HIV Adherence Bottle Intervention Study (HABIT)

An Open-Label Randomized Pilot Study of a Novel Adherence Intervention (AdhereTech Bottles) in HIV-Infected Patients with Suboptimal Adherence to Their HIV Treatment

VERSION 1.0 (8/20/13)
Addendum (9/30/16)
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This study will be a randomized, open-label, 12-week pilot study of the AdhereTech bottle with reminders vs. standard of care to improve adherence to HIV medications.

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BACKGROUND AND STUDY RATIONALE:

Patient adherence to HIV medications is critical to suppressing HIV RNA levels and preventing the emergence of drug-resistant virus in order to achieve durable clinical and survival benefits. Some HIV studies report the need for ≥95% adherence to antiretroviral medications to ensure complete virologic suppression (Ickovics, Paterson) and one recent study found over a 3-fold higher risk of death in patients with less than 95% adherence to contemporary HIV treatment regimens (Lima).

Current HIV regimens are potent, well-tolerated and as convenient a one-pill, once-daily regimens. However, even simple HIV regimens may pose challenges for some patients. A recent meta-analysis of 84 observational cross-sectional and cohort studies across 20 countries reported that ≥90% adherence was reported by only 62% of HIV-infected patients (Ortego). In one large study, the most common reasons for HIV treatment non-adherence were "simply forgot" (33%), "away from home" (27%), and "busy" (26%) (Reynolds).

Thus, interventions to improve adherence in HIV-infected patients are urgently needed. A number of strategies have been tried: a recent meta-analysis of interventions to improve adherence to HIV treatment combined a total of 19 studies with 1839 participants, but found only modest benefits with a variety of interventions, including HIV treatment education, interactive discussions, behavioral strategies, and external reminder devices (Simoni). Among the external reminder devices tested were a programmable prompting device that provided a verbal reminder at dosing time (Andrade) and a watch with a programmable timer (Samet), neither of which demonstrated a significant improvement in adherence, and an on-line pager system that improved adherence only modestly (Safren). Other studies in HIV-infected patients formally tested serial reminder phone calls (Collier) and modified directly observed therapy (Gross), but also failed to show improved adherence. These innovative strategies ultimately may have failed because they required patients to

change the way that they normally take their pills. Clearly, newer and better adherence strategies and devices are needed.

Investigators recently reported preliminary results from a clinical trial testing smart pill bottles, called Vitality GlowCaps, that were associated with an improvement of adherence rates in patients on hypertension drugs to about 98% (Watson). However, this device only measures opening and closing of the bottle and requires a base charging station.

