Testing the Combination of Behavioral Activation and Problem Solving as a Novel Behavioral Smoking Cessation Intervention for Smokers with HIV in Botswana

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Contents

BACKGROUND AND STUDY RATIONALE **6**

1 INTRODUCTION **7**

1.1 Background and Relevant Literature 7

2 STUDY OBJECTIVES **11**

2.1 Primary Objective 11
2.2 Secondary Objectives 11

3 INVESTIGATIONAL PLAN **12**

3.1 General Design 12
3.1.1 Screening Phase 12
3.1.2 Study Intervention Phase 13
3.1.3 Follow Up Phase 13
3.2 Allocation to Interventional Group 13
3.3 Study Measures 14
3.4 Study Endpoints 15
3.4.1 Primary Study Endpoint 15
3.4.2 Secondary Study Endpoints 15

4 STUDY POPULATION AND DURATION OF PARTICIPATION **16**

4.1 Duration of Study Participation 16
4.2 Total Number of Subjects and Sites 16
4.3 Inclusion Criteria 16
4.4 Exclusion Criteria 16
4.5 Subject Recruitment 17
4.6 Vulnerable Populations: 17

5 STUDY PROCEDURES **17**

5.1 Screening 17
5.2 Baseline (Week 0) 17
5.3 Study Intervention Phase (Weeks 1,3,5,7, and 9) 18
5.3.1 Pre-Quit Visit (Week 1) 18
5.3.2 Target Quit Day (Week 3) 18
5.3.3 Counseling Sessions #3 (Week 5) 18
5.3.4 Counseling Sessions #4 (Week 7) 18
5.3.5 Counseling Sessions #5 (Week 9) 19
5.3.6 Standard Counseling for Smoking Cessation (SC) (Control Arm Only) 19
5.3.7 Novel Behavioral Activation/Problem Solving (BAPS) Intervention (Experimental Arm Only) 19
5.3.8 Treatment Fidelity 19
5.4 Follow Up Visits (Weeks 10 and 26) 19
5.5 Subject Withdrawal 20
5.5.1 Data Collection and Follow-up for Withdrawn Subjects 20
5.6 Safety Evaluation 20

6 STATISTICAL PLAN **20**

6.1 Sample Size and Power Determination 20
6.2 Statistical Methods 22

7 SAFETY AND ADVERSE EVENTS **23**

7.1 Definitions 23
7.1.1 Serious Adverse Event 23
7.2 Recording of Adverse Events 24

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7.3 Relationship of SAE to Study 24
7.4 Reporting of Adverse Events and Unanticipated Problems 24
7.4.1 Follow-up Report 25
7.4.2 Investigator reporting: notifying the study sponsor 26
7.4.3 Data and Safety Monitoring Plan 26
7.4.4 Data Safety Monitoring Board 26

8 STUDY ADMINISTRATION, DATA HANDLING AND RECORD KEEPING 27

8.1 Confidentiality 27
8.2 Data Collection and Management 27
8.3 Records Retention 30

9 STUDY MONITORING, AUDITING, AND INSPECTING 30

9.1 Study Monitoring Plan 30
9.2 Auditing and Inspecting 30

10 ETHICAL CONSIDERATIONS 30

10.1 Risks 30
10.2 Benefits 31
10.3 Risk Benefit Assessment 31
10.4 Informed Consent Process 31

11 STUDY FINANCES 31

11.1 Funding Source 31
11.2 Conflict of Interest 32
11.3 Subject Stipends or Payments 32

12 PUBLICATION PLAN 32

13 REFERENCES 33

***14* APPENDIX 42**

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Study Summary

Title	Testing the Combination of Behavioral Activation and Problem Solving as a Novel Behavioral Smoking Cessation Intervention for Smokers with HIV in Botswana
Short Title	The Thotloetso ("Encouragement") Trial
IRB Number	
Protocol Number	842937
Methodology	We will randomize 650 smokers (self-reported daily smoking for > 30 days) with a confirmed HIV diagnosis to receive 9 weeks of either Behavioral Activation Problem Solving counseling (BAPS) or standard counseling (SC). The main difference in the approaches to counseling in our novel behavioral intervention is the use of problem-solving strategies to implement the behavioral activation meant to enhance substitute reinforcers and reduce complementary reinforcers. Session frequency and duration of the intervention arms are based upon past smoking cessation trials (Patten et al., 1998; Haas et al., 2004), the preliminary study of brief behavioral activation for smoking cessation (MacPherson et al., 2010), and our pilot of BAPS in Botswana. The two intervention arms will follow the same schedule (see Figure 1), beginning with a "pre-quit" session designed to help participants prepare for their Target Quit Day (TDQ).
Study Duration	The estimated study duration is 3.5 years
Study Center(s)	University of Pennsylvania, University of Botswana, and clinical sites of the Ministry of Health and Wellness of Botswana
Objectives	Primary: 1. To assess the efficacy of BAPS for promoting tobacco cessation among HIV+ smokers in Botswana Secondary*:* *2.* Assess whether depressive symptoms moderate the effects of BAPS vs. SC. *3.* Evaluate the mechanisms operative in our conceptual framework on rates of smoking cessation in the trial
Number of Subjects	650 subjects are anticipated to be enrolled from various HIV clinics in the greater Gaborone, Botswana area.

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Main Inclusion and Exclusion Criteria	Key Inclusion Criteria: ● ≥18 years' old ● Smoking cigarettes daily for the past 30 days ● HIV+ with HIV viral load of <1000 copies/mL, obtained within the 6 months prior to enrollment ● Receiving HIV care at Infectious Diseases Care Clinics (IDCCs) in and around Gaborone ● Able to communicate in English OR Setswana and provide written informed consent, able to speak and read in either English or Setswana ● Planning on residing in the geographic area for at least the next 7 months Key Exclusion Criteria: ● Cognitive deficits that impair their ability to provide informed consent ● Current untreated *and* unstable diagnosis of alcohol dependence (if past use and stable for ≥30 days, eligible) ● Psychosis ● Use of chewing tobacco, snuff or snus ● Recent, current, or planned use (next 7 months) of nicotine substitutes or smoking cessation treatments
Intervention	The participants will be randomized to receive 9 weeks of either Behavioral Activation Problem Solving counseling (BAPS) or standard counseling (SC). The main difference in the approaches to counseling in our novel behavioral intervention is the use of problem-solving strategies to implement the behavioral activation meant to enhance substitute reinforcers and reduce complementary reinforcers for smoking.

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Statistical Methodology	Primary Objective: The hypothesized effect of treatment arm (i.e., the difference in quit rates between subjects across the 2 study arms) will be tested by a treatment arm term in a mixed-models logistic regression model with covariates. Outcomes of the analyses will be characterized by odds ratios (e.g., odds of quitting smoking) and 95% confidence intervals. Secondary Objective (Aim 2): Since BAPS is hypothesized to operate in part by targeting depressive symptoms, we will formally test for moderation of its effect on smoking cessation in those with and without depressive symptoms at baseline. These analyses will be identical to those for Aim 1 however an interaction term will be included in all of the analyses coded as 0/1 for presence or absence of high levels of depressive symptoms. Secondary Objective (Aim 3): Aim 3 hypothesizes that changes in three potential mediators will be associated with success of BAPS. Namely, we will assess whether 1) decrease in depressive symptoms, 2) increase in substitute reinforcers and decrease in complementary reinforcers, and 3) increase in problem solving will mediate the effects of BAPS on bio-verified 7-day point prevalence abstinence at 10 and 26-weeks post-TQD. The primary analysis of Aim 3 will aim to establish mediation of treatment effects on this intermediate outcome using MacKinnon's approach (MacKinnon and Luecken, 2008), which is more powerful than Baron and Kenny's causal-steps method (Baron and Kenny, 1986). Secondary, exploratory analyses will also examine the effect of other mediators. We will conduct these analyses as in Napolitano et al (2008). Once mediation of the intermediate outcome (e.g., cigarette reward value) has been modeled as described above, we will estimate the remaining paths linking intermediate outcomes to abstinence via logistic regression.
Safety Evaluations	Adverse experiences will be monitored at every study session after (and including) Week 1 (pre-quit). Further, since smoking cessation requires behavior change, which disrupts an individual's (dysfunctional) routines by encouraging abstinence from smoking, it could have negative consequences for HIV medication taking behavior or because it reduces depression and increases problem solving, it may result in higher rates of viral suppression. Therefore, we will measure and compare the rates of viral suppression between the BAPS and SC arms at month 6 using Chi-squared tests.
Data and Safety Monitoring Plan	The MPIs and local PI will be responsible for the overall data and safety monitoring of the study. During the course of the study, data and safety monitoring will be performed on an ongoing basis by the DSM Board and by project staff and the Botswana-based ethics committee (IRB).

Background and Study Rationale

This study will be conducted in full accordance of all applicable University of Pennsylvania research policies and procedures and all applicable federal and state laws and regulations including Good Clinical Practice. All episodes of noncompliance will be documented.

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1 Introduction

Tobacco smoking is one of the most preventable causes of morbidity and mortality worldwide and has become a growing epidemic in developing countries like Botswana, where HIV is also a significant health crisis (Brathwaite et al., 2015). Among HIV+ individuals, smoking is of particular concern because myocardial infarction risk is elevated compared to HIV uninfected populations, chronic obstructive pulmonary disease occurs after shorter duration and lower intensity smoking than in HIV uninfected smokers, and outcomes for tuberculosis, a common opportunistic infection, are worse for smokers. Indeed, smoking may cause more life-year loss than HIV infection in this population (Helleberg et al., 2013). Unfortunately, while smoking is a growing public health crisis in lower and middle income countries (LMIC) with a high HIV burden like Botswana, there is virtually no infrastructure for treating tobacco dependence (Eriksen et al., 2015). Thus, developing the scientific basis for implementing evidence-based practices to reduce tobacco use among HIV+ individuals in Botswana is urgently needed.

1.1 Background and Relevant Literature

Dual Burden of HIV and Smoking in Low and Middle-income Countries (LMICs)

HIV has caused an epidemic of historic proportions in sub-Saharan Africa which has resulted in a large scale transformation of healthcare delivery in the most affected countries such as Botswana (Medicine, 2007). Unfortunately, other health threats have emerged in the HIV+ community, especially cardiovascular disease and cancer (Eyawo et al., 2017). These non-communicable diseases are thought to be more common in part due to the chronic inflammation that accompanies HIV and the fact that risk behaviors (e.g., acquisition of human papilloma virus, smoking) are also more common in HIV+ individuals (Magodoro et al., 2016). As such, addressing modifiable risk factors for disease mortality among those with HIV, including tobacco use, has become a critical priority (Benard et al., 2006; Reddy et al., 2016).

