A Multilevel Gaming Intervention for Persons on PrEP

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Significance

The primary prevention of HIV infection remains a crucial priority. In 2011, there were 2.5 million new HIV infections worldwide.(1) In the U.S., young minority men who have sex with men (MSM) are most likely to become infected with HIV and the use of antiretroviral medications to reduce the risk of acquiring HIV infection (Pre-exposure Prophylaxis, PrEP) is an efficacious and promising new prevention strategy.(1,2) There have been recent significant advances regarding PrEP including the definitive demonstration that PrEP reduces HIV acquisition, the regulatory approval of Truvada (tenofovir/emtricitabine) with an indication for sexual HIV prevention, and the development of clinical prescribing guidelines. Despite these promising events, the practical implementation of PrEP is likely to be challenging.(3-10) Data shows that PrEP's safety and effectiveness could be greatly compromised by suboptimal adherence to treatment and there is concern about the potential for an increase in HIV risk behavior among PrEP users.(11-15) Due to these challenges, the prescribing of PrEP should be accompanied by behavioral interventions.

Adherence to medical care is an integral factor in PrEP's effectiveness. The iPrEx, TDF2, and Partners PrEP clinical trials all conclusively showed that the level of protection from HIV infection depended on how consistently participants took prescribed medication. Significantly greater levels of protection occurred among participants with detectable levels of antiretroviral medication (ARV) in all of these trials.(16,17,18) The impact of adherence was also underscored in the FEM-PrEP and VOICE studies, both of which found that few women had detectable levels of ARVs and the studies were unable to demonstrate the efficacy of PrEP.(15,19,20) Adherence to medication is critical to prevention with PrEP, however, engaging patients in comprehensive follow-up care is also imperative.(21) Treatment with PrEP will require consistent contact between patients and clinical providers and will include laboratory monitoring, HIV testing, the detection and treatment of associated side effects, and in cases of unsuccessful prevention, the treatment of newly acquired HIV infection.(5,10-15) Individuals who are at highest risk of HIV infection, often come from populations that historically have been underserved by healthcare.(23,24) Therefore, engaging patients in care could be challenging and will require reinforcement and support for doctors and patients.(13,23) Behavioral Interventions promoting adherence to comprehensive PrEP treatment will need to be tailored to underserved and at risk populations and will need to reinforce the clinician-patient relationship.

PrEP could lead to increased behavioral risk in real world settings. Although there is great optimism about the use of PrEP for HIV prevention, a concern is that PrEP users might take more sexual risks or decrease traditional risk reduction strategies such as condom use and HIV/STI testing of partners. Behavioral models (Behavioral Disinhibition and Risk Compensation) suggest that risk could increase by reduction of self-imposed constraints or by decreasing individuals perceptions of HIV risk. This, in turn, could lead to increased incidence of HIV and other STIs.(14,22,25,26,27) Some mathematical and cost effectiveness models have suggested that even small increases in risk behavior could offset or reverse PrEP's protective benefits at the population level.(13,14) Little evidence is available regarding the actual impact of PREP on risk taking. Data from the iPREX study showed only indirect evidence of increased risk behaviors, as those participants who engaged in unprotected anal sex were more likely to have detectable tenofovir levels than those with less sexual risk taking.(17,28) In real world clinical settings, in which people know they are on an active medication, behavioral risk taking could measurably increase. Increases in risk behaviors have been documented in the context of microbicide trials, vaccine trials, and among patients living with HIV on antiretroviral therapy.(32) Therefore, HIV prevention counseling remains clinically relevant and prudent when prescribing PrEP. This practice is consistent with good clinical care and is recommended in interim guidelines for prescribing PrEP which state PrEP has the potential to contribute to effective and safe HIV prevention for MSM if "it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling."(138)

The behavioral interventions accompanying PrEP need to be scalable, cost-effective, and easily integrated into clinical settings. In order to maximize the positive impact of PrEP, it is necessary to combine the prescription of PrEP with behavioral interventions that promote both adherence and the reduction of HIV risk behaviors (2). However, these accompanying behavioral interventions need to be cost effective and easily integrated into clinical settings in which PrEP is prescribed.(33) Additionally, interventions should be enjoyable and tailored to populations targeted for prevention with PrEP. Without these necessary components, integration of behavioral interventions into clinical settings cannot be realistically sustained. Although data on behavioral interventions accompanying PrEP treatment is limited, there is a comparatively large amount of information available on interventions that promote adherence and health behaviors in similar clinical

populations and settings. This data will be used to guide the development of our promising multilevel gaming intervention.

Literature on adherence to antiretroviral treatment (ART) among persons living with HIV is available to inform behavioral interventions accompanying PrEP. Studies have examined the effects of a variety of technological aids in improving adherence in adults such as handheld devices, two-way pagers, and alarmed medication vials.(46,54-61) However, these studies show that reminder devices and alarms, utilized without informational or motivational components, are only minimally effective in enhancing sustained adherence.(48,57,60,69) Devices that record pill cap opening events for patients and providers have been most useful for measuring but not improving adherence.(62,67,68) There is a strong correlation between pill bottle opening events measured by devices such as MEMS (or the electronic pill organizer proposed in this study) and virologic response to ARV. Therefore, pill cap opening monitoring technology has remained a gold standard in measuring medication adherence.(62-68) But, for the successful promotion of sustained adherence to ARVs, the underlying causes of non-adherence must be targeted such as poor information about HIV and its consequences, inconsistent motivation, and a lack of skills needed for healthy behaviors.(70-72,77) The most promising adherence interventions have investigated multi-component interventions that couple electronic reminders and/or pill bottle opening measurements with more costly in-person interventions to improve motivation for adherence behaviors.(48,62,76,78) Reviews suggest that the optimal technology enhanced ART adherence interventions: a) utilize tools that are easy to use, do not attract attention, are familiar, relevant, and tailored to the patient population (60,63,79,80); b) promote involvement with healthcare providers (69,73,81,75); c) incorporate strategies to increase **information** (e.g., HIV treatment knowledge and consequences of non-adherence), **motivation** (e.g., treatment benefits and concerns), and **behavioral skills** (e.g., methods for adherence).(46,63,69,71,73-75,79,81-83).

The Information-Motivation-Behavioral Skills (IMB) model is a well-established conceptualization for improving adherence to treatment as well as decreasing HIV risk behaviors. HIV prevention and ART adherence interventions based on IMB have demonstrated efficacy(86-88) and reviews have suggested that interventions guided by accepted theories of change are more efficacious than those not driven by theory.(47) According to the IMB model, health information, motivation, and behavioral skills are the fundamental determinants of health behavior. In order for a PrEP-related intervention to be successful, the PrEP user must learn information that is directly relevant to PrEP adherence and HIV transmission. Knowledge is a necessary but not sufficient condition for change. Personal motivation to engage in HIV preventative behavior or adhere to treatment regimens (attitudes about health) and social motivation (perceived social and cultural support for performing these acts), is essential for change. Finally, skills for performing adherence behaviors and a sense of self-efficacy must be easily applied to an individual's cultural and social setting. A most recent review of factors associated with PrEP adherence suggests that adherence can be facilitated by "accurate knowledge of medication benefits", "medication optimism and self efficacy for adherence," and "support provided by peers and providers."(29). Our intervention will address these factors within the context of the IMB model. This model, consistent with Social Learning Theory, is broadly applicable and can be used to create theoretically consistent intervention content.(89)

Utilizing gaming technology to deliver behavioral interventions for MSM has many advantages. Most technology-based interventions that aim to improve intrinsic motivation, information, and build behavioral skills for adherence have involved in-person engagement in combination with a variety of reminder or event recording technologies. However, there are many advantages to using newer interactive technology to improve motivation and skills, rather than traditional face-to-face counseling, including scalability, efficiency and cost effectiveness. In this project, we will leverage technology, not to just remind and sensitively record adherence behaviors, but to also to engage patients in learning information, practicing behaviors and improving motivation for safe sexual behaviors and increased adherence to PrEP. The use of a combination intervention that utilizes gaming technology is particularly compelling for use with younger adults, as this age group is most at risk for acquiring HIV and this age group has most actively inquired about PrEP in our clinical settings. Young male adults in the United States, spend on average 1.13 hours per day playing interactive computer and video games. According to the Pew Internet and American Life Report, *Adults and Video Games*, 53% of all American adults play video games and 81% of all younger adults 18-29 years old play video games. Fifty percent of these young adults state they play 'everyday' or 'a few times a week'(90). Gaming technology is also popular among minority MSM, the sub-group most at risk for acquiring HIV. In the past, gaming was mistakenly identified as a primarily adolescent and heterosexually dominated activity, but current data supports that gaming is actually quite diverse.(90) MSM gamers, referred to as "gaymers" in pop-culture and main stream

articles, are highly represented online and increasingly shape the market (34,35,36,38). Additionally, within the United States, African Americans ages 18-35 yrs old represent the most active and fastest growing user group of the mobile Internet (37,39) and more than half of reported video gaming occurs on portable devices.(90,37) Furthermore, MSM have been shown to have greater access to and use of cell phone technologies compared to heterosexual populations(38) and mobile phone teledensity (i.e. number of phones per person) has reached above 90% in most developed countries. The widespread appeal and use of smart phones and video game playing creates a unique opportunity to deliver health education to MSM on PrEP, during leisure time, outside of the clinic, in a manner that is cost effective and easily scalable.(41,84,85,91)

