOICE)
May 6, 2024

NCT: TBD

SPECIFIC AIMS

Repeat and prolonged treatment interruption (TI) is common and *the* major threat to HIV epidemic control in eastern and southern Africa.[1–3] We define TI as >28 days late for last ART appointment. Each TI episode is associated with rapid viral load rebound[4] and long-term decreases in CD4 count.[5] Up to 46% of ART clients in the region experience TI in the first years after treatment initiation.[6–8] 30-50% of clients returning from TI experience repeat TI <6 months after returning to care.[2,3] **TI and repeat TI account for the majority of HIV transmissions in Malawi.**[9] Strategies to provide ongoing support to TI clients are urgently needed.

Current TI services do not work in the long-term. The few evidence-based TI interventions that exist are extremely limited in duration (usually only ~1-3 intervention visits) and services offered (counseling alone or counseling + home-based initiation). **Yet reasons for TI are different for each client and change over time. TI is rarely a one-time event.** Short term interventions can improve return to care, but do not address repeat TI.[10,11] Our recent R01 (ENGAGE; R01MH122308-05, n=735) and BMGF (IDEAL; n=569) trials with men experiencing TI in Malawi show that short-term person-centered counseling + variations of short-term home-based ART dramatically improve return to care after TI (~96% re-initiated vs 67% in standard of care – SOC; p<0.001). But rates of continued ART engagement at 6-months after re-initiation (4-5 months after interventions completed) was unacceptably low (~64% were continuously in care without repeat TI vs 48% in SOC, p<0.001).

Our trials found that clients with repeat TI had many unexpected and changing barriers that require long-term solutions. In-depth interviews with repeat TI clients in ENGAGE and IDEAL trials (n=67) showed that clients want long-term services responsive to their changing needs, and the ability to choose services.

TI clients need long-term, dynamic choice of differentiated service delivery (DSD) options. There are no one-size fits all interventions for TI clients because they experience vastly changing and different barriers to care, from distance to facility to lack of social support to limited HIV-related literacy. Ongoing person-centered counseling and choice of *how* services are delivered facilitates responsive services[12,13] and promotes client ownership over care.[14–16] Long-term and dynamic choice of DSD may be the best practical strategy to provide long-term, responsive TI interventions. There are no evidence-based dynamic choice interventions for TI clients.

We piloted a novel intervention, called CHOICE, that provides person-centered counseling (building on the success of our prior trials) + ongoing, dynamic choice of DSD services to TI clients. Our pilot (n=125) found that counseling + dynamic choice of DSD was feasible, acceptable, and showed signs of efficacy to reduce repeat TI (15% vs 50% at 3-months). A full trial is needed to test the impact on viral suppression long-term (at 12- and 24-months) and cost-effectiveness.

We propose to evaluate CHOICE in a randomized control trial (RCT) with TI clients in Malawi. TI clients will receive person-centered counseling + ongoing, dynamic choice of how services are delivered (drawing on DSD models) over 24-months. Clients can combine multiple choices for service delivery at any given time to create personalized intervention packages. Choice of service delivery include: 1) ART dispensing intervals (1, 3, 6months), location of ART distribution (facility, home, or community), and peer mentorship (varying frequency and meeting location). Clients can adjust their choice at each ART visit or via hotline throughout study period. We will compare CHOICE to SOC (1-3 counseling sessions + routine facility-based services – no choice available ≤6-months after TI. Specific aims are:

Aim 1. Test the effectiveness of CHOICE versus SOC on 12-month viral suppression among TI clients. We will conduct an individually randomized trial at 12 health facilities (n=800 individuals). Primary outcome is viral suppression (<50copies/mL) at 12-months (study collected sample). Secondary outcomes are: presence of repeat TI, time to repeat TI, and ART coverage (days with ART in possession) across 24-months.

Aim 2: Systematically evaluate the implementation of CHOICE. We will use mixed-methods to understand barriers, facilitators and needed improvements to HCW implementation of CHOICE, clients' ability to choose DSDs, and equity in intervention implementation and outcomes.

Aim 3. Estimate cost and cost-effectiveness of CHOICE. We will use a micro-costing approach to estimate the distribution of care costs by study arm, differences between arms, and incremental cost effectiveness. We will draw on patient-level resource use and unit costs developed from clinic and implementation financial data.

CHOICE will inform strategies for sustained retention among TI clients regionally and globally. The study is timely, of high-impact, and highly feasible within the Malawi health system and with our team. Malawi has a strong track record of implementing scientifically tested innovations into SOC that are high-impact and scalable, including several guidelines informed by our previous trials.[17–20]

Research Strategy

A.1 Significance of the Problem

Treatment as Prevention (TASP) is the major HIV prevention strategy for controlling HIV spread in SSA,[1,18,20–23] but only 59-66% of adult ART clients in southern Africa are virally suppressed.[18,21,22] Repeat and prolonged treatment interruption (TI) is common and the major contributor to lack of VL suppression.[1–3]

Treatment Interruption (TI) from ART services is the most pressing challenges to epidemic control in southern Africa.[24–26] We define TI as being ≥28 days late for last ART appointment because viral rebound is likely to occur around ~28 days out of care.[27,28] Around 40% of ART clients experience TI[6–8] and a quarter of those never return.[1–3,20] Those who do return cycle in-and-out-of-care throughout their lifetime,[23,29,30] with up to 50% of TI clients experiencing repeat TI <6 months after re-initiation.[2,3] In Malawi, we find across 123 health facilities that nearly 45% of TI clients who returned to care experience repeat TI within 12-months after returning to care (n=8900/20,697; 50% among male TI clients),[31] with a median 57days out of care (IQR:30-180) per TI episode.

TI accounts for the majority of HIV transmissions in Malawi.[9] We estimate that across Malawi nearly 80,000 ART clients experience TI at any given time and likely have unsuppressed viral load. Each TI event negatively impacts CD4 count and viral suppression, with those experiencing TI having lower CD4 counts than those without TI up to 3 years after the TI event.[5] Data from other areas of eastern and southern Africa show that when including clients with TI, only 59-66% of adult ART clients in virally suppressed.[18,21,22]

Rates and absolute number of TI events are likely to increase in coming years due to climate change and population growth. Malawi is one of the highest risk nations in the world for negative impacts of climate change, with the highest proportion of the population vulnerable to enter poverty due to extreme weather,[32] extreme increases in mobility and disruption of critical infrastructure.[23] These factors all increase risk of TI.[33,34] Further, population continues to grow (SSA is the fastest growing population in the world[35]). While HIV incidence is reducing, the absolute number of people living with HIV and experiencing TI will increase. Long-term solutions for clients at ongoing risk of TI are needed before the problem worsens.

Causes of TI are fluid and multifaceted. Populations face an array of barriers that require tailored support, while individuals experience rapidly changing barriers that require ongoing, flexible, and dynamic services. Common barriers are: 1) unexpected proximal events (i.e., travel, change in income or work requirements, extreme weather, family needs); 2) health services related deterrents (i.e., distance to facility, time requirements of frequent ART appointments, negative interactions with health care workers (HCWs)); 3) negative perceptions of HIV/ART (i.e., HIV/ART knowledge, perceived benefit of ART, perceived side effects); and 4) intrapersonal hurdles (i.e., limited social support and fear of stigma and unwanted disclosure).[36–39] **A recent review found that unexpected events were a major reason for TI and required rapidly responsive and flexible services.**[36] We find the same in Malawi.[10,39]

Current TI services do not work in the long-term. The few evidence-based interventions for TI clients, such as "Welcome Back" strategies, are limited in duration (usually only ~1-3 intervention visits across 0-3 months) and limited in services offered (usually counseling alone or counseling + home-based re-initiation).[11,40] These short-term TI interventions often have high re-initiation rates followed by high rates of repeat TI after interventions end.[10,11] TI is rarely a one-time event.[41] TI programs must have long-term strategies to address dynamic and changing barriers.