Recent data show that smoking rates in the US are extraordinarily high for HIV+ individuals, ranging from 50-74%, compared to 17% in the US general population (Burkhalter et al., 2005; Crothers et al., 2005; Webb et al., 2007). Our preliminary data with HIV+ Batswana show that less than 50% of males and around 6% of females are regular smokers. Moreover, smoking cessation efforts are less successful for HIV+ smokers, compared to HIV uninfected smokers. This discrepancy may be attributed to neurocognitive sequelae of HIV (Harrison et al., 2017) and/or higher nicotine metabolism (Schnoll et al., 2018) in HIV+ smokers. Both Neurocognitive deficits and faster nicotine metabolism may worsen the severity of nicotine withdrawal symptoms and decrease an individual's ability to cope with nicotine abstinence. As such, including both HIV+ and HIV uninfected smokers in the same intervention study risks yielding uninterpretable results due to fundamental differences between the groups in ability to quit. While targeting HIV+ individuals for tobacco cessation treatment is a critical priority (Akhtar-Khaleel et al., 2016) there are structural barriers to delivering behavioral interventions (Ward 2016). These structural barriers make behavioral interventions for smoking cessation particularly challenging in LMICs. The HIV care infrastructure is often the most robust medical outlet in these countries with impressive gains in quality and duration of life (Johnson et al. 2013). Leveraging this clinical infrastructure for implementing a behavioral smoking cessation intervention is not only necessary, but feasible, for our target population.

Tobacco-Related Health Consequences for Individuals with HIV

Continued smoking among people living with HIV/AIDS (PLWHA) can result in serious adverse health effects. Importantly, smoking can reduce the effectiveness of antiretroviral (ARV) therapy in PLWHA (Pollack et al. 2017). Controlling for medication adherence and comorbid illicit drug use, HIV+ smokers on ARVs had a significantly lower likelihood of achieving a viral or immunologic response and had a greater chance of developing viral or immunologic failure vs. their non-smoking counterparts.(Feldman et al. 2006). It has also been demonstrated that persistent smoking among PLWHA increases the likelihood for progression to AIDS (Nieman et al. 1993). Pulmonary tuberculosis, a major public health crisis in sub-

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Saharan Africa, also occurs at higher rates in cigarette smokers (Bronner Murrison et al., 2016). Further, smoking by PLWHA increases their risk for cardiovascular disease and cancer (Goncalves et al., 2016; Kaplan et al., 2016). HIV+ smokers have more medical complications (e.g., chronic obstructive pulmonary disease) (Risso et al., 2017) and worse quality of life (Webb et al., 2007; Cui et al, 2010) in comparison to HIV negative smokers. Overall, the achievements in ARVs, in terms of reduced mortality rates and improved quality of life among PLWHA, are being jeopardized by the cardiovascular and neoplastic diseases attributable to tobacco use in this population (Nahvi et al., 2009).

Nicotine Dependence Treatments for Individuals with HIV

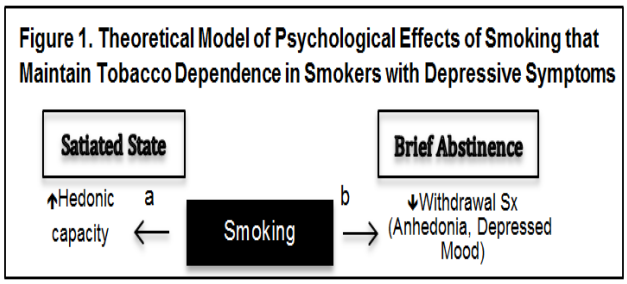
Interest in quitting smoking is high among PLWHA (Pacek and Cioe, 2015; Pacek and Crum, 2015; Frazier et al., 2018) particularly when HIV treatment is initiated (Vidrine et al., 2018) and when tobacco use treatment is integrated with HIV care (Pacek et al., 2017). However, there has been a lack of research focused on developing and testing smoking cessation interventions for PLWHA (Pacek and Crum, 2015). Reviews in this area conclude that there are insufficient data to indicate that tobacco dependence interventions that are efficacious in the general population are efficacious for PLWHA (Pacek and Cioe, 2015; Ledgerwood and Yskes, 2016; Pool et al., 2016).

Regarding behavioral treatments targeting HIV+ smokers, Vidrine and colleagues tested a cell-phone-based intervention and found significantly higher initial quit rates vs. usual care (Vidrine et al., 2018, Gritz et al., 2013). Other studies, including a group-based tailored intervention, motivational interventions, and a web-based intervention (vs. in-person or self-help) have not yielded significant increases in quit rates vs. controls (Ingersoll et al., 2009; Lloyd-Richardson et al., 2009, Moadel et al., 2012; Humfleet et al., 2013; Manuel et al., 2013; Stanton et al. 2015; Balfour et al., 2017). Two pilot studies of behavioral treatments addressing negative affect (depression, anxiety) showed promise for PLWHA (Matthews et al., 2013; O'Cleirigh et al., 2018) While no specific behavioral intervention has been identified as being uniquely effective for treating tobacco use among PLWHA, a recent review concluded that behavioral smoking cessation interventions yield moderate effects compared to standard medical care. Unfortunately, in LMICs, the costs of pharmacotherapy for nicotine addiction make medication treatments currently inaccessible for PLWHA and further emphasize the importance of novel behavioral strategies.

Distress as a Barrier to Health Behavior Change in HIV+ Individuals

While there are limited data on specific barriers to quitting smoking that are unique to HIV+ individuals compared to the general population, smoking cessation interventions that address distress may hold promise (Nahvi and Cooperman, 2009). In the US, more than a third of HIV+ patients exhibited major depression and another quarter had dysthymia (Bing et al., 2001). A meta-analysis of studies has shown that the risk for depression is at least 2-times greater for HIV+ individuals compared to HIV uninfected individuals (Ciesla and Roberts, 2001) and maybe more (Asch et al., 2003). Symptoms of psychological distress, including depressive symptoms, are associated with higher risk of smoking (Webb et al., 2007) and lower levels of motivation to quit smoking (Burkhalter et al., 2005) and are a strong risk factor for relapse following successful smoking cessation in the general population (Zvolensky et al., 2009). Consequently, nicotine dependence treatments tailored for HIV+ individuals may be more effective if the patient's psychological distress related to smoking is adequately addressed.

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The field of tobacco dependence research has acknowledged the potentially critical role of depressive symptoms in treating tobacco dependence (Mathew et al., 2017). A model of this relationship, depicted in Figure 1, is rooted in an understanding of the role of learning and conditioning processes in tobacco dependence. Smokers, during times of distress, perceive smoking as more pleasurable than other traditionally rewarding activities (Spring et al., 2003). This response may reflect a dysfunctional brain reward system that increases responsiveness to substances (e.g., nicotine) that activate these processes (Cardenas et al, 2002; Markou, 2007).

Smoking acquires high reward value through positive reinforcement (a) effects fostering reward functioning in the context of a constricted range of positive reinforcers. The positive reinforcing action of nicotine is attributable in large part to its influence on core brain reward centers (Doyle et al., 2014). Negative reinforcement (b) processes are involved in that smoking dispels withdrawal symptoms, namely anhedonia and depressed mood which accompany brief periods of abstinence between cigarettes among heavy smokers. Because these withdrawal symptoms mimic depression, smokers with depressive symptoms acquire the generalized expectation that their symptoms of distress (anhedonia, depressed mood) are relieved by smoking (Perkins et al., 2010). One clinical implication of this model is that interventions can focus on two sets of behaviors that either strengthen or counter the drive to smoke termed "complementary" vs. "substitute" reinforcers. As seen in our preliminary data, changes in these behaviors correlate with abstinence in PLWHA.

Parallels between Adherence and Smoking Cessation: Health Behavior Change Barriers

In developing an intervention to change smoking behavior in HIV+ smokers, prior successful work in changing health-related behavior in HIV+ individuals provide useful guidance. A critical behavior in HIV self-care is adherence to antiretroviral therapy. In our work on antiretroviral non-adherence, we recognized that depressive symptoms are related to suboptimal problem solving in the individual. We conceptualize depressive symptoms and poor problem solving as engendering a vicious cycle in which poor problem solving skills lead to mounting allostatic load (Ickovics et al., 2001) causing depression and the depressive symptoms stifling problem solving ability. Moreover, we recognized that there were numerous potential barriers to adherence, although no one barrier was absolute and individuals with adherence difficulties typically had multiple barriers (e.g., memory problems, logistical problems, poor self-efficacy, etc.). Similarly, the triggers for smoking are unique to the individual and the reinforcers were myriad. Given the adverse impacts of nicotine withdrawal and anhedonia on problem solving, when tasked with identifying pleasurable substitute behaviors, these individuals may find that the barriers to implementing them are insurmountable.

Several interventions have been developed that improve medication adherence, including Managed Problem Solving (MAPS), developed by our group (Gross et al., 2013). Akin to the above model for barriers to smoking cessation behavior, MAPS is derived from Problem Solving Therapy (PST) which has been used successfully to treat mild-moderate depression (Nezu, 1986) and has been adapted successfully for use with medically compromised populations (Nezu et al,. 2003). PST involves training individuals in a set of generalizable skills that allow for identification of difficulties, generation of solutions, and evaluation of outcomes. These activities involve 5 steps: 1) Defining the problem, 2) Generating alternative solutions via brainstorming, 3) Making decisions about a plan of action, 4) Implementing the plan, and 5) Assessing the implementation and effectiveness of the plan and modifying it based on accumulated data. Several studies have demonstrated the effectiveness of PST in both research and clinical patient samples (Mynors-Wallis et al., 1997; Mynors-Wallis and Gath, 1997; Barrett et al., 1999; Townsend et al., 2001). PST has been

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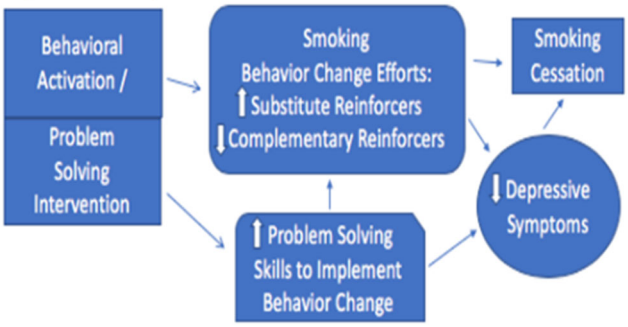
successfully delivered by a wide range of trained interventionists, from graduate students and social workers (Nezu et al., 2003) to nurses and physicians (Mynors-Wallis et al., 1997), demonstrating that the skills can be taught to personnel of differing expertise.