Interactive game play has been shown to enhance players' motivation to improve health behaviors and self-care in a variety of clinical settings and populations. Games can attract and maintain attention; a key component for effective behavior change. Compelling interactive phone based games can expose players to essential health related content thousands of times and also give players unlimited opportunities to rehearse new skills and receive personalized feedback on health choices made within the game. (92-94) Games have been shown to be efficacious in promoting fitness, improving weight management, and improving safer sex skills.(91,92,94,100) For example, a HIV/AIDS-prevention computer game called *Life Challenge* was developed by the New York State Department of Health to enhance safer sex negotiation by adolescents and young adults. The game showed significant improvement in self-efficacy for partner negotiation and condom skills for those who started with the least self-efficacy.(94) Two pregnancy prevention games, *The Baby Game* and *Romance,* designed for sexually active young adults, showed trends in improving knowledge and attitudes about parenting and unprotected sexual behaviors.(93)

Video games have also been applied to improve self-management skills and healthy behaviors in those living with asthma, diabetes, and cancer.(95-99) For example, a diabetes game called *Packy and Marlon,* demonstrates that a well-designed, educational video game can be effective in improving diabetes-related self-efficacy ($p = 0.07$), communication with clinicians and loved ones about diabetes ($p = 0.025$), and self-care behaviors ($p = 0.003$). These changes occurred after the game was played at home for six months, compared to no improvement in diabetes-related outcomes in a control group who took home an entertainment video game that had no health content.(96) In a game called *Bronkie the Bronchiasaurus,* those with asthma help a dinosaur character avoid asthma triggers (pollen, cold viruses, dust) and keep his asthma under control. An empirical study showed that playing the game for less than an hour resulted in significant improvements in a player's asthma knowledge, self-efficacy for asthma self-management, and self-efficacy for talking with supports about asthma.(95,97) Another video game, named *Re-Mission,* designed for a wide age range of patients (13-29 yrs) with acute leukemia, lymphoma, and soft-tissue sarcoma, showed promising effects as well. *Re-Mission* was designed as an action–adventure game with the main character or protagonist shooting cancer-causing agents in the bloodstream. Players gain points and strength by adhering to medications in the game fantasy world. In a randomized control study with a three month follow up, 375 male and female participants who played *Re-Mission* had significantly improved adherence to trimethoprim-sulfamethoxazole ($p=.012$) and 6-mercaptopurine ($p=.002$) compared to controls after an average of only 10.7 hours of play. Adherence to TMP/SMX was tracked by electronic pill-monitoring devices ($n=200$) and the proportion of doses taken correctly by those playing *Re-Mission* was 19% greater than those in the control group. Self-efficacy ($p=.011$) and knowledge ($p=.035$) also increased significantly compared with the control group. Interestingly, the intervention did not affect subjective self-report measures of adherence but did effect the above objective measure.(98,99) Thus, appealing interactive games can target information, motivation and skills for medical care and have led to a broad spectrum of desirable outcomes including increases in knowledge, attitude changes, and increased medication adherence.(91,100,102-104)

The video games most successful in influencing behavior have common traits. Games that utilized a theory of behavior change (with behavior-change concepts inserted in the game play) and involved the use of story and fantasy were effective.(93-103) The successful games reviewed above provided simulated interactive environments where players engaged in behavioral rehearsal.(101-102) The simulated environments of the games served as a safe place to practice self-management skills. Players could observe detrimental effects of their own mismanagement of a disease without engaging in real danger. These findings support current efforts to develop effective video-game interventions for education and training in health care.

Innovation

The use of antiretroviral medications to reduce the risk of acquiring HIV infection (Pre-exposure Prophylaxis, PrEP) is a promising new prevention strategy. Optimal PrEP treatment will require simultaneous

medical care and monitoring as well as behavioral interventions to promote adherence and safer sexual behaviors. In order for interventions to be most successful they must be targeted to populations most at risk. There are many advantages to using newer interactive technology, rather than traditional face-to-face counseling, including scalability, efficiency, cost effectiveness, and appeal. In this project, we will leverage technology, not to just record adherence behaviors, but to also engage patients in learning skills, practicing behaviors and improving motivation for adherence and healthy behaviors. We are not aware of any PrEP related intervention that integrates medication monitoring technology with a theoretically informed game that enhances information, motivation, and behavioral skills for PrEP adherence. An intervention with these components may empower and engage PrEP users, aid over-burdened clinics, and result in improvements in health.

Approach

Preliminary Studies

Our research team is composed of experts in biobehavioral HIV prevention and care, gaming to promote adherence, and we have one of the few PrEP implementation clinics in the country. We are poised to become experts in the clinical use of PrEP in the U.S. Our diverse team will inform this developmental study with a pilot RCT. The project will result in the development of a cutting edge, engaging, and entertaining app/game that successfully achieves improvements in adherence to PrEP as well as improvements in HIV prevention knowledge, skills, and behavior.

Expertise in HIV Prevention, Biomedical Research, and Technology for Behavioral Change. Dr. Whiteley and Dr. Brown are both psychiatrists with clinical and academic expertise HIV prevention, adherence, and gaming for behavior change. Dr. Whiteley has a research focus on the applicability of new technology for promoting health and adherence. Dr. Phillip Chan, Director of the PrEP clinic at Rhode Island Hospital, is an infectious disease doctor and researcher who specializes in HIV care and prevention. Dr. Michelle Lally is also an infectious disease physician with experience in HIV care and HIV biomedical research (including PrEP related research) as an investigator in the NIH Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) and the HIV Vaccine Trials Network (HVTN) (141). She is Director of the Brown University AIDS Program (BRUNAP), and co-Director (with Dr. Brown) of the Prevention Sciences Core of the Lifespan/Tufts/Brown Center for AIDS Research.

Dr. Whiteley has done preparatory qualitative and quantitative work regarding PrEP and has focused on the use of newer technologies and HIV related health behaviors. (111,112, 113) She is the PI on a recent Center for AIDS Research (CFAR) developmental study in which 60 African American young adults at high risk for acquiring HIV (18-24 yrs old) were given an online intervention that included gaming modules and informational modules on PrEP. Quantitative data determined that interest in PrEP was greatest among those with a history of anal sex (OR = 8.4, $p<.05$), even when controlling for condom use at last sex in a multiple logistic regression. As part of this study, Dr. Whiteley also conducted qualitative interviews about knowledge and attitudes towards PrEP with 25 predominately African American (79%) young adults identifying as MSM (18-24 yrs old).(139) Most participants (75%) interviewed were very interested in starting PrEP. Concerns about PrEP included: that sexual risk could increase “cause people won’t worry about what they could get,” and participants stated they would be “unlikely to take PrEP if I am with my main person,” participants also stated, “why bother using condoms, if this pill can be so protective?” Also cultural themes emerged: “we worry that White doctors actually want us to get HIV.” These data reinforce that young adults at behavioral risk for HIV, especially those engaging in anal sex, are interested in PrEP, and are concerned about issues of adherence, risk compensation, and healthcare provider motivations.