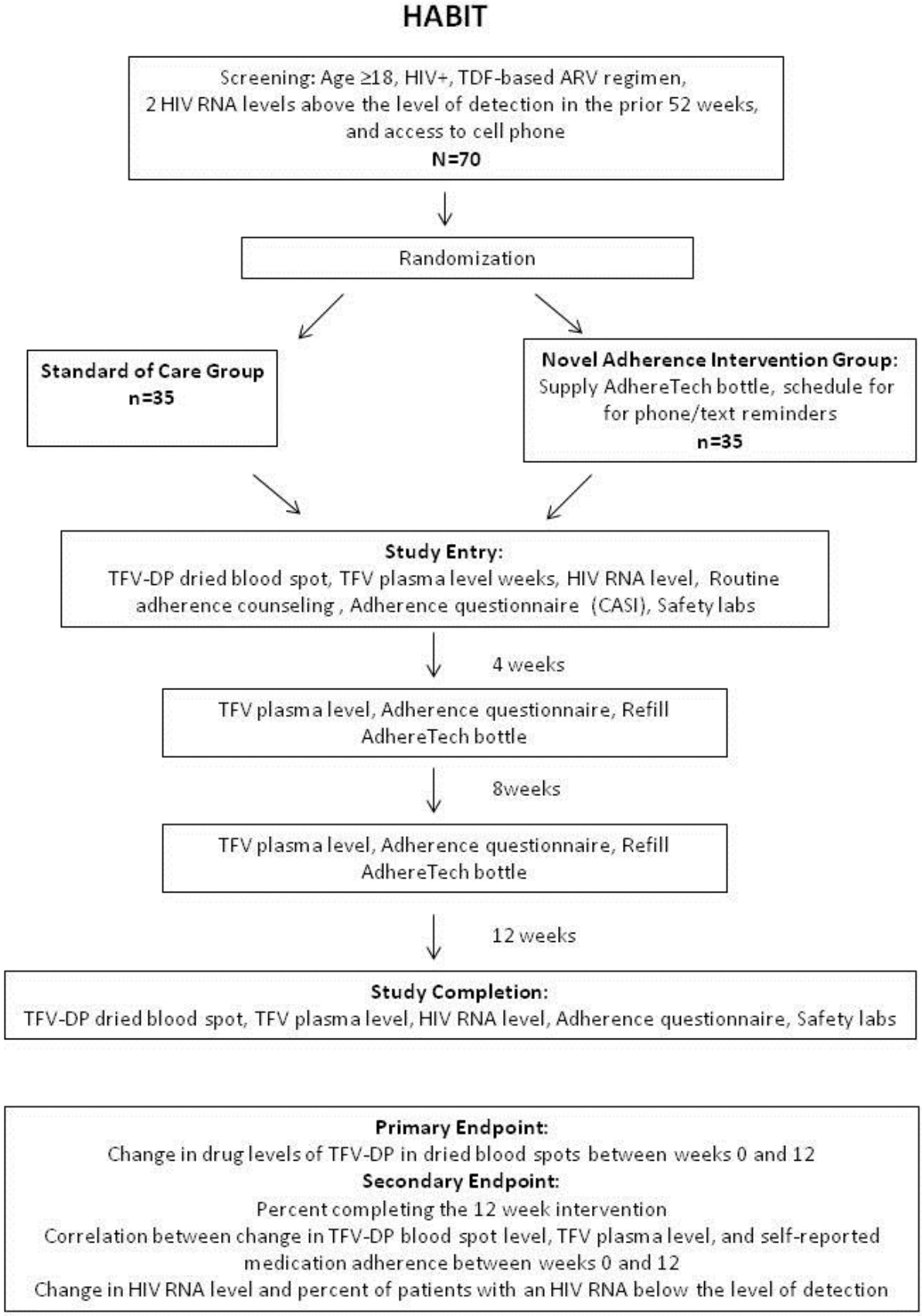
AdhereTech has created patented smart pill bottles that improve medication adherence. These bottles automatically measure the number of pills in the bottle in real-time, and wirelessly transmit this HIPAA-compliant data to a central server. If a patient hasn't taken his/her medication, the technology is able to remind them via phone call or text message. The AdhereTech bottle also has on-bottle lights and chimes that are automatically triggered to remind patients to stay adherent. When patients receive reminders the via a phone call, patients can leave feedback and information as to the main reason why they didn't take a dose (e.g., side effects, lack of information, lack of symptoms, or any other issues.) Patients use the AdhereTech bottles in the same way they use normal pill bottles. The bottles have a cell phone chip build inside, so they can work anywhere as they collect and send adherence data. The bottles never need to be charged or kept in a particular location, so patients can travel with the bottles. Thus, little, if any behavior change is needed to effectively use this adherence-promoting device.

Tenofovir disproxil fumarate (TDF, trade name: Viread) is a nucleoside analogue that is a preferred first-line drug in current HIV treatment guidelines (DHHS). TDF is used commonly as part of 3 available one-pill, once-daily combination HIV drug regimens: TDF + emtricitabine + efavirenz (Atripla), TDF + emtricitabine + rilpivirine (Complera), and TDF + emtricitabine + elvitegravir + cobicistat (Stribild), and is used commonly in other HIV regimens. TDF is phosphorylated intracellularly to tenofovir diphosphate (TFV-DP), a compound with a long half-life of 17 days in cells; the measurement of TFV-DP drug levels in dried blood spots recently was shown to estimate average drug exposure over 12 weeks (Castillo-Mancilla). This longer term measure of adherence can be compared with plasma tenofovir levels that estimate short-term adherence over 1-3 days.