In our adaptation of PST for medication adherence, the MAPS interventionist acts as a problem-solver, pursuing identified barriers to the behavior (i.e. smoking abstinence) with the participant and suggesting different tools based on the problem-solving strategy. The subject actively participates in generation of problem-solving strategies, selecting the strategies identified as having the greatest likelihood of success and implementing them. We conducted a randomized control trial with 180 HIV+ individuals on ARVs and demonstrated that an increase in adherence (~25% of doses taken) and an increase in the proportion with undetectable viral loads. Moreover, the problem-solving arm had significant decreases in depressive symptoms compared to usual care, in keeping with the model of problem solving as an effective intervention for depression (Gross et al., 2014). Based on these findings, the CDC has endorsed MAPS as an evidence-based intervention for medication adherence in HIV+ individuals on ARVs (Center for Disease Control and Prevention, 2017).

Choice of Intervention Design

In this proposal, we merge Behavioral Activation Therapy (BAT) with the principles of Problem Solving Therapy to create a novel counseling model to address the unique challenges of tobacco cessation among those with HIV: Behavioral Activation/Problem Solving for Smoking Cessation (BAPS). We have chosen this approach because BAT is as effective as cognitive behavioral therapy (CBT) in treating depression (Dobson et al., 2008) and a small pilot study showed that BAT vs. CBT increased long-term abstinence among smokers with elevated depressive symptoms (MacPherson et al., 2010). BAT targets increasing engagement in rewarding activities by reducing patterns of avoidance, withdrawal, and inactivity. Given that BAT is simpler to administer than CBT, especially for clinicians with limited experience in behavioral therapy (Cuijpers et al., 2007, Ekers et al., 2008), it may have greater potential for broad dissemination. We believe that it will be well-suited for HIV+ smokers who prefer smoking over other traditionally rewarding activities and who use smoking as a primary avoidance coping strategy (Kahler et al., 2003; Spring et al., 2003). We have merged BAT with the Problem Solving component because of the need to personalize approaches to the individual with distress who may lack the problem solving skills (either due to the distress or resulting in the distress) which prevents them from identifying and implementing strategies to avoid complementary and enhance substitute reinforcers for smoking. As shown in Figure 2, in our conceptual framework, BAPS works through 3 potential mediators: 1) reducing depressive symptoms, 2) decreasing complementary and increasing substitute reinforcer behaviors, and 3) increasing problem solving. Most importantly, we have conducted a pilot study of using BAPS in Botswana and found it to be feasible, appealing, and potentially effective; yielding a quit rate that surpasses rates of behavioral counseling for smoking cessation generally seen.

Figure 2. Conceptual Framework for Effect of BAPS



Smoking Cessation Treatment Engagement and Implementation in LMICs

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In order to begin considering implementing smoking cessation interventions in LMICs, one must first consider that little to no infrastructure exists within this realm (Eriksen et al., 2015). Without a system to identify and recruit smokers to behavioral interventions, simply making an intervention available is insufficient (Fitzgerald et al., 2016). Yet, a robust HIV care infrastructure often exists in LMIC settings. In fact, much discussion has ensued about the need to utilize the HIV care infrastructure for care of non-communicable diseases (Reid et al. 2012). Another important consideration in LMICs where skilled staff are either sparsely available or concentrated in larger centers is the ability to deliver care to remotely located individuals (Duncombe et al. 2015). Fortunately, mobile phones are ubiquitous (Kazi et al. 2017) and delivery of behavioral interventions by mobile devices have been established to improve medication adherence in HIV without loss of confidentiality (Lester et al., 2010). They also provide flexibility for implementing sessions during evening hours when venues are limited and staff and clients may prefer not to meet in person, as we observed in our pilot study. Moreover, smoking cessation interventions (including our pilot study in Botswana) have been shown to be feasible, appealing and effective when implemented by telephone (Whittaker et al., 2016).

Summary of Significance

Smoking is a critical, but barely addressed behavior in HIV+ individuals in LMICs, which puts millions of lives at particularly high risk of non-communicable diseases and premature death. This project will leverage the HIV care infrastructure present in Botswana, which mirrors that of many LMIC HIV programs, making the project likely to be exportable to the settings with the highest HIV burden, in order to implement and test a novel behavioral counseling intervention for nicotine dependence matched to the needs of HIV+ smokers. The results will yield both critical information on whether a new behavioral model for smoking cessation works better than standard guideline-based practice in this setting as well as on whether the new model of behavioral reinforcers is generalizable to this cultural milieu. As such, the results will have implications for addressing nicotine dependence in LMICs. This work will also expand our scientific knowledge more broadly with relevance to the US since we currently have little information about whether behavioral activation is more or less effective for smokers with depressive symptoms and the processes that mediate the treatment effects.

2 Study Objectives

2.1 Primary Objective

Assess the effectiveness of BAPS vs. Standard Counseling (SC) for promoting tobacco cessation among HIV+ smokers in Botswana.

- Hypothesis 1: BAPS will result in higher cessation rates than SC.

2.2 Secondary Objectives

Assess whether depressive symptoms moderate the effects of BAPS vs. SC on quit rates and test depressive symptoms, reinforcers, and problem solving as mediators of the intervention effects.

- Hypothesis 2: BAPS will have a greater effect on cessation in those with depressive symptoms.

Evaluate the mechanisms operative in our conceptual framework (Figure 2) on rates of smoking cessation in the trial.

- Hypothesis 3: Successful smoking cessation will be mediated by increases in substitute and decreases in complementary reinforcers, improved problem solving, and decreased depressive symptoms.

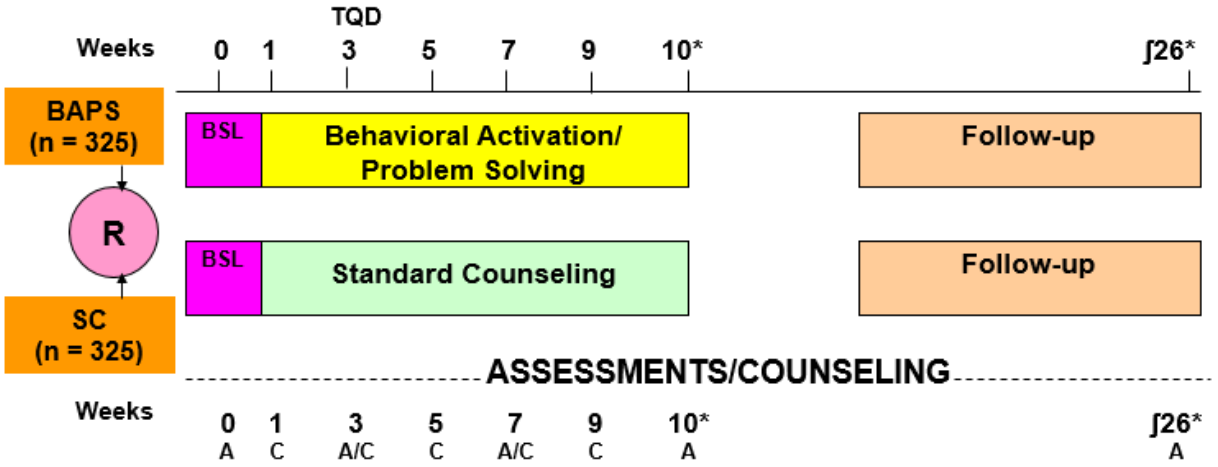
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3 Investigational Plan

3.1 General Design

In this Phase III clinical trial, 650 smokers (self-reported daily smoking for > 30 days) with a confirmed HIV diagnosis will be randomized to receive 9 weeks of either Behavioral Activation Problem Solving counseling (BAPS) or standard counseling (SC). The main difference in the approaches to counseling in our novel behavioral intervention is the use of problem-solving strategies to implement the behavioral activation meant to enhance substitute reinforcers and reduce complementary reinforcers. Session frequency and duration of the intervention arms are based upon past smoking cessation trials (Patten et al., 1998; Haas et al., 2004), the preliminary study of brief behavioral activation for smoking cessation (MacPherson et al., 2010), and our pilot of BAPS in Botswana. The two intervention arms will follow the same schedule (see Figure 1), beginning with a "pre-quit" session designed to help participants prepare for their Target Quit Day (TDQ).

Figure 1. Study Design



BSL = Baseline (Intake Session and Randomization (R)); A = Assessment; C = Counseling; TQD = Target Quit Day; *End of Treatment, ∫6 months post-TQD

The primary outcome will be 6 month biochemically confirmed tobacco abstinence rates and secondary outcomes will include changes in the proposed mediators as well as assessment of treatment moderators. The study schema is presented in Figure 1.

3.1.1 Screening Phase

Recruitment will be focused at the HIV clinics. We will post staff at each of 4 HIV clinics in Gaborone (Bontleng, BH3, BTA, Phase II). These specialized sites provide medications exclusively to HIV patients so there is no loss of confidentiality imparted by being approached for recruitment. If needed, we will add additional clinics such as Old Naledi, Nkoyaphiri or other similar large clinic located within ~1 hour drive of the BUP offices. A recruiter will approach each patient in the pharmacy and ask whether they smoke. We will note the gender of all who decline to answer. Smokers will be asked to participate in a questionnaire and offered participation. If they agree, they will be referred to the research assistant who will arrange a meeting (typically within a half hour, or if desired, later) and administer informed consent and assign a study arm. These IRB approved procedures were very effective for the pilot.

Once an individual expresses interest in participating, informed consent will be administered by the research staff. Notably, the age of consent for participation in research in Botswana has changed from 21

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to 18 years of age and thus, all potential participants will be able to consent for themselves. The consent form does not include information regarding subjects' rights under the Health Insurance Portability and Accountability Act (HIPAA) since this study takes place outside of the US with non-American citizens. However, the concepts set forth in HIPAA will be followed in principle.