Drs. Brown and Whiteley are also PI and CO-I respectively on an iPhone gaming intervention to improve adherence to antiretroviral treatment in young adults living with HIV (90% MSM, mean age 24 years) [R01 HD074846]. This game focuses on medication adherence and sexual risk reduction in those already living with HIV. Dr. Whiteley and Brown have worked extensively with the gaming company that we will use in this project (Mission Critical Studios-MCS, see below) and Dr. Whiteley was able to develop and refine her idea of linking smart technology on pill dispensers with smartphone games with MCS. This technology and iPhone game have been evaluated by 23 predominately African American participants (20 MSM, mean age 24, 70% Black/African American) living with HIV and all participants have had a very positive response to the gaming graphics and Wisepill linkage. Sixteen of the 20 MSM played the game to completion and average game play measured approximately 10 hours per week (as measured by gaming software). MSM participants rated the game very highly (mean item scores of 3.7 on the Client Satisfaction Questionaire and 3.6 on the Session Evaluation Form). Both measures are 4 point Likert items with higher numbers indicating more satisfaction

(See Approach: Open Trial/ Quantitative Assessment and Appendix).(140) Our past gaming and technology experience greatly facilitates the development of this proposed project and similar, detailed quantitative and qualitative work will ensure the same level of acceptability for minority MSM participants on PrEP.

Dr. Brown has also tailored HIV prevention interventions in four NIH-funded RO1 RCTs. All of these tailored interventions have reduced sexual risk and have focused on risk perception, decision making, and assertive prevention skills to reduce HIV risk.(105-109) One intervention outcome paper, with an impact lasting for up to 9 months, received the Reiger Award for Scientific Achievement from the American Academy of Child and Adolescent Psychiatry.(137) This expertise in HIV prevention and the tailoring of prevention programs for high risk populations is highly relevant for this project. Dr. Brown is also PI on two AIDS Trial Network (ATN) protocols that have adapted efficacious, theoretically informed interventions for young adults living with HIV. ATN Protocol 080 delivers tailored cognitive behavioral therapy (CBT) and evidenced-based medication management to treat Depressive Disorders and non-adherence to ART. ATN 069 delivered a tailored CBT and contingency management intervention to treat substance use as well as non-adherence.(42)

Dr. Lally has expertise in the areas of biomedical HIV prevention. She is the Director of HIV Vaccine Clinical Trials at Brown/Lifespan, Director of the Brown University AIDS Program (BRUNAP), and Medical Director of the Rhode Island Clinical Research Center at Lifespan/Brown. She is also an advisory board and faculty member of the STD/HIV Prevention Training Center of New England. She is an investigator in the HIV Vaccine Trials Network (HVTN) and was an investigator on a PrEP study in the NIH Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) entitled *ATN 082: Acceptability and Feasibility of a Pre-exposure Prophylaxis (PrEP) Trial with Young Men Who Have Sex with Men.* This study found that a PrEP placebo controlled trial with a behavioral intervention was acceptable to YMSM, however, only 63% of those taking PrEP had detectable tenofovir at study week 4 and only 20% by week 24.(141). Dr. Phillip Chan is the director of the HIV/STD Testing and Prevention Service at The Miriam Hospital Immunology Center. He is also the director of one of the first PrEP implementation projects in the country (in Jackson, MS and in Providence RI) funded by Gilead (Chan PI), see Setting in Approach. Dr. Chan's research focuses on HIV transmission networks and incorporates molecular genetics, behavioral sciences, and clinical medicine.

Dr. Jeffrey Fisher is the co-developer if the IMB model and an expert in IMB guided interventions. He has published extensively on factors associated with adherence and has done conceptual and empirical work in increasing HIV preventive behavior utilizing IMB theory. Dr. Fisher has designed and evaluated effective HIV prevention interventions in multiple populations. Dr. Fisher's research on HIV to date has involved MSM, injection drug users, heterosexual adolescents, and individuals who are HIV infected. He has been awarded 9 major HIV risk reduction grants from NIH since 1989. He has lectured and consulted internationally. He will be consulting regarding the use of IMB framework for the gaming intervention.(142-145)

Expertise in Gaming Technology. Game development will be done by Mission Critical Studios (MCS). They have extensive experience in developing games for implementation on PC, Mac, Apple iOS, Android, iPhone and all major Internet browsers. Mission Critical Studios has received high acclaim for their own gaming projects including *Dr. Nano - 3D Artery Adventure, Dr. Nano X: Incredible Voyage Inside The Body*, and *Frantic Freddy Bug Stomp*. Mission Critical Studios has contracted and partnered with the following companies: Unilever, IBM, Hamon, Bank of America, SNK/Neogeo, and IBM. This company has also had an enjoyable and highly successful partnership with our research team in developing a gaming intervention for RO1 HD074846. Company skills include 3D Modeling, audio mixing, motion graphics, mocap cleanup, C#, JavaScript, Unreal Scripting, game design, animating characters, Photoshop cleanup and texturing, and UV mapping (by hand through Maya or automated through Zbrush). Company tools include Lightwave, 3D Max, MotionBuilder, Photoshop, After Effects, Flash, Unity, and UDK. Platform experience includes Windows PC, Mac OS X, and Cell Phone/WAP. Mission Critical Studios is a licensed developer for Microsoft Xbox, Nintendo Wii, Nintendo Wii Ware and Nintendo DS. The IMB Adherence Game to be developed for this project is preliminarily titled *Viral Combat* (See Appendix 1, pp. 2-17, for a storyboard and screen shots of the preliminary IMB adherence app/game). *Viral Combat* will be adapted and refined from the popular Mission Critical Studios game *Dr. Nano X: Incredible Voyage Inside The Body*. **Beginning with this existing game allows the project to be done in a cost effective and efficient manner. Please see: http://www.youtube.com/watch?v=lyHzSZFzU1Q, www.missioncriticalstudios.com.**

Pill dispenser monitoring device. Compliance Meds Technologies, LLC. is the developer of the smart medication dispenser that we will be using. The CleverCap is a tamper-proof smart cap that fits onto a standard pill bottle. The CleverCap device can monitor, measure, and securely relay pill-by-pill or dose-by dose adherence behavior. The capability to record and analyze pill opening events is similar to MEMS. However, the

CleverCap device can be programmed to integrate into an array of wireless technologies and other web application interfaces. Each time a person opens their CleverCap, it wirelessly relays the data to CleverCap's HIPAA-compliant secure network. Adherence reminders are integrated through visual and auditory alerts. The CleverCap generates a CleverScore that can be used as a measure of the actual utilization of medications versus the prescribed dosage over time. This instantaneous wireless capability differs from the traditional MEMS cap. Currently, the MEMS cap requires a MEMS reader linked to an office computer in a doctor's office to update and collate bottle openings at weekly, monthly or other scheduled intervals. The wireless network infrastructure of the CleverCap device allows for timely applications to be instantly linked to their product. Compliance Meds Technologies, LLC was named the winner of the 2013 North America Frost & Sullivan for New Product Innovation Award.

Design

This research will be divided into two major phases: (1) a **Development Phase** (n=40) in which we will conduct formative research to guide the development of the gaming intervention and gain experience with its implementation in an open trial and (2) a small, pilot **Randomized Controlled Trial Phase** (n=50) in which we will evaluate the acceptability and preliminary efficacy of the IMB gaming intervention compared to a comparison condition. (A project activities timeline is in the Budget Justification section).

Sample. All MSM on PrEP over the age of 18 yrs old, will be eligible for enrollment in each phase of study according to the following criteria: 1) English speaking, 2) receiving prophylactic antiretroviral treatment (PrEP), 3) not enrolled in another PrEP related study, and 4) able to give consent/assent and not impaired by cognitive or medical limitations as per clinical assessment. There will not be overlap between subjects in the Development and Controlled Trial Phase. We are enrolling only MSM because they are the group most at risk for acquiring HIV. Limiting the study to MSM will allow for the development of an iPhone app/game that is targeted, acceptable, and engaging for this specific at risk population. Based on data below, it is estimated that 65% of participants will be Black/African American, 30% will be Hispanic and the mean age will be 27.

Setting. We will recruit participants from the PrEP Clinic directed by our co-investigator, Dr. Chan. This clinic receives the majority of its referrals from the HIV/STI Testing Clinic at Miriam Hospital, which is also directed by Dr. Chan. More than 500 new patients were seen in HIV/STI Testing and Prevention Clinic in the past year. Those at risk are counseled about and offered PrEP. Approximately, 5-8 people have been started on PrEP each month for the past 6 months (average of 7/month). Of those started on PrEP in the past year, 85% were male, all had a significant HIV sexual risk history including recent unprotected anal intercourse with a male partner, recent anal sex with an HIV infected male partner, or multiple male partners in the past 3 months with unknown HIV status. Sixty-eight percent had a history of a STI in the past year. The age of the men on PrEP ranged from 19-48 years old, with a mean age of 27 years (75% between ages18-30). Racially, 65% of the patients identified as Black/African American and ethnically, 30% identified as Hispanic. During the Qualitative Interview phase we will recruit 10 participants from the PrEP Clinic at the University of Mississippi Medical Center in Jackson, MS. These interviews will help us to develop a game that is widely acceptable to young MSM.