We propose to conduct a randomized, pilot study of the novel adherence intervention, AdhereTech bottles with reminders, in HIV-infected patients with documented suboptimal adherence to their TDF-containing antiretroviral regimen.

STUDY SCHEMA:

See below



Abbreviations: TDF – tenofovir disproxil fumarate, TFV-DP - tenofovir diphosphate (TFV-DP), TFV – tenofovir

STUDY OBJECTIVES AND ENDPOINTS:

Hypothesis: The use of a novel adherence intervention (the AdhereTech bottle with reminders) will improve adherence to HIV medications over 12 weeks.

Primary Objective: To assess adherence to a tenofovir-based regimen over 12 weeks in patients using the AdhereTech bottle with reminders compared to the usual standard of care.

Primary Endpoint: The mean change in drug levels of tenofovir diphosphate (TFV-DP) in red blood cells using dried blood spots between week 0 and week 12 in the AdhereTech intervention group compared with the standard of care group.

Secondary Objectives:
1) To assess the feasibility of using the AdhereTech bottles with phone/text reminders in HIV-infected patients.
2) To assess the use of tenofovir diphosphate dried blood spots as a marker of HIV medication adherence in comparison with plasma tenofovir levels and self-reported medication adherence.

Secondary Endpoints:
1) The percentage of patients completing the 12 week AdhereTech intervention in comparison with the standard of care group.
2.1) Compare the mean change in TFV-DP blood spot level, TFV plasma level, and self-reported medication adherence between weeks 0 and 12 in the AdhereTech intervention and standard of care groups.
2.2) The mean change in HIV level and percent of patients with an HIV RNA below the level of detection between weeks 0 and 12 in the AdhereTech intervention and standard of care group.

RESEARCH PLAN:

Selection of Participants

Type of the Participant Population

This study is open to all adults who meet the following inclusion and exclusion criteria.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- Male and nonpregnant female subjects aged 18 years and older
- A diagnosis of HIV-1
- Undergoing therapy with a tenofovir-based antiretroviral regimen
- Suboptimal adherence to the tenofovir-containing HIV antiretroviral regimen over the prior 52 weeks from the time of enrollment, as evidenced by 2 HIV RNA levels above the level of

detection following an HIV RNA level below the level of detection, with no plans to change the current HIV drug regimen.
- Access to and willingness to use a cell phone to receive voice/text reminders to take HIV medications. Subjects must also agree to maintain a stable phone number and active cell phone service for the duration of the study.
- Adequate English to provide written, informed consent and to provide reliable responses to the study interview

Exclusion Criteria:
- Planned HIV treatment interruption in the last 52 weeks or anticipated interruption in the next 12 weeks
- Any condition that would interfere with study participation in the opinion of the investigator
- Individuals considered by the study investigators to be unlikely to participate in intensive follow-up and/or unwilling to provide blood samples.
- Individuals with significant cognitive or psychiatric illness, which limits their capacity to fully understand or provide written informed consent for the study.

Special groups:

This study may enroll special groups of subjects, including those with mental illness. People infected with HIV sometimes have psychiatric co-morbidities including depression, anxiety, schizophrenia, and/or substance abuse. The investigators in this study are experienced at treating patients with HIV and psychiatric co-morbidities, and only subjects determined by the investigators to be mentally stable enough to fully understand the study and to provide written informed consent will be enrolled. The investigators may withdraw subjects if it is in the best interest of the subject.