3.1.2 Study Intervention Phase

Eligible patients will be randomized to one of the treatment arms, which will involve 5 phone-delivered counseling sessions over a 9-week treatment phase. Each study interventionist will conduct both behavioral activation problem solving (BAPS) and standard counseling (SC) smoking cessation interventions.

Standard Counseling for Smoking Cessation (SC) (Control Arm Only

Standard Counseling will be based on the 2008 PHS Clinical Practice Guideline (Fiore et al., 2008) and on SC in our ongoing two-site trials (R01DA025078; R01CA165001). Session frequency and duration are based upon past smoking cessation trials (Patten et al., 1998; Haas et al., 2004), the preliminary study of brief behavioral activation for smoking cessation (MacPherson et al., 2010), and our pilot of BAPS in Botswana. The two intervention arms will follow the same schedule (see Figure 1), beginning with a "pre-quit" session designed to help participants prepare for their Target Quit Day (TDQ). The TQD session will occur at week 1. BAPS and SC will be equated to the number of sessions and total participant-therapist contact time. The SC arm will focus on self-monitoring, identifying smoking triggers and alternative trigger management strategies, relaxation, social support for non-smoking, relapse prevention, and homework. The pre-quit session prepares participants for their TQD by reviewing their experience with quitting, beliefs about smoking/quitting, perceived barriers to cessation, and creating a quit plan to identify smoking triggers and implement alternative strategies to manage those triggers without smoking.

Novel Behavioral Activation/ Problem Solving Intervention (Experimental Arm Only)

Key components of BAPS include activity monitoring and rewarding activity scheduling, assessment of personal goals and values, assessment and altering of avoidance behavior and other maladaptive coping strategies, and contingency management. BAPS focuses on reducing stress pile-up and loss of pleasure that accompanies the cessation process and on identifying and establishing environmental/social changes to promote abstinence. BAPS addresses smoking as a behavior that prevents and restricts opportunities for contact with healthy rewarding behaviors. These changes are achieved through altering daily routines previously associated with smoking in ways that increase pleasure and mastery across life domains, reducing rumination, and increasing behavioral skills to prevent return to smoking as a means of avoiding stressors. A pre-quit session (session 1) will introduce participants to: 1) self-monitoring of mood and behavior; 2) assessment of personal values to refine the treatment plan; and 3) scheduling of substitute rewarding activities that align with their abstinence goal. At the TQD session (session 2), participant experiences with abstinence will be reviewed and functional analysis of behavior will be introduced, especially as it relates to smoking and avoidance patterns. Information obtained will be used to help generate a tailored behavioral activation plan using the problem-solving framework to increase rewarding activities and relationships, reduce avoidant responses to distressing experiences, and facilitate successful implementation of smoking trigger management strategies. Sessions 3-5 will incorporate strategies to address avoidance patterns, especially those involving smoking, and to replace them with adaptive coping strategies, again using problem-solving.

3.1.3 Follow Up Phase

After completion of the intervention, participants will have a follow-up session one week later (Week 10) and 6 months after their initial target quit day (Week 26).

3.2 Allocation to Interventional Group

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We will use permuted block randomization with random block sizes between 6 and 9 and stratified by sex and depressive symptoms. The blocks will ensure near 1:1 balance throughout the study. The random block sizes will protect against selection bias by preventing staff from predicting which intervention any one individual will be assigned. We will stratify by sex to ensure balance of women in both arms since smoking is more common in men. We will stratify by depressive symptoms to ensure balance in testing whether the effect of BAPS is differential between those with and without greater degrees of distress. While a Mood Module of PRIME-MD score of >5 symptoms is commonly used as a threshold for depression (Spitzer et al., 1994), we are also targeting lower level symptoms with this intervention having found that lower levels are associated with health behaviors such as medication adherence (Gross et al., 2017). We have therefore chosen a Mood Module score of >4 as the cutoff for high distress which is supported by the higher success rate in those with scores of 4 or greater in our pilot study.

3.3 Study Measures

Timeline Follow-Back

- This self-report measure of smoking rate will be conducted at each session, which asks the subject about the number of cigarettes, if any, that they had smoked each day, since their previous session date (when last collected). At Baseline (Wk 0) subject will be asked to provide their smoking rate over the past 7 days.

Minnesota Nicotine Withdrawal Scale (MNWS-W)

- Withdrawal over the past week will be measured using the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami, 1986), which comprises nine questions: urge to smoke, depressed mood, irritability, anxiety, difficulty concentrating, restlessness, increased appetite, and two sleep questions, each rated from 0 to 4 (0 not at all, 1 slight, 2 moderate, 3 quite a bit, 4 extreme). A composite withdrawal score is computed by summing the nine items.

Modified Alcohol Use Disorder Identification Test (AUDIT)

- As alcohol use disorders could be a potential confounding variable for outcome measures of smoking cessation and be a data validity issue depending on the severity of alcohol abuse, we will use a self-reported, modified version of the Alcohol Use Disorder Identification Test (AUDIT) The brief 7-item questionnaire measures subject's use of alcohol in the past month and past year. This version has been used in previous research projects conducted in Botswana, including the current study's pilot.

Mood module of PRIME-MD

- Participants will complete the mood module of the PRIME-MD which asks about depressive symptoms over the past two weeks. This tool was previously validated in Botswana (Lawler, et al., 2011) and used in the pilot study.

Pleasant Events Schedule

- This 45-item culturally adapted and translated version of the Pleasant Events Schedule (PES) (MacPhillamy & Lewinsohn, 1982) measures rewarding activities in a person's natural environment (Audrain-McGovern et al., 2011). The cross-product of frequency (0=none to 2=often) and level of enjoyableness (0=none to 2=very) for each item provides a measure of reward. They are also asked whether they associate the activity with smoking or urge to smoke. Activities associated with smoking are complementary reinforcers and those not associated are substitute reinforcers. The cross-products of substitute reinforcers and complementary reinforcers are summed separately to provide two scores. Scores have been associated with depression, and discriminate between ex-smokers and current smokers and predict smoking abstinence in cessation treatment (Audrain-McGovern et al., 2012, Audrain-McGovern et al., 2009).

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Cigarette Evaluation Scale (CES)

- This 11-item questionnaire (Westman, Levin and Rose, 1992) measures both the reinforcing and aversive effects of smoking based on the subject's last cigarette smoked. The 7-point Likert scale ranges from options 'not at all' to 'extremely'. Participants will only be asked to complete this form, along with their other assessments, if they report smoking in the past 24-hours since it would otherwise, not be applicable.

Social Problem Solving Inventory-Revised Short-Form

- This 25 items questionnaire measures positive and negative problem orientation, rational problem solving, impulsivity, and avoidance (Sorsdahl et. al., 2017). This instrument will be used in measuring and comparing problem solving abilities over the participants' treatment as well as across intervention arms.

Snaith-Hamilton Pleasure Scale (SHAPS)

- The 14-item Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) is used in nonclinical and clinical populations (Franken, Rassin, & Muris, 2007; Leventhal et al., 2006; Snaith et al., 1995) to characterize perception of a broad array of life experiences as rewarding and who experiences a high degree of pleasure in response to rewards.

Questionnaire of Smoking Urges-Brief Version (QSU-B)

- Craving will be measured using the Questionnaire of Smoking Urges-Brief version (QSU-Brief) (Cox, Tiffany, & Christen, 2001). The QSU-Brief is a widely used scale that yields an overall measure of cigarette craving (or urge to smoke) and two subscale scores: positive reinforcement and negative reinforcement. The full-scale score is computed by summing the 10 items. Higher scores indicate greater urges to smoke.

Environmental Reward Observation Scale (EROS)

- Behavioral activation and environmental rewards will be assessed using the EROS (Armento & Hopko 2007) which is scored on a 10 item Likert-scale.

Assessment of Severe Adverse Events (SAE)

- At each study visit after Baseline, participants will be asked the following: "Since we last spoke with you, have you experienced any serious life event that was life-threatening or disabling or that required hospitalization or serious medical intervention?" Because no adverse events are expected due to the low risk nature of behavioral interventions such as BAPS or SC, we will be using an open ended format to document, in detail, if any severe adverse events occur during the individual's study participation.

See Table 1 in Appendix (section 15) for a schedule of when study measures are collected across each session

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary outcome will be smoking abstinence, specifically, 7-day point prevalence abstinence at 6 month follow up visit. This includes self-reported abstinence from cigarette smoking (not even a puff) for ≥7 days prior to the session (24-weeks post-target quit day) and a breath CO measure of ≤8 ppm at the time-point (Hughes et al., 2003). Per convention, participants will be analyzed as smoking at week 26 if they report smoking, cannot be reached to provide data, fail to provide a breath sample for CO measurement, or provide a breath sample at the time-point that is ≥7 ppm.

3.4.2 Secondary Study Endpoints

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Smoking outcome measures
CO-verified, 7-day point prevalence abstinence at week 10 (completion of counseling).
Secondary outcomes measured at weeks 10 and 26 will include:

- Continuous abstinence, no smoking at all between the target quit date (TQD) and follow-up visit
- Prolonged abstinence, determined by a self-report of not relapsing after their quit date (i.e., not smoking for 7 consecutive days, or not smoking at least once each week for 2 consecutive weeks) following a 2-week grace period.
- Relapse, defined as 7 consecutive days of self-reported smoking after a 2-week grace period
- Number of quit attempts, defined as self-reported no smoking at all for 24 hours (not even a puff of a cigarette).
- Smoking rate, defined as the self-report average number of cigarettes smoked in the past week.

Additionally, HIV viral breakthrough is a secondary outcome measure which will be assessed. Plasma HIV viral load will be assessed using standard assays at a commercial laboratory to determine if there is a difference in the rate of maintaining viral suppression between the study arms.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

Participants will complete the initial eligibility screen, consent and baseline measures at Week 0, however this can be split up to account for participant's schedule. Their pre-quit counseling session (Week 1) should ideally be 1 week after Week 0 but can scheduled within 1 month of Week 0 being completed. Participants will be in the intervention phase for 14 weeks, and then their last follow up session is at Week 26 of the study. Their total study participation will last approximately 6-7 months, including screening and follow up visits.