Recruitment and retention. We will recruit 90 participants (40 in developmental phase and 50 in the RCT phase) over 2 recruitment periods, totaling 24 months. Conservatively estimating 6 new patients enrolled on PrEP each month and over 100 existing PrEP patients at the start of this study, we will be recruiting from a pool of 244 subjects, 85% of whom will meet eligibility criteria (207 at-risk MSM, 18yrs and older). Therefore we will only need to recruit 43% of the eligible sample. Our hospital has a long history of recruitment and engagement of adult and young patients with HIV for longitudinal and clinical treatment studies.(102,45) We have close ties with Miriam clinics and successful current collaborations with Drs. Chan and Lally. We were able to recruit >80% of eligible HIV infected subjects for our current gaming study (R01 HD074846) and the majority were younger MSM. Rhode Island's small size and few HIV treatment resources both aid in the retention of clinical samples. Previous ACTG trials in the Miriam clinic have retained more than 85% of enrolled patients after more than six months and we estimate similar retention rates. Retention techniques for the study include maintaining updated participant contact information, frequent reminder cards, phone calls and emails, keeping records of friendship contacts, and obtaining the name and telephone number of another relative or family friend who would know of the patient's whereabouts. The retention rate in Dr. Brown's previous community study (U01 MH066785) was 92% after 18 months. The retention rate in Dr. Whiteley's CFAR study with young adults at risk for HIV was 90%.

Development Phase

The goal of the development phase **(n=40)** is to develop and refine the game (*Viral Combat,* Appendix 1, pp.2-17) for the intervention. This phase will establish acceptability and feasibility by participants of the gaming intervention. These steps will be accomplished by preliminary work by the scientific investigators in collaboration with Mission Critical Studios using data from qualitative interviews with 20 subjects (see Appendix 2, pp. 43-47) and a small open trial that also includes qualitative interviews with 20 additional subjects. Multiple reviews have demonstrated that behavioral interventions shown to be most efficacious are tailored for the target population, and preceded by formative research to inform intervention development.(116-118)

Game development will be accomplished using iterative and collaborative procedures to fully integrate the experiences of participants on PrEP. As discussed in the Significance section, the app/game, *Viral Combat*, will be consistent with the IMB Model of Health.(66) The game will promote increased self-efficacy for adherence and HIV preventative behaviors by improving motivation, increasing mastery, improving information about health and prevention. Successful games are intuitive, engaging and inherently rewarding through action and feedback. Thus, many of the attributes of a successful game are a natural fit for a successful IMB-informed intervention. Screen shots for our initial draft game are included in Appendix 1, pp. 2-17.

Initial development of the IMB Gaming Intervention. A preliminary story board for the IMB app/game proposed, *Viral Combat*, is currently drafted (Appendix 1, pp. 2-17). *Viral Combat* will be adapted and refined from the popular Mission Critical Studios game entitled *Dr. Nano X: Incredible Voyage Inside the Body* (see YouTube video- **http://www.youtube.com/watch?v=lyHzSZFzU1Q** , also see app store- http://itunes.apple.com/us/app/dr.-nano-x-incredible-voyage/id398001397?mt=8). This is a five star rated game in the iTunes app store and is available on both Android and iPhone. We have experience creating a game with MCS and tailoring it for predominately African American young adults living with HIV (See Preliminary Studies) and this past experience informs our protocol for the development process **(See Appendix 1, Mission Critical Dev. Plan, pp. 18-28)**.

The proposed game in this application *(Viral Combat)* differs significantly from the game previously developed for young adults living with HIV (R01 HD 074846). Participants playing the *Viral Combat* will be fighting virus before it infects and enters the body. The game will take place on the surface of the skin, in the arterial system, in the penile and anal canals (rather than in the brain, liver, kidneys as developed for the R01 HD074846). HIV related educational material and games will be tailored to prevent HIV (i.e. importance of testing and using condoms), and not tailored to persons living with HIV (i.e. how viral load affects transmission and health). Adherence messages will be relevant to participants using PrEP for HIV prevention (i.e. taking PrEP doses as prescribed corresponds to level of protection) rather than for persons living with HIV (i.e. ARV adherence impacts viral mutations, CD4 counts, opportunistic infections). Similarities include software for motion controls, touch screen capabilities, integration with electronic pill dispenser, and tracking game usage. These similarities allow for the development of an iPhone app that is unique but within the proposed budget.

***Viral Combat* storyboard (See Appendix 1, pp. 2-17)**. The IMB game/app, *Viral Combat,* will employ graphics, characters, action content specifically chosen to be appealing to our target population. *Viral Combat* takes place inside the human body and starts with a narrator, in a deep and dramatic voice, explaining the storyline and objectives of the game. The player is told by the narrator, “you have been chosen to be cloned. Your clone will be shrunk by the groundbreaking nano shrinking machine and turned into a nanobot! As a nanobot, you will enter your own body to destroy attacking viruses that are trying to gain entry.” The narrator accompanies the player through the shrinking process. The narrator explains to each player “you will need weapons and tools to successfully destroy virus attempting to enter your body. You will earn protective gear, character enhancements and weapons by picking up pills, taking medication and building alliances with doctors and clinicians.” Players can skip this narrative, if they prefer, after the first time gaming. At the start of play, participants can also choose and design their individual, colorful nanobot characters with skin tones that can be customized. The first level begins on the skin’s surface. If players successfully battle virus, engage with providers, take medication, and make healthy decisions, they move to the next exciting level - the penis. During each mission, the player’s score (health status and adherence pill count) is shown. As players become expert nanobots, they move through the arterial system, and other body systems such as the anal canal and the mouth. All organ systems are vibrant and distinctive. Answering questions from the doctor/clinician, and building adherence and HIV prevention knowledge, allows each player to earn strength and points throughout *Viral Combat*. During play, if an answer to a question or skill building exercise is wrong, the player is alerted, and the correct answer is explained (**See Appendix 1, p.10).** “Health Facts” will reinforce HIV prevention information during scene changes. HIV prevention skills will be built with a condom “puzzle” and the “condom

use challenge" that promotes continued condom use with all partners and models assertive safer sex discussions **(See Appendix 1, p. 14)** If a participant misses a dose, the CleverCap software will send a game graphic and message to the participant's phone. Each level in Viral Combat provides new challenges and unique and colorful environments, however, the mission stays the same: kill virus and build strength through taking medicine, learning HIV prevention information, improving motivation, and engaging with healthy charcters in order to build skills. All character control and gaming is done by cutting edge touch screen technology on the phone, no additional accessories are needed for play. Throughout the game the terms "HIV," "AIDS," "antiretroviral" and other identifying verbiage is avoided to protect the players' medical status and to avoid possible stigmatization that could occur from someone seeing a participant playing the game **(see Appendix 1, p.10)**. During the development stage we will also illicit feedback from participants regarding this issue and about the title. Necessary changes will be made if participants feel the game content or title is revealing, insensitive or stigmatizing.

At the beginning of the project, all investigators and the collaborators will review the above elements of the proposed game and suggest modifications to improve its appeal, understandability, utility, and enjoyment by participants. We will also be assessing its consistency with the IMB Model. Modifications will be made by Mission Critical Studios. The process of development and initial adaptation will be done in the first 3 months of the project.

Individual qualitative interviews (months 3-9). Initial detailed, in depth, structured, audiotaped individual interviews about the utility and appeal of the preliminary IMB Gaming Intervention, electronic dispenser, and study procedures will occur with MSM participants (est. mean age 27) receiving PrEP (See sample and setting) during months 4-9. The interviews will ensure that the assembled intervention is relevant to our target population. (116,117,119). We will perform interviews on a sufficient number of each relevant sub-group (Black vs. non-Black, older vs. younger than 25 yrs) until there is redundancy in themes and general feedback. All interviews will focus on how sexual orientation, race, stigma, culture, and age influence information, motivation and behavioral skills for the major targets of the gaming intervention (PrEP adherence, medical care adherence, and HIV prevention behaviors). Participants will give general reactions to intervention content and we will also look for deeper, or more complex, emerging themes to guide game graphics, content, and messages. For example, participants will be asked "As a black, gay male, how worried are you about getting HIV? How effective do you think PrEP is at preventing someone from getting HIV." After viewing a preliminary storyboard or game, participants can be asked, "Which parts of the storyboard/game would influence how concerned you are about HIV?" "Which parts of the game increase your knowledge about how protective PrEP is?" "Could these messages be made more relevant to you and your friends, partners?" Participants will also be queried about the acceptability and relevance of game actions and graphics as they relate to race and culture. As currently proposed in our storyboard, players will be able to personalize their characters so that the game feels racially, culturally and personally relevant. Interviews will aid in determining the scope and design of this personalization. If characters are needed with darker or lighter skin, or more or less colorful clothing is needed, this variability can be added to game options.