Our recent trials show that TI clients need long-term interventions that provide both person-centered counseling + flexible and tailored service delivery strategies. Our ENGAGE trial (n=735; PI:Coates; R01-MH122308)[42] and BMGF-funded IDEAL trial (n=565; PI:Dovel, INV-001423)[40] aimed to improve ART re-initiation and retention among men experiencing TI in Malawi. Primary outcomes for the trials were 6-month retention or 6-month viral suppression. We found that 1-3 short-term person-centered counseling sessions combined with variations of short-term home-based ART (0-3 months) dramatically improve return to care after TI (~96% re-initiated vs 67% in standard of care – SOC; p<0.001).[43] But short-term interventions were not enough – rates of continued ART engagement at 6-months after re-initiation were unacceptably low (only ~64% were continuously

in care without repeat TI at 6-months vs 48% in SOC, p<0.001). Median time to repeat TI across intervention arms was 3.6 months – showing that TI reoccurred quickly *after* intervention components were completed.[10]

Clients who failed in our trials (i.e., had repeat TI <6months) wanted long-term counseling and the ability to choose flexible, responsive services that support their unique needs. We traced and interviewed clients in intervention arms who experienced repeat TI during the trial period (n=65). Clients wanted long-term support but did not want a one-size-fits-all package. They specifically wanted services and counseling that met their unique needs and were flexible. Clients desired varying combinations of services to: 1) peer support HIV/ART knowledge and concerns around social support; 2) ongoing support for navigating unexpected life events amidst ART care; and 3) more flexible HIV services (see Fig 1). Ongoing relationships with HCWs + flexible services that can adjust to changing needs were seen as essential to helping clients navigate unexpected events, a key cause of TI identified in the literature[36] and our own work in Malawi.[37–39] Repeat TI clients often wanted multiple service options with distinctive combinations – importantly nearly all combinations were within the current capacity of what facilities in Malawi can offer.

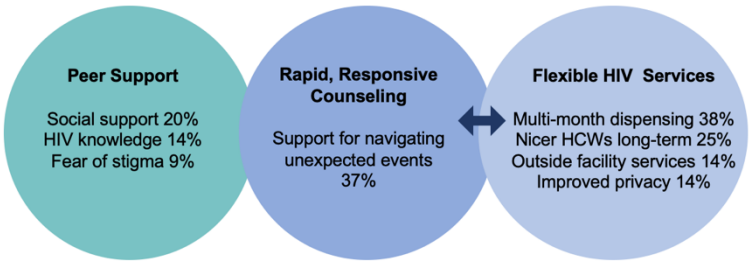

Fig 1. Desired interventions among male ART clients in IDEAL/ENGAGE trials with repeat TI (n=67)

A.2. Solution to the Problem –

TI clients need long-term, responsive interventions. There are no one-size fits all intervention to support long-term care for TI clients because clients experience vastly different and changing barriers to care. While health facilities do have limited capacity for adding new services, existing services can be packaged differently to meet clients' needs.

Long-term, dynamic choice of services is one way to provide responsive services[12,13] and promotes client ownership over care.[14–16] We propose to give TI clients long-term, dynamic choice of *what* services they receive and *how* they receive it (drawing from key building blocks of DSD).[44] Long-term, dynamic choice puts clients in the driver's seat and may be the best practical strategy to provide long-term and responsive TI interventions that are tailored to clients' evolving life circumstances. Dynamic choice is frequently used for HIV prevention and family planning products, whereby clients select the type of health product that works best for them (i.e., condoms, injectables, etc.).[45,46] Choice of these services is strongly associated with improved outcomes.[45,46] Recent evidence shows that long-term, dynamic choice of HIV prevention strategies dramatically outperforms SOC in eastern and southern Africa.[47] But dynamic choice is not offered in routine care for *how* ART treatment is distributed. Dynamic choice may be a critical missing piece to ART programs' ability to engage TI clients long-term. Choice increases clients' sense of autonomy, self-efficacy and ultimately client satisfaction,[14,48] all contributing to positive health service outcomes.[49,50]

Ongoing, dynamic choice of differentiated service delivery (DSD) models is a feasible and likely safe way to optimize the benefits of choice and provide responsive services for TI clients. DSDs emphasize flexible service delivery options by tailoring services across three building blocks: *what, when* and *where* HIV services are provided.[44] DSD models that have been widely implemented among established ART clients already successful in care have a range of benefits, including increased access,[51] privacy, acceptability,[51–54] and improved or non-inferior retention and viral suppression.[30,52,55] But DSD models have not been tailored to TI clients and are rarely offered to this population.[54] We are unaware any dynamic client choice offered for ART services linked to DSD.

Table 1. CHOICE components and barriers addressed for TI clients

Intervention	Barrier Addressed
Long-Term, Person-Centered Counseling	• Perceptions of HIV/ART
Long-Term, Dynamic Choice Choices Offered *(DSD principles: when, what, where)* • Dispensing interval *(1, 3 or 6 months)* • Location of dispensing *(facility, home, community)* • Peer mentorship (*frequency, when, where*) Hotline for rapid support and change of choice	*Choices Offered* • Health service delivery • Interpersonal factors* Unexpected events** * *if peer support selected* ** *i.e., dynamic choice* *Hotline* • Unexpected events

Our CHOICE intervention will provide long-term person-centered counseling + long-term, dynamic choice of DSD services to TI clients in Malawi. CHOICE builds on lessons learned from IDEAL and ENGAGE trials, ensuring that we address gaps that resulted in sub-optimal long-

term ART retention within those trials (i.e., we fixed the problem of short-term and not offering responsive, adjustable service delivery options). In CHOICE, TI clients will receive long-term counseling + long-term choice throughout study duration (24-months; see Table 1 for intervention components).

TI clients will be offered long-term person-centered counseling tailored to TI clients. The Malawi Ministry of Health adopted findings from our previous trials and is incorporating short-term person-centered counseling into standard of care (SOC) for TI clients. This will be our SOC control condition. But as we pointed out, the effects of short-term interventions only last as long as the intervention itself. We now need to bolster SOC with long-term interventions for TI clients. Ministry of Health is interested in long-term strategies but are not willing to adopt them until there is clear and rigorous evidence that they are worth the additional cost.

CHOICE builds on this finding by using similar counseling techniques but extending counseling efforts across 24-months. Person centered counseling uses motivational interviewing techniques to foster compassionate interactions that are responsive to clients' treatment history, life priorities and personal motivations.[56–58] Person-centered counseling should 1) build rapport, 2) connect with clients' intrinsic values and priorities, 3) understand individual experiences and evolving barriers, and results in 4) co-developed, tailored action plans to overcome barriers.[59–61]

Clients who agree to re-initiate ART will receive long-term, dynamic choice of *how* they receive care, building on the barriers and action plan from counseling (above). Choice will focus on DSD principles of *what, when* and *where* HIV services are provided,[44] within the capacity of healthcare facilities to deliver. Exact choices offered were informed by the literature and lessons from IDEAL/ENGAGE trials, clinical safety considerations, and district and national Ministry feedback on what could be scaled, if cost-effective. Based on existing clinic capacity and DSD models, we provide multiple choices around: 1) ART dispensing intervals; 2) location of dispensing; and 3) peer mentorship. **Clients can combine multiple choices at any given time to create personalized intervention packages** and can adjust their choice over 24 months (duration of study period). A CHOICE hotline will be made available for rapid counseling and rapid dynamic choice to support needs from unexpected events.