4.2 Total Number of Subjects and Sites

All 650 participants will be enrolled at participating HIV clinics in Gaborone. Study sites are IDCC clinics in and around Gaborone, including Bontleng, BH3, BTA, and Phase II. If needed for recruitment, additional sites such as Old Naledi and Nkoyaphiri will be added.

4.3 Inclusion Criteria

- Over 18 years of age
- Daily smoking (1 or more cigarette/day) for the past 30 days
- Receiving HIV care at the Infectious Diseases Care Clinics (IDCCs) in and around Gaborone
- Exhibit viral load of <1000 copies/mL, obtained within the 6 months prior to enrollment
- Able to communicate fluently in English or Setswana (speak and read)
- Must be able to provide written informed consent
- Planning on residing in the geographic area for at least the next 7 months and able to attend in person research visits

4.4 Exclusion Criteria

- Current, untreated and unstable diagnosis of alcohol dependence
    - Current is defined as past 30 days. If past use and stable for >30 days, eligible
- Recent (past two weeks), current or planned use of nicotine substitutes or smoking cessation treatments in the next 7 months
- Current participation in a different smoking cessation program

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- Use of non-combustible tobacco products (i.e. chewing tobacco, snuff or snus)
- Cognitive deficits that impair their ability to provide informed consent
- Psychosis

4.5 Subject Recruitment

We will post study staff at each of the 4 HIV clinics in Gaborone (Bontleng, BH3, BTA, and Phase II). If needed, we can also add additional sites such as Old Naledi and Nkoyaphiri for recruitment. A recruiter will present the study to the queue of patients in the waiting area as the clinic opens in the morning. They will then move to the pharmacy area where they will approach each patient as they leave the pharmacy with their antiretroviral medications and ask about their smoking status. If they report smoking, we will perform an eligibility screen and if eligible, offer participation in the trial. If they agree, the informed consent will be administered and the study arm will be assigned.

4.6 Vulnerable Populations:

Children, fetuses, neonates, or prisoners are not included in this research study. Pregnant women, the elderly, individuals of low literacy, and the economically disadvantaged will not be excluded from participation since this is a behavioral intervention with low risk.

5 Study Procedures

5.1 Screening

A recruiter will approach each patient in line at the IDCC or in the IDCC pharmacy and ask if they smoke cigarettes. We will note the gender of all who decline to answer. Smokers will be asked to complete a questionnaire and asked to show the study staff their identification card and medical card. Staff will collect the participant's most recent viral load count from the medical card and document for eligibility purposes. The initial eligibility screen will ensure that they meet all other inclusion criteria and do not endorse any item from our list of exclusionary criteria. If they meet study criteria, the participant will be offered a chance to enroll. These IRB approved procedures were very effective for the pilot study.

After an individual expresses interest in participating, and is deemed initially eligible based on the brief screening questionnaire and their Viral Load results, they will be referred to the research assistant who will arrange a consent meeting (typically within a half hour, or if desired, later) and administer informed consent. The age of consent for participation in research in Botswana is 18 years of age and thus, all potential participants will be able to consent for themselves. The consent form does not include information regarding subjects' rights under the Health Insurance Portability and Accountability Act (HIPAA) since this study takes place outside of the US with non-American citizens. However, the concepts set forth in HIPAA will be followed in principle.

5.2 Session Windows

The final eligibility session (Intake) must be completed within 60 days of the initial eligibility screen. If over 60 days have passed, the initial eligibility screen will have to be re-done before completing the intake. The Pre-Quit visit (Week 1) should be scheduled for within 2 weeks of the intake visit. After 60 days from the intake, if the pre-quit session has still not yet been achieved, then the participant will have to complete another intake session. The Target Quit Day phone session must (Week 3) may occur 7-10 days after the

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Pre-Quit. The Week 5, Week 7, and Week 9 visit may occur +/- 7 days from the target date. Weeks 10 may occur +/- 4 days from the target date. The Week 10 CO visit must occur within 2 weeks of the Week 10 session. Week 26 may occur up to 4 weeks after the target date. The Week 26 CO visits can be completed immediately after finishing the Week 26 phone session and up to +4 weeks after their phone session.Sessions may occur a few days outside the session window with PI approval. Assessments and counseling can occur on different days, as long as they both occur during that session's window.

5.3 Baseline (Week 0)

Once enrolled, participants will complete various baseline assessments. Participants can choose to do all assessments in person or over the phone at a later date or time. All participants will complete a brief medical history questionnaire and be asked to complete questionnaires regarding their smoking history, smoking rate for the past week (TLFB), nicotine dependence (FTND), smoking urges (QSU-B), and withdrawal symptoms (MNSW-W) as well as their alcohol use (Modified AUDIT). Additional baseline measures will ask about substitute and complementary reinforcers for smoking (PES), smoking and environmental rewards (CES and EROS), and depressive symptoms (Mood module of PRIME-MD and SHAPS).

Participant will be randomized to BAPS of SC and schedule their first phone-counseling session at the Baseline session. Subject will be given a counseling binder which will include homework as well as worksheets to be discussed with the interventionist at their upcoming counseling sessions.

5.4 Study Intervention Phase (Weeks 1,3,5,7, and 9)

Participants will be asked about their self-reported smoking rate, measured by the Timeline Follow Back at every session. The staff member conducting data collection assessments will differ from the interventionist conducting the smoking cessation counseling with the subject. These 5 phone-delivered counseling sessions will occur over the 9 week treatment phase. Subjects will also have the option to complete these sessions in person at an office in the University of Pennsylvania and Botswana Partnership building. The counseling sessions, which will be by-in large phone-delivered, will last between 30-60 minutes. Behavioral activation problem solving (BAPS) and standard counseling (SC) are equated to the number of sessions and total participant-therapist contact time. Each study interventionist will conduct both BAPS and SC smoking cessation interventions. Section 5.3.6 and 5.3.7 detail each intervention arm separately for the complete intervention manuals.

5.4.1 Pre-Quit Visit (Week 1)

Participants will be asked about their self-reported smoking rate, measured by the Timeline Follow Back (TLFB) and then complete a counseling session to prepare them for their upcoming smoking cessation attempt.

5.4.2 Target Quit Day (Week 3)

All assessments which were completed at Baseline (except for the smoking history questionnaire, FTND, and AUDIT) will be completed before the counseling session. This should ideally be the date that the participant begins their smoking cessation attempt.

5.4.3 *Counseling Sessions #3 (Week 5)*

Only participants' self-reported smoking rate (since their last visit) will be measured by the Timeline Follow Back (TLFB) before they complete their counseling session

5.4.4 Counseling Sessions #4 (Week 7)

All assessments which were completed at Baseline (except for the smoking history questionnaire, FTND, and AUDIT) will be completed before the counseling session.

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5.4.5 Counseling Sessions #5 (Week 9)

Only participants' self-reported smoking rate (since their last visit) will be measured by the Timeline Follow Back (TLFB) before they complete their counseling session

5.4.6 Standard Counseling for Smoking Cessation (SC) (Control Arm Only)

SC is based on the 2008 PHS Clinical Practice Guideline (Fiore et al., 2008) and on SC in our ongoing two-site trials (R01DA025078; R01CA165001). The TQD session will occur at week 3 The SC control arm focuses on self-monitoring, identifying smoking triggers and alternative trigger management strategies, relaxation, social support for non-smoking, relapse prevention, and homework. The pre-quit session prepares participants for their TQD by reviewing their experience with quitting, beliefs about smoking/quitting, perceived barriers to cessation, and creating a quit plan to identify smoking triggers and implement alternative strategies to manage those triggers without smoking.

5.4.7 Novel Behavioral Activation/Problem Solving (BAPS) Intervention (Experimental Arm Only)

Key components of BAPS include activity monitoring and rewarding activity scheduling, assessment of personal goals and values, assessment and altering of avoidance behavior and other maladaptive coping strategies, and contingency management. BAPS focuses on reducing stress pile-up and loss of pleasure that accompanies the cessation process and on identifying and establishing environmental/social changes to promote abstinence. BAPS addresses smoking as a behavior that prevents and restricts opportunities for contact with healthy rewarding behaviors. These changes are achieved through altering daily routines previously associated with smoking in ways that increase pleasure and mastery across life domains, reducing rumination, and increasing behavioral skills to prevent return to smoking as a means of avoiding stressors. A pre-quit session (session 1) will introduce participants to: 1) self-monitoring of mood and behavior; 2) assessment of personal values to refine the treatment plan; and 3) scheduling of substitute rewarding activities that align with their abstinence goal. At the TQD session (session 2), participant experiences with abstinence will be reviewed and functional analysis of behavior will be introduced, especially as it relates to smoking and avoidance patterns. Information obtained will be used to help generate a tailored behavioral activation plan using the problem-solving framework to increase rewarding activities and relationships, reduce avoidant responses to distressing experiences, and facilitate successful implementation of smoking trigger management strategies. Sessions 3-5 will incorporate strategies to address avoidance patterns, especially those involving smoking, and to replace them with adaptive coping strategies, again using problem-solving.

5.4.8 Treatment Fidelity

The same study therapists will conduct both the BAPS and SC interventions. Therapists will use condition-specific session checklists to guide session content. Sessions will be audio-recorded and a random sample of 25% of BAPS and SC sessions, respectively, will be assessed for protocol adherence per study site. The fidelity assessment will provide scores for therapist competence, adherence, and contamination. To assure ongoing fidelity, therapists will attend bi-weekly supervision by teleconference for review of audio-recorded sessions. Retraining will be triggered if adherence is less than 90% or if there is any evidence of cross-condition contamination.

5.5 Follow Up Visits (Weeks 10 and 26)

After completion of 9 weeks of treatment, participants will have follow-up phone sessions at Weeks 10 and 26. Only those who self-report abstinence in the last seven days will be asked to attend a subsequent in-person session for CO verification. A breath sample for CO measurement will be collected, as well as smoking rate.

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5.6 Subject Withdrawal

Subjects are free to withdraw from the study at any time without impact to their care. Subjects may be deemed "ineligible" at any time per the exclusion criteria listed above. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules or SAEs. The Investigator or the Sponsor may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

5.6.1 Data Collection and Follow-up for Withdrawn Subjects

No follow-up data collection is required for participants who withdraw or are deemed ineligible throughout the study.