Drs. Brown and Whiteley have used qualitative and formative work to adapt interventions for persons at risk for HIV, those living with HIV, and minority MSM. For example, Dr. Brown and collaborators designed, with extensive qualitative work, a culturally tailored STI/HIV prevention campaign for African American teens with a TV/radio media component (119, 120), and Dr. Whiteley also designed, with qualitative work, a culturally tailored Internet based STI/HIV Intervention for African American young adults and MSM (See Preliminary Studies). Drs. Whiteley and Brown will conduct all interviews and code major topic and subtopics from the interviews and review findings with the investigators and collaborators as themes emerge.

Revision to the IMB game (months 9-11): Drs. Whiteley, Brown, and Fisher will assess the intervention's suitability for participants receiving PrEP, and its ability to improve adherence with material and techniques consistent with the IMB model. The team will assess the strengths and weaknesses of intervention components and indicate revisions to the preliminary IMB Gaming Intervention. We will also put all written content through a reader program to ensure that the reading level is appropriate. Mission Critical Studios will implement the changes using our iterative development process (see MCS Development Plan, Appendix pp. 18-28).The investigators will review protocols and technological revisions for consistency, and potential technological problems.

Open Trial: Qualitative and quantitative assessment of the gaming intervention (months 12-18). A 12 week open trial of the IMB Gaming Intervention, with individual qualitative exit interviews, will be conducted with 20 new participants on PrEP during the first half of year 2. The preliminary intervention will be tested in

order to refine the protocol, IMB app/game, electronic pill dispenser, and any other technological requirements. Procedures: After assessment and consent, each participant will receive ONLY a CleverCap electronic pill dispenser and instruction on its use. After one month of using the CleverCap dispenser only, participants will return for assessment. This intervening month will provide a period of time for participants to get oriented to the CleverCap dispenser, and it will also provide investigators with baseline measures of adherence without the IMB app/game. At this one month assessment participants will also be introduced and oriented to the adherence intervention game (*Viral Combat*) and the smartphone. The basic elements of the game will be demonstrated and the participants will have an opportunity to practice the game, with study staff, in order to build interest. Participants will be shown that each pill taking event, recorded by the CleverCap device, will trigger a game graphic text (e.g. missed doses will receive encouraging messages). Participants will demonstrate that they can operate the smartphone, game, and CleverCap dispenser. They will also be given contact information for technical assistance or protocol questions if needed prior to the 12 week study visit. Participants can receive technical assistance from trained RAs, Dr. Whiteley, and the technical staff at Mission Critical Studios.

Quantitative Assessment: Participant's overall satisfaction with the preliminary IMB Gaming Intervention will be surveyed using a modified version of the Client Satisfaction Questionnaire (CSQ-8) at the 12 week assessment. The CSQ is an 8-item measure with good reliability and validity. They will also complete a modified Session Evaluation Form (SEF), which has 13 items that reflect areas of feasibility and perceived utility of the intervention. Responses to items on these questionnaires will help determine the initial feasibility and acceptability. Subjects will also complete measures of HIV-related knowledge, attitudes and behaviors at baseline and at 12 weeks during this open trial (See Appendix 2, pp. 29-42). These measures are described below in the RCT phase as well. Mission Critical Studios can collect generalized, non participant linked, data on game usage through TestFlight software integrated into the game. This data shows the amount of time players spend on the game, percentage of times players complete levels, levels in which players spend more or less game time, etc.

Qualitative Assessment: Drs. Whiteley, Brown, and staff will again use the structured individual qualitative interviews at the 12 week assessment to evaluate participants' opinions on the goals of the gaming intervention, the clinical utility and relevance of the game, its strengths and weakness, its ease of use and barriers to use, and the ability of the study measures to capture their experience (See Appendix 2, pp. 43-52 for preliminary structured interview guide, CSQ and SEF). There will be an emphasis on examining participant feedback for racial, cultural, or sexual specific trends in order to further tailor intervention content. The investigators will use all data to assess feasibility and acceptability of the intervention and make changes as needed. Based on these data, *Viral Combat*, will be modified by Mission Critical Studios during month 19-20 using our iterative development process (see MCS Development Plan, Appendix pp. 18-28). The game and intervention procedures will again be reviewed and revised by investigators to create a final version of the IMB Gaming Intervention for the RCT.

Randomized Controlled Trial Phase

During months 21 to 33, we will evaluate the preliminary impact of the IMB Intervention (IMB app/game + CleverCap dispenser), compared to a comparison group- COMP (iPhone with non-IMB game + CleverCap dispenser) in a Randomized Controlled Trial with 50 participants on PrEP (eligibility criteria above, see Sample). Smartphones will be available to participants in the IMB Gaming Intervention and in COMP for the entire 24 week study period. The COMP participants will be given smartphones and a non-PrEP comparison game (also designed by Mission Critical Studios, see below) to control for attention, time, and any influence the receipt of a smartphone or game has on adherence behaviors or the physician-patient relationship. CleverCap dispensers in both conditions will record adherence. Our primary outcome will be the CleverCap openings measured daily for 6 months. Secondary outcomes such as self report of medication adherence and sexual risk, HIV related knowledge and attitudes, clinical records (appointments kept, STI treatment), and ARV levels (tenofovir diphosphate, **TFV-DP** and Emtricitabine, **FTC-TP**) will be evaluated at 12 weeks and 24 weeks. **Randomization** will occur after enrollment, using a random assignment program, located on the PIs computer, with stratification based on history of PrEP (newly starting vs. already on PrEP > 3 months) and age (18-25 vs 25 and older), since these factors may be associated with adherence and response to the intervention.

The IMB Gaming Intervention. The IMB Gaming Intervention is designed to improve information, motivation, and skills about adherence and HIV preventative behaviors throughout play **(See Appendix 1, pp. 2-17).** All content will be chosen for its appropriateness for the target population and with refinements made

during the Development Phase. With input from the research team and PrEP users, we will produce a sensitive, stylistically and theoretically consistent intervention. Each level in Viral Combat provides new challenges and unique and colorful environments. However, the mission stays the same: kill virus and build strength through 1) taking medicine, 2) learning HIV prevention information, 3) engaging with healthy characters in order to improve motivation and build skills. Participants will be told to take PrEP daily and phones and software will be coded to record and react to daily dosing. If a participant misses a dose, a message is sent from the CleverCap dispenser to study investigators' database on a secure server. This data is then read electronically by a CleverCap software program. This software in turn sends a game graphic with a supportive message such as "Missing you: Get in the Game" to the participant's phone. A similar procedure and software have been successfully developed, implemented and utilized in our R01 HD074846. At all times during the study, participants in both conditions will be able to use their phone regularly, with all the features available to them within phone plan limits. Throughout the gaming intervention subjects will continue routine clinical care visits and HIV testing (as recommended by PrEP prescribing guidelines) in the PrEP clinic. The developed IMB game, *Viral Combat,* and the integration of the CleverCap dispenser with phone, are the two unique, necessary, and defining elements of the IMB Gaming Intervention.

Comparison condition (COMP): CleverCap and non-IMB iPhone game. This condition will be matched with the IMB Gaming Intervention for appeal, time and attention. Subjects in COMP will each receive smartphones with the same data service plan as the active arm. Smartphones given to participants in COMP will have a stylistically similar non-PrEP, non-IMB game designed by Mission Critical Studios (*Dr. Nano X: Incredible Voyage Inside The Body,* **http://www.youtube.com/watch?v=lyHzSZFzU1Q** *)*. This is the same game that *Viral Combat* is being adapted from. Therefore, the iPhone game in COMP will have a look and feel that is very similar to our intervention game but without IMB, PrEP, and HIV prevention related content. Participants will also receive a CleverCap device, which records pill dispenser openings, but there will be no dose related messaging. Similar to the Intervention group, participants will have routine clinical care visits in the PrEP clinic (or more frequently if needed for urgent care).