CHOICE will support clients to build self-efficacy and activate client engagement while simultaneously ensuring health facilities provide responsive services that are feasible within existing health systems and meet client needs.[36]

B.1. Conceptual Framework:

We draw from Andersen's Emerging Model of Health Services Use, phase 4[62] to develop CHOICE. Andersen's model examines how environment and structure of health systems interact with clients' enabling resources and perceived need to influence ART engagement. Fig2 shows factors we hypothesize CHOICE will influence, and the recursive nature of service utilization. Each interaction with CHOICE provides clients an option of dynamic choice, allowing for continuously adaptive and responsive services, which in turn can strengthen client satisfaction understanding of their own needs, client self-efficacy, and client ability to overcome future barriers to care. The recursive nature of service utilization means that each interaction with CHOICE can strengthen client characteristics and health behavior. All these influence sustained ART retention and viral suppression.

We use this cyclical nature of the Andersen model to understand how CHOICE may impact ART coverage and viral suppression over a 24-month period (12-month viral suppression primary outcome, 24-month secondary outcome as we understand retention is not linear[30]). We hypothesize CHOICE will increase overall retention and make it easier for clients to return from care after repeat TI (i.e., result in less time out of care) (Fig 3[41]).

B.2. Innovation

- **CHOICE** is a highly innovative strategy that has significant potential to lead the field in developing strategies to engage TI clients long-term to improve their health and reduce onward transmission
- **TI clients need and want long-term interventions.** But nearly all TI programs to date are short in duration. We need a full trial to examine the cost effectiveness and the cost at scale as sustainable and integrated activities are key to future HIV national programs. Malawi is an innovator at implementing such programs once proven effective, cost-effective, and scalable.

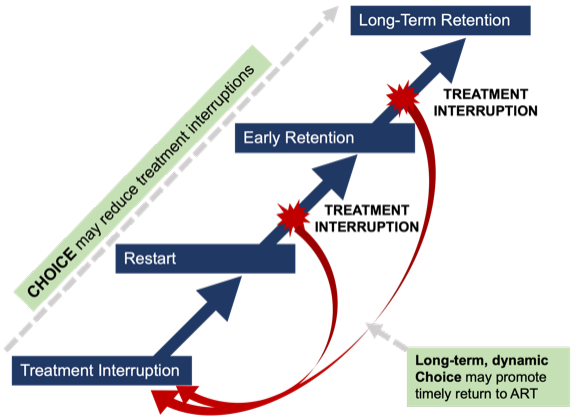

Fig 3. CHOICE hypothesis, adapted from Ehrenkranz et. al conceptualization of a revised treatment cascade

- **Choice** has been successful in other areas of public health, and especially reproductive health and thus has a strong track record making it highly likely of success in this application as well. Choice increases clients' sense of autonomy, self-efficacy and ultimately client satisfaction,[14,48] all contributing to positive health service outcomes.[49,50]
- **Choice can pragmatically allow responsive, tailored services for key populations:** Individuals and sub-populations such as men, pregnant women, MSM, and adolescents need tailored and highly responsive approaches to service delivery.[63]. CHOICE uniquely facilitates targeted services that meet the specific needs of sub-population by gender, age, or behavioral risk to enhance potential scalability and broader relevance in real-world settings.
- **CHOICE will provide important evidence on the safety and impact of offering TI clients choice of how services are delivered.** CHOICE will be one of the first DSD interventions specifically designed for TI clients, the group at highest risk of repeat TI. To date there are no DSD-related interventions tailored to TI clients, who stand to benefit the most from differentiated service delivery since standard care did not work from them. [34,108] . Clear and definitive evidence is needed to determine safety and cost-effectiveness.
- **We will assess viral suppression out to 24 months post-baseline.** Many studies only track for 6 or even 12 months but the long-term assessment is essential to establish long-term efficacy and cost-effectiveness.
- **Malawi has a strong track record of implementing innovations in HIV prevention and treatment when those innovations have proven to be effective in well conducted clinical trials and cost-effective.** Examples of our work include uptake of 3- and 6-month MMD as SOC for stable clients[20,64] and adoption of HIVST strategies into national guidelines.[17,19,65,66]

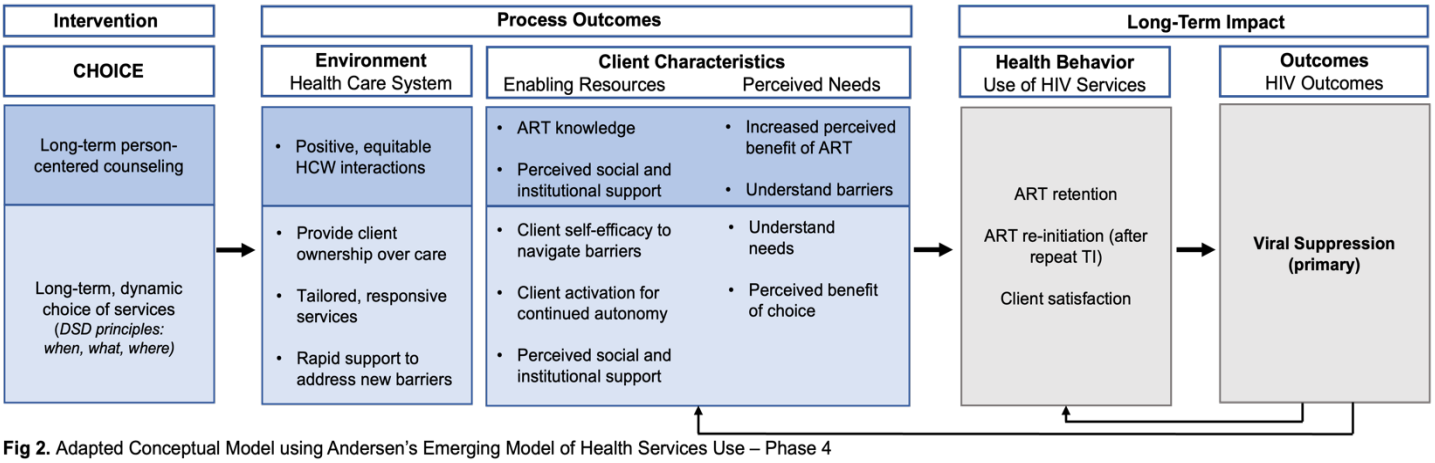

Fig 2. Adapted Conceptual Model using Andersen's Emerging Model of Health Services Use – Phase 4

C. Approach

C.1 Pilot Data and Preliminary Studies

Pilot study shows CHOICE is acceptable, feasible and has promise for impact: We piloted CHOICE (but only with choice of dispensing intervals, not all DSD models) in two Malawian health facilities for 3-months, using a case-control design and matching case-control 1:1 by facility and sex (N=116). 13 HCWs were trained and supported to implement CHOICE. 58 TI clients were in the case (i.e., intervention) group (22 male and 36

female TI clients) and 58 were in the control (i.e., SOC, 22 male and 36 female group TI clients). Mean age was 40 (IQR:37-42), and mean years since first ART initiation was 6 years (IQR: 3.6-9.8) and mean duration of current TI upon enrollment was 48 days (IQR: 42-55). Primary outcome was ART retention at 3-months.