5.7 Safety Evaluation

Given the low risk limited to withdrawal symptoms and psychological distress, the Study Coordinator will primarily monitor adverse experiences through a checklist. The local PI is a Family Medicine physician at the University Of Botswana Faculty Of Medicine who will be responsible for secondary assessments if the Study Coordinator identifies more serious concerns (e.g., HIV medication non-adherence due to withdrawal or suicidality). We will also be monitoring HIV viral loads at the end of treatment to ensure no adverse effect of quitting on ARV adherence.

5.8 Virologic Evaluation

If an individual does not have a viral load test from the public sector within two months of completing the trial, we will obtain an additional viral load at the final closeout visit (Week 26) by sending them to Diagnofirm, an accredited laboratory with phlebotomy facilities. Those results will be communicated back to the participants for inclusion in their medical record in addition to inclusion in their study record.

6 Statistical Plan

The overarching principle of the analysis plan will be "intention-to-treat." Although this trial tests a strategy, because smokers need sufficient motivation to attend counseling sessions, we will use a modified intention to treat approach where all individuals who attend the first counseling session will be included. Dropouts thereafter will be included as failures. Dropouts prior to the first session will be replaced. Secondarily, we will conduct a 'completers only' analysis. Formal statistically powered analyses of moderation by depressive symptoms will be performed. While we are stratifying by sex to achieve balance, because the intervention is tailored to the individuals' personal preferences, rather than generic strategies that might differentially appeal to men and women, we do not expect differences in the effectiveness of the intervention by sex and thus, the primary analyses will not be performed stratified. Secondary analyses will formally test for effect modification by sex using a study arm by sex interaction term.

6.1 Sample Size and Power Determination

The sample size (N=650) was chosen to detect important differences in the rate of abstinence between the two trial arms in the presence of a moderator (effect modification by depressive symptoms at baseline). While a larger sample size could have been chosen to answer the mediation analyses more precisely, if one of the arms is superior, it will be important to provide this information as quickly as possible to the key

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stakeholders. Fortunately, the sample size required for the Aim 2 moderator analysis provides sufficient power to detect the main effects in the absence of moderation for Aim 1 and important changes in the mediators when analyzing the RCT as a cohort study of individuals trying to quit smoking.

Detectable Differences for Cessation Outcome (Aims 1 and 2)

We used the following assumptions to calculate power for the moderator analysis of Aim 2. For the logistic regression equation: $\text{Log}(P/(1-P)) = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ$, where $P = \Pr(Y = 1|X, Z)$ and X and Z are binary. Power is the probability of rejecting a false null hypothesis, N is the sample size, and P_0 is the response probability at X = 0, Z = 0. Percent X=1 is the percent of the population in which the exposure is 1. Percent Z=1 is the percent of the population in which the confounder is 1. $OR_{int} = \text{Exp}(\beta_3)$ is the odds ratio of the interaction (i.e., the effect size). $OR_{yx} = \text{Exp}(\beta_1)$ is the odds ratio of Y versus X. $OR_{yz} = \text{Exp}(\beta_2)$ is the odds ratio of Y versus Z. OR_{xz} is the odds ratio of X versus Z in a logistic regression of X on Z. Alpha is the probability of rejecting a true null hypothesis. Beta is the probability of accepting a false null hypothesis.

A logistic regression of a binary response variable (Y) on a binary independent variable (X) and a binary confounder variable (Z) with a sample size of 650 observations achieves 81% power at a 0.050 significance level to detect the X-Z interaction odds ratio of 0.100 (Other settings: OR_{yx} = 2.000, OR_{yz} = 1.500, OR_{xz} = 1.500, P_0 (prevalence of Y given X = 0 and Z = 0) = 0.050, prevalence of X is 50.0%, and prevalence of Z is 50.0%). Calculations are based on a two-sided Wald test. Power calculations were completed using PASS 16 (NCSS, LLC. Kaysville, Utah, USA).

Given the ability to detect an important magnitude of interaction with a sample size of 650, we then determined the detectable differences in the absence of an interaction (Aim 1). Table 2 provides a range of week 26 cessation rates expected in the SC arm and a range of detectable differences. We will have 80% power to detect an 8% difference if the quit rate is 10% and 90% power to detect a 10% difference if the quit rate is ≤15%. Lastly, we have 90% power for a 12% difference even if the SC quit rate is an implausibly high 25%.

The HIV clinics in Gaborone care have approximately 29,000 patients on therapy, the vast majority of whom have undetectable viral loads (Gaolathe et al., 2016). Based on our preliminary data (Mosepele et al., 2017), we expect a smoking rate of ~20% overall, and 40% in males. We selected 5 clinics which provide care to >10,000 patients including the clinic at Broadhurst Traditional Area (BTA) which caters mostly to males who work in the trades. This will provide at least 2,000 eligible patients, of whom only 33% will need to enroll over 3.5 years to reach the sample size. Based on the participation rate in our pilot trial and our other HIV research in Gaborone, the sample size is quite achievable.

Table 2. Detectable Differences for Aim 1 with N=650

Quit Rate in SC-SC	80% Power	90% Power
5%	6%	7%
10%	8%	9%
15%	9%	10%
20%	10%	11%
25%	10%	12%

Detectable Differences for Mediators (Aim 2)

For the Aim 2 mediators analysis, we hypothesize that increases in the mediators will predict greater smoking abstinence at the 26-week follow-up. Using the structural equation modeling (SEM) package in STATA (STATA Corp, College Station, TX), we will test the treatment effect on the slope of the mediators versus time, with pre-quit values representing the intercepts. [143,145-147] We will examine the proportion of treatment effect explained[148,149] and test with a delta method generated z-score (Type I error of .05). There are three primary proposed mediating pathways between treatment and outcome, so our Type I error will be corrected to 0.0167. For smoking abstinence, a sample of 650 gives us 80% power to detect small effects (δ=0.32) for changes in the proposed mediators, where serial observations are uncorrelated within subject. Even a modest within-subject correlation (ρ=0.3) provides 80% power to detect a small treatment effect (δ=0.20).

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6.2 Statistical Methods

The overarching principle of the analysis plan will be "intention-to-treat." Although this trial tests a strategy, because smokers need to have sufficient motivation to attend counseling sessions, we will use a modified intention to treat approach where all individuals who attend the first counseling session will be included. Dropouts thereafter will be included as failures in the arm to which they were randomized. Individuals who drop out prior to the first session will be replaced. Secondarily we will conduct a 'completers only' analysis. We are stratifying enrollment by degree of depressive symptoms because BAPS targets depressive symptoms as an important determinant of smoking behavior and thus, it may operate more effectively in those with depression. Formal statistically powered analyses of moderation by depressive symptoms will be performed.

While we are stratifying by sex to achieve balance, because the intervention is tailored to the individuals' personal preferences, rather than generic strategies that might differentially appeal to men and women, we do not expect differences in the effectiveness of the intervention by sex and thus, the primary analyses will not be performed stratified. Secondary analyses will formally test for effect modification by sex using a study arm by sex interaction term.

Primary: The hypothesized effect of treatment arm (i.e., the difference in quit rates between subjects across the 2 study arms) will be tested by a treatment arm term in a mixed-models logistic regression model with covariates. Outcomes of the analyses will be characterized by odds ratios (e.g., odds of quitting smoking) and 95% confidence intervals. The primary outcome will be 7-day point prevalence abstinence at week 26 (24-weeks post-TQD; self reported abstinence for 7 days prior to the assessment and breath CO ≤8 ppm). Secondary outcomes will include CO-verified 7-day point prevalence abstinence at week 10 (end of treatment (EOT)) and per guidelines 115: prolonged abstinence (relapse defined as 7 consecutive days of self-reported smoking after a 2-week grace period), continuous abstinence (no smoking between TQD and follow-up) both at 10 and 26 weeks, and time to 7-day relapse. In the absence of imbalance of baseline characteristics, chi-squared tests will be used to compare the two study arms with respect to the dichotomous primary outcome.

Secondary: Since BAPS is hypothesized to operate in part by targeting depressive symptoms, we will formally test for moderation of its effect on smoking cessation in those with and without depressive symptoms at baseline. These analyses will be identical to those for Aim 1 however an interaction term will be included in all of the analyses coded as 0/1 for presence or absence of high levels of depressive symptoms. In secondary analyses, we will include the value of the Mood Module score as the moderator in the interaction term. While tests of interaction with continuous variables typically require smaller sample sizes than those with dichotomous moderator variables, they are harder to interpret both scientifically and for policy decisions and therefore are considered secondary. Additional secondary analyses will compare the maintenance of virologic suppression rate between the arms using the same approach as for the primary outcome of smoking cessation.

Aim 3 hypothesizes that changes in three potential mediators will be associated with success of BAPS. Namely, we will assess whether 1) decrease in depressive symptoms, 2) increase in substitute reinforcers and decrease in complementary reinforcers, and 3) increase in problem solving will mediate the effects of BAPS on bioverified 7-day point prevalence abstinence at 10 and 26-weeks post-TQD. The primary analysis of Aim 3 will aim to establish mediation of treatment effects on this intermediate outcome using MacKinnon's approach (MacKinnon and Luecken, 2008), which is more powerful than Baron and Kenny's causal-steps method (Baron and Kenny, 1986). As explained in Cerin and MacKinnon (Cerin and Mackinnon, 2009) and successfully implemented by Papandonatos et al. (Papandonatos et al., 2012), we will determine whether: 1) there are greater changes in the proposed mediators of BAPS' effect (depressive symptoms, reinforcers, and problem solving) among the participants who receive the BAPS vs.SC; 2) ; changes in mediators were predictive of abstinence over and above any direct effects BAPS compared with SC; and 3) these conditions held simultaneously for changes across the different proposed mediators. Let

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the regression path coefficients between intervention arm and mediators (action path), mediators and abstinence (theory path), and intervention arm and abstinence controlling for the effect of changes in mediators (outcome path) be denoted by a, b, c respectively. Successful mediation through changes in mediators requires that the 95% confidence interval for the a*b product of path coefficients includes zero. To accommodate skewness and kurtosis, interval estimation will be based upon bias-corrected and accelerated (BCA) bootstrap confidence intervals (Preacher and Hayes, 2008). We will test the treatment effect on the slope of the mediators versus time, with pre-quit values representing the intercepts. Longitudinal change in the mediators will be represented with a slope factor (based on observed repeated measures of each mediator) (Piper et al., 2008).