Design Considerations

Intervention contamination. Participants in the COMP condition could hear from those in the IMB Intervention about the IMB app/game but they will not have access to it on their phone. Although it is possible that the COMP participants could play the game once on an Intervention participant's smartphone, it is unlikely to be a frequent occurrence. Nevertheless, we will assess familiarity and usage of the game by self report at follow-up. In addition, we will assess the occurrence of cross talk between subjects in the two conditions at follow-ups and adjust the analyses accordingly, if needed.

Smartphones: access and confidentiality. Data suggest that average adults and young adults have access to smartphones and studies suggest that within 2 years the majority of phones owned will have these application capabilities, so the IMB app/game will be designed for this almost universal technology. (37,39,40,55) Some participants will already have a smartphone, if it is not an iPhone or Android, we will provide them with a new study phone for the duration of their participation. The phone will be provided to minimize technical difficulties with the CleverCap data transfer and the operation of the game that is designed for iPhones and androids but not other devices. This ensures that all intervention subjects have the same gaming experience with the same displays, graphics, sounds and controls. Loss of a phone is possible but other studies suggest that it is infrequent.(121,122) In our ART adherence study utilizing iPhones given to participants, not one phone was lost throughout the development stage and open trial. Participants report they are motivated to care for the phone because it becomes theirs after the study period. The phone will be password protected, so call logs and texts will not be accessible. None of our technology partners: Mission Critical Studios, Compliance Meds Technologies, LLC, or the phone carrier will have PHI data. There will be no link to personal subject information because all phones will be purchased by a hospital account and linked back only to the hospital/PI. Only the PI will have the linkage of phone (designated by product number) with participant name. This information will be stored and destroyed following the same HIPPA and IRB procedures as all other personal data collected (See Human Subjects).

Assessments. All assessments will take place in a quiet room near or in the PrEP clinic. Complete assessments of attitudes and behavior will occur at baseline, 12 weeks and 24 weeks, and will take 45 minutes to complete. Clinic records will also be coded for biologic outcomes at these 3 assessments. We will use tracking procedures (See Sample and Recruitment) to maintain contact.

Measures. An audio-assisted computer self-interview (ACASI) will be used to assess behavior since it is confidential, allows for complex branching/skip patterns, and detects greater rates of risk behavior.(123) Standard instruments will be administered to gather demographic data (including age, educational level, sexual orientation, SES, race, ethnicity and stability of housing). The measures below will be used to evaluate HIV related knowledge, attitudes, and risk behavior (see Table 1 below for linkage to constructs and intervention).

Table 1. Linkage between constructs, intervention foci, and assessment instruments

IMB Constructs	Intervention Foci	Assessment Instruments
Information: about HIV/STI sexual risk knowledge	↑ HIV knowledge, Perceived vulnerability to HIV/STIs	HIV/STI knowledge scales
Motivation: for adherence and risk attitudes and intentions	↑ Motivation for adherence ↑ Motivation for safer sex ↓ Perceived barriers	Adherence & risk attitudes scales
Behavior: medical adherence, sexual risk, behavioral self-efficacy	↑ Medication and visit adherence, safer sex skills	CleverCap dispenser openings, adherence and sexual risk self report, ARV levels, self-efficacy for adherence and sexual safety

Primary outcome (measured daily by CleverCap):

CleverCap openings. The number of days participants take doses correctly in each of the six months will be our primary outcome. The data is collected wirelessly by CleverCap, and stored daily on a HIPAA compliant server as previously described.

Secondary outcomes (measured at baseline, 12 and 24 weeks):

Self-report of PrEP adherence. This consists of two items: "How many days in the past month did you miss or not take your PrEP medication?" and "How many days in the past week did you miss or not take your PrEP medication?"

ARV (TFV-DP and FTC-TP) levels. Intracellular TFV-DP and FTC-TP will be measured in red blood cells using dried blood spots. TFV-DP levels provide a measure of long-term adherence over the preceding month (like hemoglobin A1C) and a detectable FTC-TP provides information about recent dosing (i.e. if FTC-TP is detectable, a recent dose was ingested Y/N). The level of intracellular TFV-DP can be used to estimate how many doses/week the participant is taking on average (eg 7/wk on average, 4-7/wk on average, 2-4/wk on average, <2/wk on average). 25µL will be drawn each time. The blood samples will be sent to Skaggs School of Pharmacy and Pharmaceutical Sciences at The University of Colorado Aschutz Medical Campus. TFV-DP and FTC-TP levels and laboratory analyses will be done by **Peter Anderson, Pharm.D** who is the leading expert in conducting and interpreting these results.(148)

Medical history. Staff will abstract from the clinic record the number of medical visits kept and missed in the past 12 weeks.

The Risk Behavior Assessment. The RBA (used in Dr. Brown's other federally-funded projects) is a reliable and valid computer-assisted structured interview assessing self-reported sexual behaviors. It assesses type of sexual behavior (i.e., anal, oral, vaginal) in the past 12 weeks, frequency of sex, and number and gender of partners. Additional questions cover sex with high-risk partners, frequency and quantity of substance use and having sex while using alcohol/drugs.(132)

IMB construct outcomes (measured at baseline, 12 and 24 weeks):

HIV & STI knowledge. The HIV Knowledge Scale assesses knowledge about issues such as risks for HIV, using 18 items with "true," "false," or "do not know" response options. Test-retest reliability (r=0.73) and internal consistency (alpha=0.90) were satisfactory in studies with at-risk young adults.(43) The STI Knowledge Questionnaire uses similar response options with 10 items assessing risk for and treatment of sexually transmitted infections. Test-retest reliability (r=0.88) and internal consistency (alpha= 0.86) were both satisfactory in studies with at-risk young adults (Appendix 2, pp. 29-30).(44)

Attitudes towards adherence. This checklist was from attitude items used from several AIDS Clinical Trials Groups and will be modified to reflect adherence to a medication to prevent HIV. The checklist assesses

16 common barriers to taking ARV as prescribed and 10 aids to taking ARV. The original measure is being used in several on-going trials (see Appendix 2, pp.31-38).

Motivational readiness for adherence. Rollnick's Readiness Ruler (127) will be used to assess motivation for adherence to medication and medical visits. Respondents rate how ready they are to take PrEP as prescribed and to keep medical appointments on two items from 1 (not ready) to 10 (ready to be consistent or already consistent) each month. Subjects will also complete the 10 item Likert-style IMB PrEP Motivation Scale from the LifeWindows Project Team. It will be modified to assess personal and social motivations for PrEP, rather than ART (Appendix 2, pp. 39-40).(125)

Medication & appointment self-efficacy. This measure was developed based on Bandura's (1986) theory of self-efficacy(89) and was shown to have strong reliability (alpha>0.8) in a study of HIV medication adherence.(128) The instrument consists of Likert style items (with five response options). Three items assess self efficacy for taking medication as prescribed and three items assess self efficacy for adherence to medical appointments (Appendix 2, pp. 36-37). IMB PrEP Behavioral Skills Scale has 14 Likert style items and will be modified to assess perception of the ability to perform the necessary PrEP skills rather than ART skills. It has an internal consistency of 0.9 with infected adults (Appendix 2, pp. 41-42).(125)

Demographics and Sample Characteristics (measured at baseline, 12 and 24 weeks). We will assess these factors to further characterize the sample.

Relationship with Providers. This five item measure assesses the perceived relationship with health care providers using Likert type items suggested by an ART adherence intervention with adults (Project HEART) (Appendix 2, pp. 34-35).(129)

Social Support for Medication Adherence. This six item measure assesses social support for taking medications, going to medical appointments and other tasks related to adherence using Likert style items with a four point scale. It is being used in AIDS Clinical Trials studies. A single score for social support can be generated from these items or single items can be analyzed, such as support for medical appointments, as this project will do (See Appendix 2, pp. 37-38).

Brief Symptom Inventory. Mental health issues will be assessed by the Brief Symptom Inventory (BSI), which requires only eight to ten minutes in which to complete. It yields nine primary symptom scales and global indices and has norms for adolescents and adults. The reliability, validity, and utility of the BSI has been extensively tested and internal consistency for the sub-scales (dimensions) range from .71 to .85.(130)

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST V2.0). The ASSIST is an eight item questionnaire that screens for all levels of problem substance use. The instrument covers tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants (including ecstasy), inhalants, sedatives, hallucinogens, opioids and "other drugs." It demonstrates significant concurrent, construct, predictive and discriminative validity and it is able to discriminate between low, moderate and high risk use.(131)

Data Analytic Plan

Hypothesis One: The IMB Adherence Intervention will be judged by participants to be feasible, appealing, relevant, and useful. A total of 40 qualitative interviews during the Development Phase will assess acceptability and appeal of the Intervention, and 20 of the subjects will also complete an open trial of the intervention for perceived feasibility, participant motivation and engagement (See Appendix 2, pp. 43-52). We will review the interviews for any game material that is unfavorable to participants and we will make revisions. Any game modules that receive a mean score on the Session Evaluation Form that is <20 (smaller scores = less satisfaction) will be reviewed to determine what content should be revised, changed or discarded.