- **Feasible within routine settings:** CHOICE sessions were recorded for quality assurance (n=51), with mean 38 min duration for first person-centered care + choice session. 86% (44/51) articulated their choice of ART services – 73% (37/58) received 3- or 6-month dispensing in intervention vs 32% (19/58) in control groups.
- **Acceptable to HCWs**: 12 pre-post interviews were conducted with HCWs. Prior to CHOICE pilot, HCWs were skeptical of time required to implement CHOICE and if clients would want to choose. After the pilot, HCWs were very enthusiastic about the intervention and expressed increased job satisfaction due to positive interactions with clients. We need a full trial to assess cost and cost-effectiveness overtime and if CHOICE is a viable option to take to scale.
- **Impact:** TI clients who received the CHOICE intervention were significantly less likely to experience repeat TI at 3-months (16% repeat TI vs 50% in control group); aHR: 0.32, 95% CI:0.24-0.44; see Fig 4). It is critical to test ongoing feasibility with all choices, safety, impact, and cost-effectiveness of CHOICE.

Acceptability and Need

- **Female TI clients want CHOICE.** We conducted surveys with 103 female TI clients across 14 facilities who recently returned to care to ensure the CHOICE design was gender sensitive and inclusive. Forty-three percent of female TI clients (34/103) reported that their ART clinic did not provide person-centered, responsive services. After describing CHOICE, 96% (99/103) of female clients said they wanted to participate in the intervention – 88% (91/103) were confident they could make choices about service delivery strategies that same day (12% wanted to consult a friend or family member prior to making decisions). They believed CHOICE should include the following to meet women's unique needs: 1) welcoming and confidential environments that facilitate open discussion, 2) HCWs actively elicit questions and feedback from clients; and 3) ability to ask for reminders about future appointment dates.

Safety

- **Client choice is safe:** No severe adverse events (progression to advanced AIDS, death) were associated with the CHOICE pilot or the larger IDEAL and EGAGE trials (short-term intervention of person-centered care + variations of short-term home-based ART). A full trial is needed to assess long-term safety of CHOICE. Our programmatic work at 123 Malawian facilities shows that nearly all TI clients who return to care are healthy (WHO stage 1 or 2) and do not require additional clinical monitoring – most will be eligible for CHOICE.

C.2 Overview of Interdisciplinary Research Team

We have extensive experience with TI clients overtime,[37–39,67] person-centered ART strategies,[40,42,68,56,69] and differentiated services.[1,18,20–22] We are productive, multidisciplinary, and well positioned to conduct high-impact, scalable research.

UCLA (prime) and Partners in Hope (PIH): PIH and UCLA have collaborated for the last 20 years on over 25 clinical trials and implementation science studies within the overarching structure of a PEPFAR clinical care grant (serving 123 facilities). We have over 80 publications and directly contribute to regional and global guidelines in HIV testing, TB diagnosis, ART services for men, and DSD models. Our previous trials informed the scale-up of index partner and facility-based HIV self-testing,[17,19,65] 6-month multi-month dispensing for stable clients,[20,64] and most recently person-centered counseling for TI clients.[70] We are uniquely positioned to successfully implement this trial in a way that is innovative, impactful and, if effective, scalable by Ministry of Health.

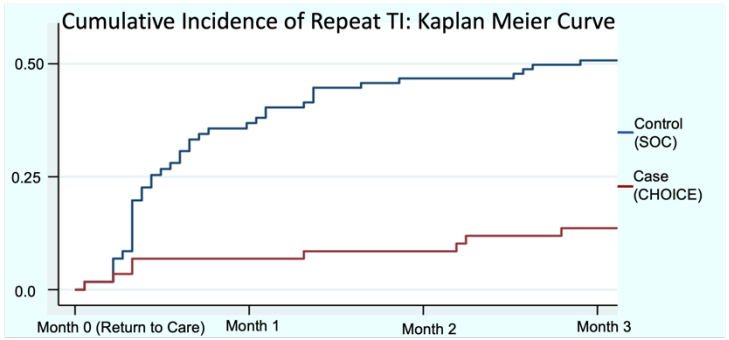

Fig 4. Cumulative incidence of repeat TI following CHOICE Pilot

Principal Investigators: Kathryn Dovel, PhD, Associate Professor of Medicine, UCLA Division of Infectious Diseases, is a Behavioral Scientist focused on responsive services for HIV testing and treatment among hard-to-reach populations.[19,38,67,71–73] She is an expert in facility-level barriers to care[38,72,73] and has led numerous interventions to facilitate various strategies for person-centered services.[69,74,75] She is PI of a K01 and the IDEAL trial, and has played key leadership roles in studies on women's unique needs and solutions

for treatment continuity.[76,77] Dr. Dovel lived in Malawi for 9 years working with PIH. **Augustine Choko, PhD (MPI),** based in Malawi, is an Epidemiologist at PIH and Malawi Liverpool Wellcome Trust. Dr. Choko is a world-renowned researcher on effective and responsive HIV testing and treatment uptake strategies in the region.[66,78,79] He is a co-chair for the World Health Organization's Working Group for HIV self-testing and site lead for the ENGAGE and IDEAL trials.

Fig 5. Study facility (cluster) map

Co-Investigators: Rose Nyirenda, MD (Co-I), is the Director of the Malawi Ministry of Health HIV/AIDS Unit. Dr. Nyirenda and team co-designed the intervention. She will lead health system components to ensure sustainability and compatibility with HCW workflow and job satisfaction. **Sam Phiri, MD (Co-I),** based in Malawi, is the Director of PIH's PEPFAR activities across 123 facilities. He is an expert in scalable interventions within health systems.[80–82] He will be responsible for ensuring intervention feasibility for national scale-up, if effective. **Risa Hoffman, MD MPH (Co-I),** is a clinician and expert in HIV care among pregnant/breastfeeding women[83–85] and the impact of MMD.[20,53,86,87] She will provide clinical guidance around safety and best practice. **Thomas Coates, PhD** (**Co-I)** Distinguished Research Professor of Medicine in the Division of Infectious Diseases and world-renowned researcher in gender-sensitive HIV services (for both men and women)[5,88,89] and PI of the ENGAGE trial. He will advise on project development and implementation and guide behavior change analysis in Aim 2. **Bruce Larson (Co-I)** is a health economist with extensive experience estimating the costs, and cost-effectiveness of HIV treatment and DSD models in Africa. He will be responsible for all cost and cost-effectiveness activities.[90–92] **Sydney Rosen (Co-I)** is a health economist with extensive experience in TI, repeat TI, risk factors and solutions, including DSD.[54,93,94,21] She will contribute to conceptualizing of cyclical TI and ensure the trial is situated within larger regional and international discussions of solutions for cyclical TI. **Chi-Hong Tseng, PhD (Co-I)** is a biostatistician in clinical trials, including four trials with this team. He will serve as the biostatistician for all components of CHOICE.

Advisor: Lawrence Long, PhD, is a behavioral scientist and leader of one of Africa's first behavioral economics units at Wits University SA.[52,95,96] He will provide insight to client choice and fidelity of CHOICE.