Secondary, exploratory analyses will also examine the effect of other mediators (see Table 2 for variables). We will conduct these analyses as in Napolitano et al (2008). Once mediation of the intermediate outcome (e.g., cigarette reward value) has been modeled as described above, we will estimate the remaining paths linking intermediate outcomes to abstinence via logistic regression.

7 Safety and Adverse Events

The MPI and local PI will be responsible for the overall data and safety monitoring of the study. During the course of the study, data and safety monitoring will be performed on an ongoing basis by the DSM Board and by project staff and the local ethics committee in Botswana. The Project Staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. The Study Coordinator will perform regular chart review to verify data integrity. The study medical personnel will be available to review assessments for each participant on an ongoing basis. Project Staff will meet on a regular basis to reconcile data queries and safety concerns. The site IRB will review the trial, including SAEs, on an annual basis. The DSMB will review the trial data as described below.

7.1 Definitions

7.1.1 Serious Adverse Event

A Serious adverse events (SAE) are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

For additional information on definitions and clarifications which may be helpful in creating the safety monitoring portion refer to appendix 15.7

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7.2 Recording of Adverse Events

The research team will review initial eligibility and monitor adverse events during the trial. Participants will be monitored for SAEs at each session between weeks 0 and 26 weeks, as well as through open-ended questions during assessments. Trained study staff will assess participant treatment reactions with established symptom checklists and validated depression scales. These assessments are conducted at each visit before, during, and after the 9 week treatment phase by a research staff member. Additionally, participants will be given a 24-hour emergency number they can call if necessary.

We will use an established coding and reporting system for adverse effects also used in our previous trial (DA020830). In this system, personnel are trained to administer side effects measures, including validated scales. If a side effect report or a score on an established scale indicates a safety concern, the Study Coordinator will be notified and will assume responsibility for the determination of a course of action (e.g., continue to monitor, refer to the local PI who is a Family Medicine physician). Participants are given contact information so that, if an adverse event occurs, they can contact study staff 24-hours a day. Serious adverse events are reported to the IRB and NIDA in accordance with DSMP reporting procedures.

7.3 Relationship of SAE to Study

Study leaders will be alerted to any severe adverse effects. The local PI will review the information provided by the research staff and if applicable, will contact the study participant to gather more information and determine the appropriate course of action for the subject. Ultimately, the local PI will decide if the SAE (e.g. suicidality) is related to study treatment and whether the subject should discontinue the study. The relationship of the severe SAE to the study will be classified as: related (definitely related, probably related, possibly, unlikely related) or unrelated.

7.4 Reporting of Adverse Events and Unanticipated Problems

Information surrounding SAEs will be initially recorded on the appropriate source document, the SAE form and/or any document in which the SAE information was originally recorded. All applicable SAEs will then be documented on a cumulative SAE log maintained within the regulatory binder.

SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur during the entire time the participant is involved in the study. Study staff will assist the DSMB, NIH, or other regulatory staff in investigating any SAE and will provide follow-up information reasonably requested

SAE Reporting Procedures. If an event is to be classified as a SAE, the following reporting procedures must be followed:

- This research protocol has SAE reporting obligations to the following organizations:
    - National Institutes of Health - NIDA
    - Local Ethics Committee
    - Data Safety Monitoring Board
- Please see the SAE Reporting Checklist table below to guide SAE reporting to each organization.
- Reports to the local ethics committee may use site-specific forms as needed.

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Completed documentation of applicable SAEs will include the following information:

- Protocol name and number
- Subject identifiers
- Demographic data
- Date Site Notified
- Date and time of SAE onset
- Date and time of SAE resolution, if available
- Course/Description of Event (including sequelae)
- Action Taken
- Outcome
- Follow-up plan
- Serious Status (What makes the event an SAE)
- Relatedness to the study procedures (PI and/or Study Physician):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Clinical assessment of subject conducted at time of SAE (if appropriate)
- Results of any laboratory tests and/or diagnostic procedures (if appropriate)
- Autopsy findings (if appropriate)
- Concomitant medications and therapies (excluding treatment of event)
- Relevant Medical History (if appropriate)

7.4.1 Follow-up Report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed

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information will be submitted to the local ethics committee. At a minimum, follow-up information will include SAE onset/resolution, description of event/course, severity, action taken, outcome, and possible relation to intervention. The MPI and local PI are responsible for ensuring that all SAE are followed until either resolved or stable.

7.4.2 Investigator reporting: notifying the study sponsor

Any SAE that was unexpected and potentially related to the intervention (e.g., suicide) will be reported to the study sponsor, NIDA, within 48 hours of the team's awareness of the event. The Penn IRB will receive aggregated SAE data annually. However, if the local ethics committee in Botswana deems an unexpected SAE to be related to study procedures, the Penn IRB will be notified within 48 hours of this determination by the local Botswana IRB.

Reporting Process:

Unanticipated SEAs deemed likely due to study procedures will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths (more rapid reporting requirements):

Deaths that occur during the course of a research study and that are:

- Unexpected; AND
- Related to the research study; AND
- When other participants are believed to be at an increased risk of harm
- Must be reported to the IRB within 3 days from the time the investigator becomes aware of the death.

7.4.3 Data and Safety Monitoring Plan

7.4.4 Data Safety Monitoring Board

A protocol-specific Data Safety Monitoring Board will be used for this trial since this is considered a Phase III trial. The operation of this board will adhere to the guidelines for DSMBs outlined by the NIH. The specific aspects of the DSMB for this study are below.

As a clinical trial of the efficacy of two different smoking cessation behavioral interventions, we have empaneled a Data and Safety Monitoring Board. Board members will include three scientists with complementary backgrounds. Jean Nachega MD PhD will Chair the DSMB. Dr Nachega is an Infectious Diseases physician-scientist, Professor of Medicine at Stellenbosch University in South Africa, and senior clinical investigator in HIV clinical epidemiology. He has two decades of experience as a researcher, including of clinical trials in HIV. The other members will include: Lisa Cox PhD Associate Professor of Preventive Medicine and Public Health at University of Kansas School of Medicine is a Clinical Psychologist with an NIH funded research program focusing on smoking cessation interventions in underserved populations. Lucky Mokgatlhe PhD is Head of Department of Statistics at the University of Botswana and an NIH funded HIV clinical research investigator and trainer. He has extensive experience analyzing clinical trials, behavioral data, and HIV related research.

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The DSMB will be charged at least 1 month prior to enrolling the first participant in the trial. They will be given the opportunity to review the charge and request modifications to be discussed with Drs. Gross and Schnoll. The focus of the DSMB will be to help the investigators monitor enrollment. They will also review any unexpected adverse events to determine the unlikely possibility that the interventions are doing harm. They will have the responsibility of notifying the investigators if they believe the trial is imposing risks that need to be further mitigated or in the unlikely event they believe the trial needs to be halted. There will be no formal stopping rules for either efficacy or futility. We will not stop for efficacy of one arm over another because the likelihood that either counseling intervention will be implemented will require the strongest level of evidence presented to the Ministry of Health and Wellness, which will only be achieved with the full sample size. We will also not stop for futility since both arms might work equally well, which will also encourage the Ministry of Health and Wellness to implement the counseling intervention they find more appealing or feasible. Dr. Bilker and the dual PIs will be responsible for interfacing with the DSMB. They will provide reports of enrollment and any major adverse events after the first 100 participants are enrolled and then annually. The meetings will be held by Skype or teleconference as preferred by the members. During the trial, major unexpected adverse events will additionally be reported to the University of Botswana Ethics Board and the University of Pennsylvania IRB and the PIs will discuss the event among the investigators to determine if a halt in
enrollment to modify the study is warranted.

COVID-19 Protocols
All safety protocols put in place due to COVID-19 will be followed diligently. Our study staff will be required to wear face shields and masks and be provided with hand sanitizers. These will all be purchased using study funds. Rooms at the clinics will be cleaned between participants. They will limit their face-to-face interactions to one participant per session ensuring recommended social distancing.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

To start, confidentiality will be protected by having all conversations between research staff and participants will be conducted in either a private room in the clinics or outside away from earshot of others. The specific room or location will differ by clinic and be specified through an agreement between study staff and site Head Matron.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Data Collection and Management

Overview

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CRCU (Clinical Research Computing Unit) staff will develop and maintain a data management system (DMS) that will allow the automated randomization of participants into the two trial arms. The DMS will ensure that all data collected via ACASI are securely transferred to and stored at the CRCU.

The following activities will be performed:

Project Management

CRCU staff will coordinate project start-up activities between Dr. Gross' team and CRCU team; participate in project meetings relative to the design, development and implementation of the project; ensure compliance with CRCU and University of Pennsylvania School of Medicine SOPs and maintain documentation as appropriate to record procedural compliance.

Data Management Process Design

During the design phase of the study, the CRCU project team will work closely with Dr. Gross and his team to develop an understanding of the data collection and storage needs of the study. Requirements governing all aspects of the study will be identified.

Once all patient data to be collected have been identified, CRCU staff will design procedures for management of data flow and data processing.

Data Management System (DMS) Design, Development, Testing, Implementation and Maintenance

The following components of the DMS will be developed by CRCU staff:

- An electronic database will be created to hold the study data. The database will be hosted on secure CRCU computing servers and its access will be restricted to authorized individuals. Electronic audit trails of changes to database contents will be incorporated into the design and will capture and record those changes automatically.

- A data capture module will be developed to allow remote entry of data for the purpose of randomizing enrolled subjects. The module will be available to any computer with a persistent internet connection and will be run using standard web browser software. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and skip pattern enforcement.

- A randomization module will be configured to allow site personnel to randomize subjects into one of the two trial arms using permuted block randomization stratified on baseline depressive symptoms and sex. At the randomization attempt, the DMS will check the eligibility data to confirm that randomization is valid. A randomization ID number will then be assigned.

- An electronic data transfer module will be configured. All data collected via ACASI at the Gaborone site will be imported in the database through this module. The layout of the electronic files will be agreed upon by the CRCU and the providers of the data, with written specifications for the agreed upon layouts. It is expected that the file formats will remain consistent over the course of the project, unless the CRCU and the data provider agree on desired changes. The module will include checks to insure that all data in the files are loaded completely and accurately.

- A data quality module will be configured to assess data entered into the database in relation to a set of rules that describe expectations for those data items. CRCU staff will work closely with Dr. Gross to define this set of data validation rules to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. Clinical site personnel will review the results of the data validation and take any required corrective

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action for invalid data. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

- A reports module will be developed to facilitate the monitoring of study progress. A set of standard reports will be created to clearly illustrate the results of study recruitment efforts. Additional reports may be developed where regular feedback is desirable.