Hypothesis Two: Compared to subjects in the control group, participants in the IMB Gaming Intervention will show: improved adherence, improvements in biological measures (TFV-DP and FTC-TP), decreased HIV risk behaviors, greater increases in HIV knowledge, improved self efficacy and improved attitudes for treatment adherence. The primary outcome (number of doses taken correctly recorded by CleverCap) will be analyzed as the count of correct doses taken each month for the six study months. Generalized estimation equations (GEE) with a Poisson distribution and log link function will be used to model outcomes with a count distribution. The GEE analysis will account for nesting of assessments within participants and allows for data that follow non-normal distributions. Secondary outcomes that have count data (self report of adherence, unprotected sex, medical appointments) will be similarly analyzed. The IMB constructs and levels of TFV are continuous variables and will be evaluated using Repeated Measures Analysis of Variance (RMANOVA). FTC levels reveal a recent ingestion (yes/no) and will be analyzed by tests of proportional difference. Dr. Anderson will

consult on appropriate analyses for TFV and FTC. In all analyses, we will test for differences in linear change over time between intervention and control groups on each outcome variable. We will examine baseline differences across all outcome measures to assure that randomization was successful and that groups were equivalent at baseline. We will control for demographic variables that show pretest differences.

Power. As this is an intervention development study and the impact of the experimental intervention is not known, there may not be adequate power to determine the efficacy of the IMB Gaming Intervention and pilot studies are not designed to provide accurate estimates of effect sizes upon which to base large trials.(135) Nevertheless, the pilot RCT may provide a "signal" of impact on outcomes and IMB constructs. Power was estimated using Monte Carlo simulation in Mplus 7.11. We assume 85% retention over the trial period. For the primary outcome, assuming an initial rate of 16 doses per month, this study will have power of .80 to detect a rate ratio of 1.28. In other words, this study will be able to detect an increase from 16 to 20 doses per month (one additional dose each week), assuming the control group maintains at 16 doses per month. For the RMANOVAs, this study will have power to detect a large effect size (Cohen's *d* = .80).

Protection of Human Subjects and Safety Monitoring Plan

Human Subjects Involvement, Characteristics and Design

The proposed research study is comprised of two phases. Firstly, a **Development Phase** (n=40, 18 years of age and older, receiving PrEP) in which we will conduct formative research to guide the development of the IMB game and conduct an open trial in which the integration of the Information-Motivation-Behavioral Skills (IMB) based game and the CleverCap electronic dispenser is implemented. Secondly, a **Controlled Trial Phase** in which we will evaluate the preliminary efficacy of the IMB Gaming Intervention compared to a comparison condition (n=50, 18 yrs of age and older, receiving PrEP). Subjects will be recruited from the PrEP clinic at Miriam Hospital (See Facilities and Other Resources). A project activities timeline is in the Budget Justification section.

Inclusion Criteria. All male persons on PrEP over the age of 18 yrs old, will be eligible for enrollment in each phase of study according to the following criteria: 1) English speaking, 2) receiving prophylactic antiretroviral treatment, 3) not enrolled in another PrEP related study, and 4) able to give consent/assent and not impaired by cognitive or medical limitations as per clinical assessment. There will not be overlap between subjects in the Development Phases and Controlled Trial Phase.

Rationale for Including Special Classes of Subjects. The age, gender, and medical status of our participants are dictated by the need for research in the area of HIV prevention for young adults and adults at risk for HIV.

Sources of Materials

Research Material Obtained from Living Human Subjects. Research material obtained from participants include the following 1) all questionnaire data, 2) audio-tapes from qualitative interviews, 3) ARV blood levels, 4) adherence data collected from the CleverCap dispenser, 5) subject engagement with IMB game. For the Development Phase, subjects will complete qualitative interviews in-person regarding their reactions to the IMB informed game and its integration with the wise pill dispenser. These interviews will be recorded and they will take place at the Miriam Hospital. The audio-taped interview and written surveys of their reactions to the Intervention will be the sources of material for this phase. For both the Pilot and Randomized Controlled Trial study phases, participants will complete questionnaires about their demographic information, sexual behavior, adherence behaviors, and attitudes. Questionnaires will be completed at entry to the study and at 12 and 24 week assessments. Biological measures will also be obtained during routine clinical care, and used as outcome data during the RCT phase of the study. The 12 and 24 week assessments and the collection of biological data will be done in the Miriam Hospital Clinical care areas, in designated clinical spaces that are HIPAA compliant. Engagement in game analyses, provided by Mission Critical Studios will be participant non-specific and generalized. For example, Mission Critical Studios can collect data on game usage like any other app or website owner that shows percentage of times players of the game complete levels, percentage of players that stop using the game in particular places. For example data collected by Mission Critical studios would state: x% of players quit the game in the skin Level, or x% of players stop playing the

game after 7 minutes. This data is not linked to a particular participant, and is not linked to the particular phone in use, which is designated as owned by lifespan (not the study patient/participant). This gaming data is not connected or linked to any participant's name, demographic information or health status/diagnosis. Adherence data connected to a CleverCap device is also not linked to participant name, demographic information, health status or diagnosis. An example of CleverCap data is the following. CleverCap ID 7678→1 opening 1/2/12, 1 opening 1/3/12, etc.

Linkages to Subjects and Access to Subject Identities. For each stage of the research, participant names and contact information will be maintained in a recruitment/enrollment database during the course of the study. Once individuals enroll in the study, names will be linked to participant ID number in this database, which will be kept in a restricted access folder on a secure server. All name/ID number files will be assigned a code name unrelated to the name of the study. All phones will be purchased by the Lifespan Corporation/Rhode Island Hospital and the phone contract will have only Lifespan/Rhode Island Hospital recorded as the designated owner of the iPhone. Study personnel will designate participant's iPhone by assigning the iPhone the participant's ID number and this linkage will again be accessible only to study personnel. A similar process will occur with CleverCap adherence data. Subjects will be linked to CleverCap adherence technology and measurements by ID number only. CleverCap maintains a secure, HIPAA compliant data transfer platform and there is no identifying, or demographic information linked to a patient using a CleverCap dispenser. Access to adherence data measured by CleverCap is only granted to approved study personnel on a secure network. Names of medications, names of study participants, or name of the study not collected or recorded in the CleverCap network. Only pill opening events, designated by a CleverCap ID number, are recorded in their database. In the case of investigator needing technological assistance (for an individual's phone, smart cap, or game (CleverCap, Mission Critical Studios), study personnel will only refer to a individual's phone or technology by the ID number for that particular technology, not by the participant's name. For example "CleverCap ID number 7678 is not working properly." Signed consent and assent forms will also be kept in a locked file cabinet, separate from any other project data. Once data collection is completed, the corresponding recruitment/enrollment database will be deleted, as it is unnecessary to maintain the link between participant identity and study data. Destruction of the Master Clinic Patient Lists must be witnessed and documented on the Master List Verification of Destruction document, which will be maintained in the site's regulatory files. Furthermore, any information collected as part of this study will be accessible only to research staff that has completed mandatory training in the protection of human subjects.

Potential Risks

Every effort will be made to ensure that study participants are protected from risks. The risks are as follows: 1) potential coercion, 2) loss of confidentiality, 3) emotional discomfort during the assessment and/or program sessions, 4) medical complications from venipuncture. The protection against each risk is described in detail below under Adequacy of Protection Against Risk.

Adequacy of Protection Against Risk

Recruitment and Informed Consent. The risk of potential coercion will be minimized by following standard procedures for obtaining the informed consent. Study personnel will fully explain the study procedures, risks, benefits, and alternatives to participants. Participants will also be reminded that study participation is voluntary and that refusing to participate or withdrawing from the study at any time will not result in any negative consequences. Recruitment for all phases of the project (Development Phase and Randomized Controlled Trial Phase) will involve the same screening procedures. Research staff will search for participants who are eligible for the study in the clinical setting of their routine care: Miriam Hospital STI/HIV Testing and Prevention Clinic. Subjects will be assured that their routine clinical care will not be disrupted, or negatively affected, by their choice to participate or not participate in the study. Subjects approached about the study will be approached and consented regarding the phase of the study that is relevant at that time (i.e. qualitative interviews, open trial, or randomized controlled trial). In all cases above, participants will be assured that they are free to withdraw from the study at any time and that if they do withdraw any data collected up to that point will be destroyed/stripped from any data files (see Protection Against Risk for data handling procedures).