C.3 Setting

Malawi is a pioneer of innovations in HIV service delivery,[97] with robust monitoring and evaluation systems and a strong public health approach to HIV care that makes it an ideal setting to test new models for vulnerable populations such as TI clients. Study activities will be integrated into a large PEPFAR-USAID program (CAN:72061219CA00003) led by PIH that supports HIV services at 123 health facilities in 9 of 28 districts in Malawi (>200,000 ART clients supported). PIH has been a PEPFAR implementing partner since 2006 and has been re-funded by USAID four times. Twelve high-burden facilities will participate in the study (Fig 5). PIH provides HIV clinical and support services, monitoring evaluation, and quality improvement strategies within these facilities. Approximately ~4,300 adult ART clients will experience TI each year at the twelve participating facilities (i.e., eligible for the study). Based on our previous successes in IDEAL and ENGAGE trials with the same population, we expect to find and screen 2,795 TI clients (65%) and have 1,696 (61%) of those traced who are eligible and willing to enroll – more than enough to reach our sample size of 800 participants. A 65% success rate in identifying and screening TI clients is extremely successful for the region[98,99] and is more than feasible within our team (we reached 65% within IDEAL and ENGAGE trials).

D. Research Design and Methods:

D.1 Aim 1: Test the effectiveness of CHOICE versus SOC on 12-month viral suppression among TI clients. We will conduct a cluster randomized trial at 12 health facilities (n=800 individuals). Primary outcome is viral suppression at 12-months (<50copies/mL). Secondary outcomes described in Fig 6 and Table3.

Study Population. Our eligibility criteria include: ≥15 years of age; living with HIV; initiated ART for the first time ≥3-months ago (i.e., not a new initiate); non-pregnant; and experienced TI during their most recent ART appointment (>28 days late). We exclude pregnant women because the ART/antenatal care (ANC) programs are integrated and require additional considerations and linkages with antenatal services.

Randomization. We will cluster at the facility level using constrained randomization (constrained on ART clinic size and geographic location) to allocate each cluster 1:1 to either CHOICE or SOC arms. All participants each

facility (cluster) will receive the same intervention, implemented by routine facility staff (see Fig 6). Randomization will be done at a group meeting with facility leads from participating facilities. Results will appear as a picture on the tablet, allowing meeting participants to view the randomization to maximize transparency and buy-in.

Screening and Consent: The same procedures for screening and consent will be used across arms. National guidelines have two strategies for reaching TI clients: 1) community tracing by a lay cadre (called Treatment Supporters) to encourage return to care; 2) screening at facilities by Treatment Supporters to identify TI clients who are newly re-initiating that day. TI clients identified through either strategy will be immediately referred to study staff to complete same-day eligibility screening. Written informed consent and baseline survey will occur immediately following eligibility screening prior to randomization and receiving any intervention or clinical services. Ineligible TI clients and those who refuse will be referred to appropriate clinical services at the nearest facility. We successfully used the same strategies for IDEAL and ENGAGE.[40,42]

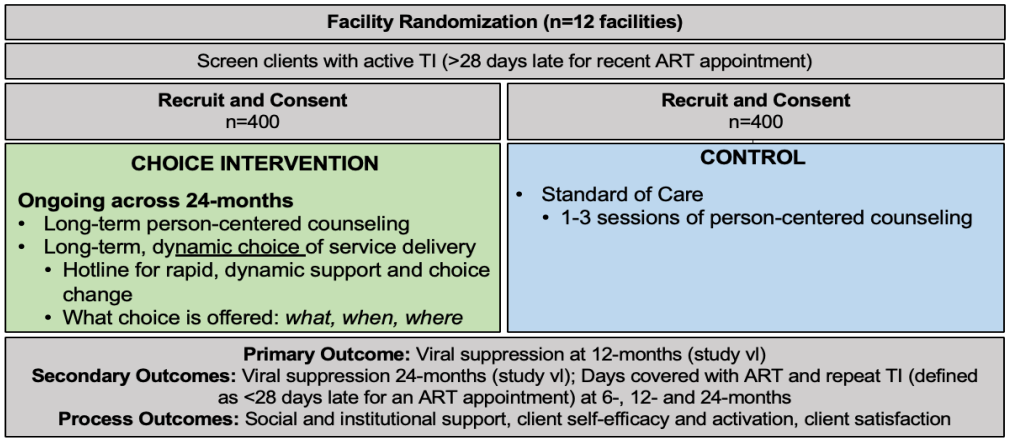

Fig 6. Study flowchart by arm

The Intervention: CHOICE

CHOICE was designed based on prior research with TI clients and the environmental factors, enabling resources and perceived needs identified from Andersen's Theoretical Model[100]. Clients will be offered:

STEP 1. Person Centered Counseling + Choice Sessions (implemented by Treatment Supporters): Treatment Supporters are a lay cadre specializing in client counseling. Immediately following enrollment and the baseline survey (described above), TI clients will receive one-on-one sessions that first provide person-centered counseling, followed by discussions and job aids to support client decision making around choice of service delivery options. First session will last ~60 minutes. Additional sessions will last ~15-60 minutes, based on client needs, wants and HCW time available.

Person-centered counseling for TI clients: the overarching goals of person-centered counseling are: 1) build rapport through kind, equitable interactions; 2) understand individual experiences and evolving barriers; 3) emphasize benefits of ART by linking ART to clients' intrinsic values and priorities; and 4) support clients to develop personalized strategies to overcome barriers, a key component to building self-efficacy and client activation.[59–61] Treatment Supporters will use motivational interviewing techniques to elicit client perspectives and link with internal motivation.[14,58] We have used similar curriculum that has shown short-term increases in clients perceived self-efficacy and activation.[56]

CHOICE TI counseling materials are refined from IDEAL/ENGAGE's short-term (1-3 session) TI curriculum[101] and Malawi Ministry of Health's adapted TI counseling job aids from IDEAL/ENGAGE (see Appendix A). *Location:* Counseling will take place immediately after enrollment in a community location of clients' choice (for clients enrolled via community tracing) or at/near facilities (for clients identified when returning to ART services). We have extensive experience offering TI tailored, person-centered counseling in various settings.

Supporting decision-making for choice: Clients who agree to re-initiate ART will be given dynamic choice of *how* they want to receive care, building on the barriers and action plan in the above counseling. Client choice will focus on DSD principles of *what, when* and *where* HIV services are provided.[44] We will provide multiple choices around: 1) ART dispensing intervals (1-, 3-, 6-months); 2) location of dispensing (facility, home, community); and 3) if they want peer mentorship (if yes – frequency, when, where). Clients can combine multiple choices at any given time to create personalized intervention packages. A decision aid will help clients visualize benefits and challenges of each choice (*when, what, where;* see Table 2 for a description of specific choices available*)*. Clients who want to consult family/friends prior to making a choice (18% of women in preliminary data), will be given SOC ART services that same day (to promote medication in hand) and a decision aid pamphlet to facilitate further discussions with social networks. Choice can be made anytime via CHOICE hotline or facility visits.

Client choice will be recorded in medical charts and clients given a laminated "choice card" with their selection to act as a commitment device to nudge discussion about desired choice with ART providers.[32,56,69,73,74] Those counseled in the facility will immediately take their choice card to an ART consultation to receive services (see below. Those counseled in the community will be either escorted to the facility or scheduled for a facility appointment at their earliest convenience. The curriculum has been developed, piloted and refined – it resonates with clients and is feasible among HCWs.