The DMS will be subjected to extensive functional testing prior to deployment. Successful completion of user acceptance tests will mark the end of development and predicate the deployment of the DMS for use in storing and managing active study data.

An initial training session will be conducted via webinar prior to study start. This session will cover the use of the randomization and data transfer features.

CRCU staff will interface with the site to provide assistance with problem solving related to use of the data management system, as needed.

Any modifications made to the DMS after being deployed will be conducted in accordance with change control procedures. CRCU staff would work closely with Dr. Gross to identify any desired modifications and to assess the impact of the proposed changes.

Database administration services, including user account maintenance, database security, performance monitoring and tuning will be provided throughout the life of the study.

Data Transfers and Quality Management

All study data will be transferred to the CRCU from the Gaborone research site. CRCU personnel will conduct transfer procedures, train site staff and monitor the integrity of transfers. The RCT interviews are expected to include up to 100 variables each.

Data Reporting & Study Close-Out

Periodic reports on subject accrual, study progress and data quality will be generated and provided to Dr. Gross and any study quality and safety monitoring boards as may be specified by the protocol and applicable regulations.

The CRCU will grant read-only access to the study data for biostatisticians to perform their final analysis. Data dictionaries and any other relevant information will be provided to the biostatisticians to facilitate their analyses.

CRCU staff will lock the database once all data have been collected. Study data will be packaged for data sharing purposes. A snapshot of the database will be taken and stored in a secure folder.

All paper records of participant information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All databases containing participant information will be password protected, and again, accessible only to authorized study personnel on password-protected and encrypted networks. Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. Each participant will have a unique study ID number for all data collected. In all datasets, we will use ID numbers only. A separate data set linking names with ID numbers will be accessible only by the study biostatistician. All communications about participants will use the ID number only and never include names or other personal information. All data will be stored until all analyses are completed. No data will be shared with any unauthorized party (i.e., aside from study personnel and regulatory officials). Any publication of data will not identify subjects by name or with an identifier that could be used to reveal identity. Data will be accessible to the study PIs and co-investigators.

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8.3 Records Retention

Data collected from participants will be used for as long as the study is active (about 5 years). Paper records are saved in an archive for 10 more years and are then destroyed.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

Drs. Gross and Schnoll will be responsible for the overall data and safety monitoring of the study. During the course of the study, data and safety monitoring will be performed on an ongoing basis by the DSMB and by project staff and the local ethics committee (IRB). The project staff are responsible for collecting and recording all clinical data. This includes ensuring that source documents exist for all the data collected on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. The study coordinator will perform regular chart review to verify data integrity. The local PI will be available to review assessments for each participant on an ongoing basis. Project staff will meet on a regular basis to reconcile data queries and safety concerns. The local ethics committee will review the trial, including SAEs, on an annual basis. The DSMB will review the trial data as described below.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

10.1 Risks

The primary risks include feelings of failure from not achieving abstinence and symptoms of withdrawal from nicotine. The likelihood that an individual will be coerced, enrolled without informed consent, or lose confidentiality due to this study is low and will be minimized by the procedures discussed below. Breach of confidentiality (e.g., regarding HIV status) resulting from participation in the trial may cause participants some level of psychological, social, or financial distress but strategies are in place to minimize the chance for this risk.

Assessments: Subjects may experience emotional distress during assessments from discussing feelings and attitudes about smoking or from learning about the risks from smoking. These events happen very rarely and in almost all cases are short-lived and of low intensity, lasting for 1-2 weeks. Study personnel will be alerted to expect this from a small number of subjects and will be trained to make referrals for mental health services as needed. Personnel will be trained to query for adverse emotional reactions during assessments and will be trained to deal with such reactions and to provide additional referrals if needed. In addition, if assessments indicate psychiatric concerns, referrals to appropriate psychological services will be provided.

Withdrawal Syndrome: Many individuals who quit smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity,

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lasting for 1-2 weeks. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

Potential Loss of Confidentiality: Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential. All conversations between research staff and participants will be conducted in either a private room in the clinics or outside away from earshot of others. The specific room or location will differ by clinic and be specified through an agreement between study staff and site Head Matron. We will store subject information in a secure room with limited access. Only people working on this research project can work with subject information. We will control access to the computer files that hold this information. This information will not be released to anyone. When the results of the study are published, no names or identifying information will be used. Additionally, because this study is conducted by phone, participants will set a code word only known to them and the study personnel and will be required to use this code word prior to commencing counseling and data collection processes

10.2 Benefits

The potential direct benefit to the research participants is abstinence from smoking, if the counseling interventions are effective. By participating in the research study, this may further help contribute to the development of an effective and feasible smoking cessation intervention for PLWHA in Sub-Saharan Africa. If either (or both) intervention(s) work(s), Botswana's Ministry of Health and Wellness is eager to implement a smoking cessation program based on our findings. If the hypotheses about changes in mediators are proven, greater efforts to disseminate this intervention globally are likely since we would have further established this scientific principle about smoking cessation in HIV generally.

As outlined above, the importance of the knowledge gained by this study is potentially large. If the hypothesis is correct, it has the potential to decrease smoking and in turn, smoking related illness in HIV+ individuals in an LMIC. Further, we will have contributed significantly to understanding the generalizability of our hypothesized mechanisms of smoking and abstinence behavior to help further combat this threat to the health of HIV+ individuals in LMICs.

10.3 Risk Benefit Assessment

Given the low and mitigated risks to the research participants, and the potential benefit to science and the population, the risk-benefit balance of the study is quite favorable

10.4 Informed Consent Process

All subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. Subjects will be consented by the study research member in a room we have selected in which to perform consent, at the IDCC, where the individual was screened. Potential subjects will review the consent form in detail with the study research member and have the ability to take the consent home for further review. In order to provide informed consent, participants must be able to understand Setswana or English and acknowledge having had the trial goals and procedures explained to them by providing either their signature or mark on the consent form

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the National Institute on Drug Abuse (R01 DA045604).

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11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

Participants in this trial will be compensated in cash with 200 Pula (~$16.00) per study visit for 3 visits each and then 400 Pula (~$32.00) for the 26 week closeout visit as an additional incentive to encourage retention. Participants will be instructed to come to the office to pick up their compensation after the visit.

Visit	Compensation Amount
Baseline	200 Pula
Week 3	100 Pula
Week 7	100 Pula
Week 10	200 Pula
Week 26	400 Pula
Total	**1000 Pula (~$81.00)**

12 Publication Plan

We will follow standard methods for publishing the results of this study and in accordance with any publication policies of the University, Department, Division or Research Center.

The proposed trial will be registered with Clinicaltrials.gov in accordance with NIH and Penn policy. This will be stipulated in the Informed Consent documents. Results from the trial will be disseminated primarily through publication of findings through academic journals and scientific meetings, including Cancer, Tobacco and Infectious Disease conferences.

The Investigators on this proposal will make every endeavor to disseminate the information learned and the resources developed through the completion of this study to individuals within the scientific community after publication. We will assure the timely release and sharing of appropriate data no later than the acceptance for publication of the main findings from the final dataset and will protect the rights and privacy of human subjects who participate in NIH-sponsored research by redacting all identifiers and adoption of other strategies to minimize risks of unauthorized disclosure of personal identifiers in accordance with authorization and consent documents. Requestors will be required to obtain approval by the Health Research and Development Committee of the Botswana Ministry of Health and Wellness, in accordance with their national policy. We agree that data sharing and dissemination is essential for expedited translation of research results into knowledge, products, and procedures to improve human health.

Regardless of the results, the Thotloetso trial will provide critical information on expansion of a counseling-based smoking interventions to scale up either BAPS or SC into clinical practice. When the results are available, we will meet with stakeholders including, but not limited to the Permanent Secretary of the Ministry of Health, the Permanent Secretary of the Ministry of Education, academics at the University of

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Botswana including Dr. Mosepele, Vice Chair for Research in the Department of Medicine and a US-trained Infectious Diseases physician and clinical investigator, and relevant NGOs. They will be presented with the proposed intervention to help identify future adopters and advocates. They may identify better sites of service provision for the future, such as TB clinics. The themes of these meetings will be discussed among the investigative team in conference calls and the final scale up plan will be presented back to the stakeholders to obtain their buy in.

We have developed a plan for resource sharing and dissemination of study results to the extent allowed:

1. **Availability of the Dataset:** After data collection is complete, the full dataset (redacted of all identifying information) will be made available on the study website.

2. **Publications:** Manuscripts based on results from this proposed study will be published in peer-reviewed journals. We will select "open access" options for these manuscripts whenever possible.

3. **Dissemination of Analytic Programs**: We will make available the code (i.e., analytic programs) used for data analysis. This will facilitate related research by other investigators.

Specific Requests: Requests for additional analyses of the study dataset that have not been performed but are within the allowed scope of the study will be evaluated by the study PIs. If such analyses are permissible within the limitations of the study and the data use agreement, we will perform these analyses and provide results to the requesting individuals

13 References

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14 Appendix

Table 1: Schedule of Study Procedures

Measures	Week 0	Week 1	Week 3	Week 5	Week 7	Week 9	Week 10	Week 26
Smoking Hx	x							
Fagerstrom Test for Nicotine Dependence (FTND)	x							
Modified AUDIT	x							
Mood module of PRIME-MD	x		x		x		x	x
Pleasant Events Schedule (PES)	x		x		x		x	x
Social Problem Solving Inventory-Revised Short-Form	x		x		x		x	x
Cigarette Evaluation Scale (CES) *(at wk 3, 7, 10, and 26 if smoking)*	x		x		x		x	x
Snaith-Hamilton Pleasure Scale (SHAPS)	x		x		x		x	x
Environmental Reward Observation Scale (EROS)	x		x		x		x	x
Questionnaire of Smoking Urges-Brief Version (QSU-B)	x		x		x		x	x
Minnesota Nicotine Withdrawal Scale (MNSW-W)	x		x		x		x	x
Timeline Follow-Back (TLFB) and past 24 hour smoking confirmation	x	x	x	x	x	x	x	x
SAE Assessment		x	x	x	x	x	x	x
Viral Load Collection	x							x
CO Breath Measure *(if abstinent)*							x	x

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