Protections Against Risk

Breach of Confidentiality. Potential risk will be minimized by strictly adhering to the guidelines for research outlined by the Lifespan IRB, Rhode Island state law, the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations ("HIPAA"), and the DHHS Federal Policy for the Protection of Human Subjects (45 CFR Part 46 Subpart D). This will include identifying participant research data by numeric ID only and maintaining any records containing potentially-identifying information separate from any research data. All research data (written records and audiotapes of program sessions) will be kept in a locked file and electronic data will be password-protected. All of these study-related materials will only be accessible to research staff. No names, only identification codes, will be used in presenting data in lectures, seminars, and papers. Information will be released only with written consent of the parent/guardian.

All data collection will take place in secure and supervised clinical settings at the Miriam Hospital. All study personnel on this application have completed training and received certification in Human Subjects Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with hospital policies.

Participants will be asked to provide informed written consent to audiotaping at the time of study entry if they are participating in the qualitative interviews during the Development Stage. To assure confidentiality and protection of the participants during audiotaping, all tapes will be stored in locked file cabinets in a secured office. Only Drs. Whitely and Brown will have access to the audiotapes so that ongoing guidance can be provided as to the conduct and design of the study.

To further protect the privacy of the study participants, we will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the researchers cannot be forced to turn over identifying information about a study participant in any federal, state, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Emotional Distress. We will minimize distress by presenting questions/program techniques in a supportive manner, assuring participants that they may refuse to answer any questions that make them uncomfortable, and may terminate participation in the intervention at any time. All subjects may receive medical or mental health treatment at any time during the study. Clinical need will determine whether it is appropriate for the participant to stop continuation in the study.

If a participant reports feeling distressed, or has any acute concerns, as a result of their involvement in any phase of the research project (i.e. consenting, baseline assessment, interview session, follow-up, collection of biological data), clinical resources will be offered on-site. The clinical locations used in this study are ideal as they each provide easy access to medical and mental health clinicians. If a subject contacts study staff because of distress or concern due to participation in the study or directed activities that occur away from the clinical space (such as a concern that phone use or activities led to a dispute), the subject will be assessed first over the phone, and then, if needed, as described below.

During any phase of the study, if research staff determines that a participant is an acute medical or psychiatric risk, the PI or licensed designee will meet with the participant individually for further assessment of any clinical needs. Acute risks would include severe medical illness, or the development of any other severe psychiatric symptoms or disclosure of sexual or physical abuse. Any subjects who exhibit acute risks will be evaluated immediately by emergency room clinical staff at Miriam hospital, or if less acute, by an independent clinician that day. Less severe medical needs or distress can be managed by staff or PI over the phone or with an individual interview. The PI and/or staff will meet with participants to review concerns and to make referrals for continuing care as needed. Of note, members of the proposed research team have substantial prior clinical (medical and psychiatric) and research experience in care of young adults and adults as evidenced through their biographical sketches.

Complications from Venipuncture. Participants will require venipuncture to collect blood samples for ARV blood level tests to be performed. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can occur at the blood draw site. This assessment should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery. However, if a medical

complication occurs, the patient will be given immediate and appropriate clinical care as described above. Any subject who exhibit acute risks will be evaluated immediately by emergency room clinical staff at Miriam Hospital, or if less acute, by an independent clinician that day.

Potential Benefits of the Proposed Research to the Subjects and Others

Importance of Knowledge to be Gained. All phases of the proposed study will provide important information for PrEP related intervention development. We hope that our intervention will be successful in improving treatment adherence and reducing HIV in our subject population and think that the clear examination of these questions outweighs the previously mentioned risks. The effectiveness of a novel, scalable, technology driven, intervention integrated into treatment with PrEP is understudied. Given the significant health sequelae associated with HIV infections, and the paucity of data on PrEP related adherence and behavioral intervention programs, the knowledge to be gained from this research is significant. The risks to participants are reasonable in relation to the importance of the knowledge to be gained.

Reimbursement for Time and Effort. Subjects will be reimbursed $50 for each qualitative interview during the Development phase. During the Interview phase, participants will be reimbursed $5 for every level of the game they complete, up to $30. Subjects will be reimbursed $50 for their baseline and 12 week assessments during the Open Trial and $50 for a qualitative interview at 12 weeks. During the RCT phase subjects will be reimbursed $50 for baseline, 12 week, and 24 week assessments. Each participant in the open trial and RCT will also receive an iPhone with a paid data service plan for the study duration (iPhone 4S: $100, data package through Lifespan/ AT&T $60/month).

Data and Safety Monitoring Plan

The nature of the population warrants the development of a Data Safety and Monitoring Plan. To address the NIH policy for Data and Safety Monitoring, the PI has developed a system for oversight of the proposed study and its participants. The Data and Safety Monitoring Plan for this application will begin by implementing standard procedures for day-to-day monitoring of the study. Weekly meetings with the research team will be conducted to evaluate the progress of the trial and to review data quality, recruitment, study retention, and examine other factors that may affect outcome. Participant experiences with the study procedures and the rates of adverse events will also be reviewed to determine any changes in participant risk. The PI will immediately report any adverse events that are observed to the Lifespan Internal Review Board (IRB) and NIMH. Serious adverse events (SAEs) will be reported to the Lifespan IRB immediately by telephone and by written report within 24 hours of our receipt of information regarding the event; SAEs will also be reported in writing to NIMH. Actions taken by the IRB in response to SAEs will also be reported to NIMH, as will reports of changes or amendments to the protocol as a result of an SAE. Reports of changes or amendments to the protocol in general must be requested first in writing to the Lifespan IRB, which then will grant or deny permission to make the requested change or amendment in protocol. Modifications to study aims or design will also be submitted to NIMH for approval prior to instituting them. Finally, if significant medical or mental health risks occur during the study period evaluation by the Miriam hospital emergency department will be immediately initiated to determine whether hospitalization or urgent care is needed. In the event that a research participant either withdraws from the study or the investigator decides to discontinue a research participant due to SAE, the research participant will be monitored by the investigator via ongoing status assessment until either a resolution is reached (i.e. the problem requiring hospitalization has resolved or stabilized with no further changes expected), the SAE is determined to be clearly unrelated to the study intervention, or the SAE results in death. Outcome of all SAEs will be periodically reported to NIMH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIMH.

Educational Training

Since October 1, 2001, Lifespan has required that researchers and IRB members read Protecting Study Volunteers in Research (Dunn & Chadwick) and complete the related exam. This process has served as an

initial certification. In June, 2005, the Office of Research Administration contracted with CITI, a Collaborative Institutional (modular) Training Initiative program, for our Human Subjects Protection and HIPAA training for all research personnel. Currently this program offers researchers a basic human subject's protection course as well as a refresher course that is required every three years. Documentation of successful completion is automatically generated and can be printed directly by the researcher

Additional and continuing education opportunities for clinical researchers include the Office of Research Administration newsletter that is circulated to > 900 recipients every 6 weeks. Relevant information concerning research review is available on the ORA web page at www.lifespan.org/research/. In addition to standard institutional research information, the web page contains links to other sites such as CenterWatch, NIH, PRIM&R/ARENA.

Inclusion of Women and Minorities

Women. Women will not be included in this study because this research focuses on the most at risk population for acquiring HIV in the U.S., MSM. The PrEP clinic at Miriam Hospital has prescribed PrEP to MSM only at this time. It is anticipated that approximately 100% of the sample will be males, reflecting the population of the PrEP clinic from which the sample will be recruited, so women will not be represented. Selection of only MSM for this study allows the iPhone app to be tailored to their specific needs as is appropriate for this phase of research.

Minorities. The aim of our recruitment strategy is for the resulting program materials to be appropriate for racial and ethnic minorities. We anticipate that in terms of race 65% of the enrolled participants will self-identify as Black/African American and 30% will self-identify as Hispanic or Latino.

Inclusion of Children

Children. Approximately 25% of the participants in this study will be comprised of youth ages 18-21. Currently, the gaming content selected in the intervention has been designed for children 18 and older. Preliminary sessions are therefore designed to be appropriate for the developmental and cognitive level of youth. Thus, the proposed program is appropriate for children as defined by NIH. During the Development Phase, intervention material and content will be further tailored to the developmental and cognitive level of our participants.