Table 2. Long-term, dynamic CHOICE intervention components across 24 months

Step 1: Counseling + CHOICE Session (Treatment Supporter) – 60 min	Step 2: ART Consultation (Provider) - 15 min	Step 3: Follow-Up ART Visits (Combined Step 1 + 2)
Long-Term Person-Centered Counseling • Kind, equitable interactions • Understand clients' evolving barriers • Strengthen perceived benefit of ART • Co-develop tailored strategies for retention **Long-Term, Dynamic Choice** How Choice is Offered • Decision aid + choice card w/ decision • Hotline for rapid support and changes to choice What Choice is Offered *DSD Options (when, what, where)* • Dispensing interval *(1, 3 or 6 months)* • Location of dispensing *(facility, home, community)* • Peer mentorship (*frequency, when, where*)	**Medical Assessment** for contraindicating conditions **Discuss client choice card** • Provide client choice of services if clinically safe (if contraindicating conditions present) • Offer modified choices deemed clinically safe	**Truncated Counseling + CHOICE Session** (Treatment Supporter, 15-60 min) • Abbreviated Step 1, based on needs of clients **ART Consultation** (Provider, 15 min) • Same as Step 2 **CHOICE Hotline** (Treatment Supporter) • Available 24/7 for rapid support and changes to choice ***If Repeat TI*** • *Standard community tracing* • *Repeat all CHOICE activities upon tracing* • *Refer for advanced counseling and services as needed*

STEP 2. *ART Provider Consultation:* Prior to ART initiation, providers will conduct routine medical assessments to screen for contraindicating conditions (opportunistic infections or significant co-morbidities that may limit the clinical safety of some service delivery choices. The provider will actively elicit and discuss client choice of DSD, discussing what are clinically safe options (based on above assessment) and using person-centered communication strategies.[102] Clients without contraindicating conditions should be given their chosen service delivery options as specified in their choice card. Clients with contraindicating conditions will be offered modified choices that are deemed clinically safe at that visit, at the providers clinical discretion. Choice options will increase in future ART visits as clients become clinically stable.

STEP 3. *Follow-Up ART Visits:* A truncated person-centered counseling + CHOICE session will be offered during all subsequent ART visits until completion of the study (24 months), or client opts out. This ensures long-term, dynamic choice for TI clients to facilitate responsive services and client self-efficacy. CHOICE sessions will: 1) review core principles of self-efficacy; 2) discuss life experiences, unexpected events (experiences or anticipated), and any challenges/concerns with HIV services; 3) facilitate informed choice of service delivery options (~15-60 minutes).

Clients with repeat TI or poor adherence (defined by SOC) will receive standard tracing and enhanced adherence counseling in addition to the CHOICE intervention – they will still have choice of services unless deemed clinically unsafe. From our prior work, we anticipate <3% of clients to have clinical complications.

Hotline for Rapid Choice/Support: We will establish a toll-free "hotline" for participants to call for rapid support on navigating unexpected barriers/events, receiving general support, or changing their choice of services (i.e., dynamic choice). Participants will be given the hotline number upon randomization and reminded during each counseling + choice session. For example, clients with unexpected travel could be linked with facilities where they are traveling. Clients with new sexual partners can be counseled on navigating disclosure.

Strategies to Support HCW Implementation of CHOICE

It is critical that HCWs be supported to implement CHOICE with fidelity. We will complete the following training and adaption individual HCW monitoring/evaluation systems to support CHOICE within routine care. We have extensive experience with this within RCTs.[17,19,20,69,73,103,104]

Training: We will recruit HCWs (Treatment Supporters and ART Providers) who have prior experience in basic counseling skills (active listening, reflection, and information gathering), and with basic facts of HIV transmission, HIV testing and treatment. The study team will receive a 5-day training. The training will include pre-post assessments for HCW buy-in and skill acquisition using self-report and role-play observations.[105] We will utilize didactic learning, group discussion, role play, and peer feedback to achieve HCW buy-in, skills, and peer support for implementing CHOICE. Additional training will be provided iteratively based on training post assessments.

Additional training/support will be given if there are >30% discrepancies in client choice vs. actual DSD given, poor client satisfaction with intervention, or HCWs express additional need – all training will be documented and costed for Aim 2 and 3 analysis.

Routine Quality Improvement (QI): CHOICE implementation will be embedded within larger PIH QI efforts conducted as a PEPFAR implementing partner, including routine QI oversight and mentorship. PIH has conducted over 90 QI projects that have improved facility-level performance.[73,103,104]

- Identify HCW "Champions": Each facility will designate two HCW "Champions" to spearhead CHOICE efforts (one Treatment Supporter, one ART provider). Champions will receive a small stipend from the study to support the efforts and will provide immediate troubleshooting and encouragement to other HCWs at their facility. They will also represent HCW concerns/needs to study team in real time.
- Ongoing HCW monitoring & evaluation: During routine facility QI meetings (monthly meetings about quality of ART services broadly), HCWs will receive feedback on CHOICE implementation with facility-level data visualization. HCWs will be encouraged to discuss challenges, solutions and participate in peer mentorship for optimizing CHOICE. HCWs will work together to identify monthly goals and strategies to reach goals.[106]

Standard of Care (SOC) Arm

The intervention arm will be compared against SOC services for TI clients, including 1-3 person-centered counseling sessions for TI clients (no choice of services) and 1-3 month ART distribution for the first 6-months. The study will not alter any facility protocols or routine practices. Based on our formative work at 24 facilities, we find that 64% of clients are given 1 month dispensing after TI and nearly none receive community services. HCW monthly evaluations are largely based on number of clients retained, not service quality.

Aim 1 Measures and Data Collection. All measures are informed by Andersen's Theoretical Model.[100] Our primary outcome is viral suppression (<50copies/mL) at 12-months (collected by the study) to capture any long-term impacts of the intervention and cyclical engagement in care. We include secondary outcomes of: ART coverage (measured by days client has ART in possession) at 6, 12 and 24 months; a secondary study viral suppression at 6 24 month; and time to and duration of repeat TI throughout the study period. Implementation science measures (from client, HCW and facility-level) are in Aim 2.

Study viral load sample at 12 months (primary outcome) and 24-months (secondary outcome): We will conduct study viral loads for all participants at 12- and 24-months after enrollment (regardless of ART retention). Blood samples will be collected during routine facility visits when possible, and through client tracing when needed (i.e., for clients not in ART care). We used similar strategies in ENGAGE trial and ascertained samples for 92% of participants at 6-months.

Medical Chart Review at 6, 12 and 24 months: We will conduct medical chart reviews to determine: 1) days covered by ART based on quantity of ART dispensed and refill dates at each appointment; 2) repeat TI at any point (defined as >28 days late for any ART appointment) and time to and duration of repeat TI; 3) progression to advanced HIV disease (AHD, defined as WHO stage ¾ or CD4<200, whichever measure is available in records), opportunistic infections or death during the study; and 4) client choice of services vs actual services given (to be used in Aim 2). Study staff will ensure medical records are complete and accurate prior to collection. We used the same strategy for IDEAL/ENGAGE trials, with 10% missing data.

Baseline Survey, 6-, and 12-Month Follow-Up Survey: Baseline, 6- and 12-month surveys will be conducted in-person by a research assistant in the local language. Location and time of surveys will be determined by client preference. Measures are based on our adapted Andersen theoretical framework.

- **Environment – Health System:** Health system- and HCW-level moderators will be evaluated in Aim 2.
- **Client – Enabling Resources:** (i) HIV/ART knowledge using the comprehensive HIV/AIDS knowledge question tool from Demographic Health Surveys (DHS) regularly conducted across the region;[107–109] (ii) Social support and stigma experiences using the Medical Outcomes Study Social Support Survey (MOS-SS) for measuring perceived social support among chronic condition patients[110,111–113] and the validated HASI-P tool for internalized and perceived stigma;[114] (iii) HIV Self-Efficacy Questionnaire specific to ART access and adherence;[115] (iv) Client activation measures to assess ongoing, activate autonomy over self-care including confidence and ability to seek additional information from HCWs, self-management behaviors and resiliency toward unexpected events;[116,117] (v) Client satisfaction with HCW interactions and services received using adapted Service Provision Assessment (SPA) used routinely in Malawi.[118]
- **Client – Perceived Needs:** i) Perceived need for ART[119]; (ii) Identifying personal barriers and needs[120]; (iii)

Perceptions of CHOICE (for intervention arm) and if services are responsive to needs

- **Health Behavior – Use of Services:** Use of i) HIV and ii) related services (STI, family planning, TB, antenatal care) *prior* to enrolment and *during* study period will be documented through individual medical record books (kept by clients and updated at every facility visit – clients cannot receive services without presenting their medical record book). Individual medical records will supplement medical chart reviews and ensure measures of repeat TI are accurate (i.e., we account for any ART services received at non-study facilities). Pregnant women will be excluded from the study and linked to appropriate routine ANC/ART services as needed.
- **External (non-intervention) mediators:** (i) Sociodemographics (age, wealth/education, marital status and parity, etc.) ongoing barriers to care; ii) presence of unexpected proximal events (changes in work, mobility, familial health and/or responsibilities, extreme weather events, etc.);[36] and (iii) previous use of HIV services. Facility-level changes in service provision (due to extreme weather, changes in national policy or PEPFAR priorities, loss or addition of personnel, etc..) will be measured through quarterly facility reports.

Study Data Supervision, Quality Assurance, and Minimizing Potential Contamination*:* Research Assistants are distinct from HCWs and responsible for enrollment and all study data collection – they will not participate in any intervention/SOC activities. Research Assistants receive daily monitoring, supervision, weekly team meetings with the Study Coordinator, and periodic observation, back checks and quality "spot checks".

Data Management: Systems for data management are described in 3.3 Data and Safety Monitoring Plan.

Power and Sample Size – Aim 1: With 12 clusters available for randomization and 800 clients enrolled in the study (assuming 67 participants per cluster), we will have >80% power to detect a difference in 12-month viral suppression (regardless of ART retention) of 15% (i.e., 55% in SOC as seen in ENGAGE 6-month viral suppression data vs 75% in CHOICE), assuming that 15% of individuals will be lost to follow-up in either arm (treated as failures for outcome evaluation). We use conservative outcome estimates based on preliminary data. Existing literature shows an intracluster correlation coefficient (ICC) of 0.004 between facilities in the region,[130,151] but we conservatively power to an ICC of 0.02 to ensure sufficient power. Assuming that 61% of TI clients screened will be eligible and enrolled in the study (based on CHOICE pilot and IDEAL/ENGAGE trials), we will screen ~ 1,311 TI clients to reach the 800 sample (see Section 4.3 *Statistical Power and Analysis* for details*).*

Data Analysis – Aim 1:

Table 3. Study Measure for Aim 1

Outcome	Measurement	Source
Primary Effectiveness Outcome		
Viral suppression (<50copies/mL) at 12-months	Proportion of clients virally suppressed 12-months after enrollment (regardless of recorded ART re-initiation)	Study viral load
Secondary Effectiveness Outcomes		
Advanced HIV at 12- and 24-months	Presence of WHO stage 3 or 4 based on a clinical assessment conducted during the 6-month study viral load	During study viral load (at 12- and 24-months)
Viral suppression (<50copies/mL) at 24-months	Proportion of clients virally suppressed 24-months after enrollment (regardless of recorded ART re-initiation)	Study viral load
ART re-initiation at 3-months	Proportion of clients who re-initiate ART 3-months after enrollment	Medical chart review
Repeat TI at 6-, 12- and 24-months	Proportion of clients who ever experience default (>28 days out of care) at any point during the first 6-, 12- and 24-months after study enrollment	
Days covered with ART at 6-, 12- and 24-months	Total days with ART in possession, reflecting cumulative time spent in care at 6-, 12- and 24-months	
Adverse events (biomedical) at 6-, 12- and 24-months	Presence of opportunistic infections or death since enrollment in the study	
Process Outcomes		
Client perceived social and institutional support	Client perceptions of the help or guidance they can access from their social networks and health service providers, including emotional, physical, informational assistance with HIV and/or ART related matters	Follow-up survey at 6- and 12-months
Client self-efficacy and activation	Ongoing, perceived and experienced autonomy over self-care including confidence and ability to seek additional information from HCWs, self-management behaviors and resiliency toward unexpected events in relation to treatment engagement	
Client satisfaction	Client satisfaction with HCW interactions and services received using adapted Service Provision Assessment (SPA) used routinely in Malawi	

Data Analysis – Aim 1: We will use generalized linear mixed effects models (GLMMs) as the main analytic approach, as they are recommended for group-randomized RCTs to estimate causal effects of interventions on individuals, adjusted for clustering within groups. This method performs well in situations where the number of

observations per cluster is large and for unequal cluster (facility) sizes.[152,153] Intention-to-treat analysis will be performed for all outcomes. The primary outcome is viral suppression at 12-months and will be analyzed by mixed effects logistic regression models with intervention as a predictor, adjusted for random facility effects, and pre-specified socioeconomic and demographic variables that differ at baseline (sex, age, poverty, etc.).

In the secondary endpoints analysis, GLMMs will be performed with binary and count outcomes of viral load suppression, days client has ART in possession, TI, and adverse events. We will stratify results by self-reported reason for TI at enrollment (collected in baseline survey) to explore causal mechanisms for any relationship between reason for TI, CHOICE and primary outcomes, and conduct multi-variate analysis on who benefits from CHOICE, including variables like age, sex, poverty, mobility, frequency of unexpected proximal events, and ART history. This will provide strong evidence for *whom* CHOICE works; We use two strategies for missing data: 1) missing data due to loss to follow-up (LTFU) will be treated as outcome failures; 2) multiple imputations, as if LTFU participants behave similarly to the SOC arm.[121,122] We will explore if LTFU clients are distinct, using baseline survey data. Our current IDEAL and ENGAGE trials have 90% retention for primary outcome data.

D.2 Aim 2: Systematically evaluate implementation of CHOICE.

We will use a mixed-methods approach to determine what refinements are needed to make the intervention as successful as possible. Aim 2 has three sub-objectives: understand 1) client perceptions of CHOICE acceptability, impact and remaining needs/changes desired; 2) HCW and stakeholder perceptions of CHOICE feasibility, acceptability and scalability; 3) fidelity/quality of CHOICE implementation and what influences fidelity to inform ensure fidelity/quality efforts in routine settings, if effective.

We place measures from the Andersen Theoretical Model[100] (see Table 4) within the consolidated framework for implementation research (CFIR) to assess the implementation contexts that influence how CHOICE is implemented, accepted and any predictors of.[123] We examine 4 domains within CFIR (Table 4).

Client perceptions of CHOICE

We will conduct 50 in-depth interviews with a subset of clients in the CHOICE arm at 6- (n=25) and 12-months (n=25) after study enrollment to understand experiences with CHOICE, intervention acceptability and desired changes, and perceptions of key CFIR domains, drawing specific factors from the Andersen Theoretical Model within each domain: Characteristics of individuals (Enabling Resources and Perceived Need) and characteristics of the intervention (intervention components + how clients experience the health system environment). We will stratify clients by sex and presence of repeat TI during study period. Interview will be conducted by local research assistants in the local language.

Table 4. CFIR domains examined in CHOICE

Domains from consolidated framework for implementation research (CFIR)
Characteristics of individuals: factors such as sociodemographics, social support, knowledge and perceptions about ART, and previous experiences with ART services.
Characteristics of the intervention: components of the intervention that support or inhibit successful outcomes for clients, or high quality implementation by providers.
Inner context: factors within facilities that influence how an intervention is implemented and HCW buy-in (workload and capacity of HCWs, training, monitoring and evaluation).
Outer context: factors external to the health facility that may influence how the intervention is implemented (existing policies, guidelines, priorities).

HCW and Stakeholder Perceptions of CHOICE

We will conduct in-depth interviews with 50 Treatment Supporters and ART providers and 25 district and national stakeholders to assess feasibility and scalability of CHOICE outside study settings, and what is required (and feasible) to ensure fidelity of CHOICE at national scale. Guides will draw from perceived individual- and intervention-level characteristics that influence CHOICE outcomes, and the facility- (inner context) and national- (outer context) level factors that impact fidelity of implementation and scale-up of CHOICE. We have experience eliciting information from HCW discussions across the CFIR domains[123] and will use visual aids and "anonymous case studies" from Phase 1 to facilitate detailed conversation. If CHOICE is successful, findings will identify strategies for scale-up and intervention fidelity. If unsuccessful, findings will identify key components to be adapted for additional research.

Fidelity/quality of CHOICE Implementation. We will assess how HCWs implement CHOICE, and what influences implementation. We will use an explanatory sequential design (i.e., quantitative data will inform qualitative methods) to explore how CHOICE works and what is required to achieve fidelity/quality.

50 CHOICE person-centered counseling + dynamic choice sessions and 50 ART consultations will be recorded to assess quality. For counseling and choice sessions we will measure quality of counseling, support to help clients navigate and make informed choices, and support of client autonomy using the Motivational Interviewing Treatment Integrity 4 (MITI 4) coding manual. For ART consultations, we will measure quality of ongoing choice discussions and shared decision making using a Roter Interaction Analysis System (RIAS).[124] We have completed similar analyses in ENGAGE and IDEAL.[125]

Using surveys and medical chart reviews from Aim 1, we will assess client choice, discrepancies between choice clients wanted and actual services given in the ART consultation. We will assess individual-level changes to desired choice and discrepancies between client choice and actual services given over time to understand how multiple exposures to CHOICE influence client choice and services provided.

Data Analysis – Aim 2*. Qualitative Data:* Data will be transcribed and translated into English. Codebooks for each qualitative datasets will be developed based on a priori themes from literature, Andersen's Theoretical framework, CFIR, and inductive themes that emerge from the datasets. Selected investigators will pilot the codebooks. Through an iterative consultative process, each investigator will revise their codebooks until there is high interrater reliability among the group. Disagreements will be resolved by consensus. For client interviews: we will use constant comparative methods[126] to analyze data, comparing similarities and differences by those with repeat vs no repeat TI. For HCW interviews: we will use thematic analysis – all within Atlas.ti v9.[159] We will use the consolidated criteria for reporting qualitative research (COREQ) to ensure positionality, reflexivity, etc. are covered to ensure rigor.[127] ***Quantitative Data:*** We will use descriptive statistics to understand discrepancies in client choice and actual services given. We will use logistic models to understand if specific client characteristics predict the presence of dispensing discrepancies. **Mixed-methods analysis:** We will triangulate quantitative and qualitative data from Phase 2 to gain in-depth understanding of how characteristics of individuals and inner context effect implementation of CHOICE.

D.3 AIM 3: Aim 3. Estimate the cost and cost-effectiveness of CHOICE. We will use a micro-costing approach, based on patient-level resource use and unit costs developed from clinic and implementation financial data, to estimate the distribution of costs of care by study arm, differences between study arms, and to estimate incremental cost effectiveness.

Costs from the provider's perspective (the Malawi government): We will use standard micro-costing methods[128] to estimate the cost per study participant in each arm of the study over the 24-month follow-up period from the provider (healthcare system) perspective.[91,92,129,129] This approach parallels the team's costing approach for the IDEaL study. We will first create an inventory of all the resources used during the study period to achieve the observed study outcomes. Resources (quantities of inputs) include all medications, laboratory tests, HIV-related clinic visits and off-site interactions (including tracing eligible clients), other services provided (phone calls), any equipment procured (e.g., bicycles for patient supporters if relevant, cells phones, etc.), and training required for implementing CHOICE services. Unit costs of resources will be developed based on external suppliers and the site's finance and procurement records. For each subject, the quantity of each resource multiplied by the unit cost estimates the cost per subject in the study. These cost data can then be summarized by study arm (mean, median, probability density function) and stratified by achievement of the primary outcomes (with 95% confidence intervals for mean differences adjusted for the clustered study design). Cost data will be reported in Malawian Kwacha (MWK) and US dollars (USD), with all cost information inflation adjusted to reference year (e.g., the year during which most clients complete study follow, using Gross Domestic Product deflator information available through the International Monetary Fund).

Cost-effectiveness of intervention compared to SOC: Estimating an incremental cost effectiveness ratio (ICER) comparing the CHOICE study arm to the SOC arm is logical if the CHOICE arm on average costs more but achieves more (based on 12-month retention). In this case, we will report the estimate ICER along with a 95% confidence interval for the ICER (bootstrapping the confidence interval because it is a ration of differences).

Costs and benefits to recipients of care: Choice of services may result in substantial savings to recipients, far outweighing savings to health systems.[30,94] We will use baseline and endline surveys to understand participants estimated costs incurred for seeking HIV treatment, including direct (cash) costs such as transport and indirect (productivity) costs such as lost work-time spent seeking care. We will multiply estimates by the observed number of events/years to calculate average cost/participant/year by arm.

D.4 Solutions for Expected Challenges: We thought carefully about potential challenges. 1) high Buy-in from the health system and HCW skill acquisition is essential. We have extensive experience with pragmatic trials and quality improvement strategies embedded within routine clinical practice.[19,43,72] We successfully piloted CHOICE and found high fidelity and buy-in with HCWs. The Malawi Ministry Director for HIV/AIDS is a co-investigator for the study (a rarity!) because the intervention is high priority to the government, although it cannot be adapted until cost-effectiveness and safety concerns are addressed through a full trial. Three districts in Malawi actively requested CHOICE be tested in their facilities because they see the potential for positive impacts among HCWs and clients (see LOS). Our other trials and CHOICE pilot show that lay cadres can implement complex counseling and client choice with fidelity and quality.[69] 2) CHOICE intervention is feasible within Malawian facilities and the national HIV program. Malawi has a long history of implementing innovations into standard of care that are proven efficacious and cost-effective including results from our own trials.[64] 3) CHOICE provides immediate and responsive strategies at the individual- and health systems-level to navigate and circumvent structural causes of TI. CHOICE aims to provide an immediate solution for these structural challenges while changes to poverty, inequity and social exclusion must be simultaneously pursued. The choice is not "either-or" but rather "both-and." 4) We have made specific considerations for key populations such as MSM and sex workers**.** HCWs will be sensitized to the needs of key populations. CHOICE strategies will teach clients how to navigate barriers to care and have needs addressed in HCW-client interactions. Interventions addressing criminalization of key populations and other systemic discrimination are required in addition to CHOICE and would complement CHOICE. 5) We have a strong history maintaining high levels of study retention overtime. Our ENGAGE trial collected 6-month study viral load samples with 92% retention among men with TI. ENGAGE also collected 6- and 12-month surveys with the same population, achieving 90% retention at 12-months. 6) We have established that short-term single interventions do not work for TI clients. Long-term counseling + dynamic choice of services are complimentary and promise to optimize the impact of each other – there is no other option but a multi-component intervention.

The trial will set the stage for how to best provide long-term, dynamic choice interventions to TI clients throughout the region. It is timely, feasible, and of high impact.

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