Study Design:

Study Overview:

This is a randomized, open-label, 12-week pilot study involving 70 HIV-infected subjects taking a tenofovir-containing antiretroviral regimen with documented suboptimal adherence over the prior 52 weeks. Subjects will be randomly assigned to study groups in a 1:1 ratio with the use of a computer-generated randomization table. 35 subjects will receive usual care with routine adherence counseling and 35 subjects will receive routine adherence counseling plus a novel adherence intervention – the AdhereTech bottle with phone call or text message reminders.

Study Visits:

At screening, all patients will sign an informed consent form (Appendix A) and undergo a baseline history and physical exam. The history will elicit demographic information (gender, age, race, ethnicity), past medical history/current co-morbidities, current HIV medical regimen, and history of psychiatric disease and substance use. Upon enrollment, all patients will receive standard counseling regarding the importance of HIV medication adherence. Each subject assigned to the novel adherence intervention group will be supplied one AdhereTech bottle and the research team will transfer all of their tenofovir-containing medication to the bottle (either a single tablet combination anti-retroviral medication or the tenofovir component of a multi-pill antiretroviral

regimen). During the initial visit, the study coordinators will program the AdhereTech bottle for a patient's preferred medication schedule and supply the patient with a toll-free number so they can further customize the bottles reminder features during the study.

The AdhereTech bottle will monitor the patient's adherence and wirelessly send this encrypted HIPAA compliant data to a central server. Based on the results, an automated phone call or text message will be generated to remind patients to take their medication from the AdhereTech bottle as scheduled. To protect patient privacy, the phone/text message will not disclose the patient's HIV status or the name of their HIV medication. In order to avoid accidental overdoing of HIV medications, the reminder will not specifically instruct the patient to take a dose of their medication at that time, but rather advise that s/he adhere to his/her normal dosing schedule. In the instance of a phone call, the patient will be able to leave feedback as to why they are missing their medication doses – this data will be recorded for subsequent analysis.

Before patients enroll in the study, we let them know that they are the true arbiter of when they need to take pills. Our device will remind them, but if they think there is an error then they should not take a pill. We will utilize a particular language to lessen the risk of medication errors. Our phone/text reminders will say "Please be sure to stay adherent to your medication dosing schedule". The reminder technology will never tell a patient that s/he missed a dose or instruct a patient to take a dose."

Patients in both groups will be required to come in for study visits every 4 weeks for a total of 4 visits over 12 weeks. At weeks 4, 8, and 12, all patients will undergo an interval history. At weeks 4 and 8, the study coordinators will refill the AdhereTech bottle for patients in the AdhereTech group.

At weeks 0, 4, 8, and 12, each subject will undergo a blood draw for a plasma tenofovir level and complete an adherence questionnaire via computer assisted self-interviewing (CASI). The adherence questionnaires will utilize forms QL0751, QL0752, and QL0742, developed by the Outcomes Committee of the AIDS Clinical Trials Group, sponsored by the NIH/NIAID, and are included in Appendices B-E.

At weeks 0 and 12, patients will undergo testing for dried blood spot tenofovir diphosphate (TFV-DP) level, HIV RNA level, CD4 cell count, and safety labs (complete metabolic panel, phosphorous, liver function testing, and complete blood count). Please see tables 1 and 2 for the schedule of assessments and treatment plan.

All patients will receive reimbursement in the form of a Metro card, which will cover the cost of two subway rides (value $5.50, in addition to the card purchasing fee). The cards will be provided at each visit, except for the initial screening visit.

Schedule of Events:

The schedule of study events is included below.

Table 1 – Schedule of Assessments

Visit Day and Window	Screening (Day – 45 to Day -1)	Enrollment (week 0, Day 0)	week 4 (+/- 7 days)	week 8 (+/- 7 days)	week 12 (+/- 7 days)
Obtain informed consent	X				
Randomization		X			
History and physical exam	X				
AdhereTech bottle filled and dispensed		X	X	X	
Interval history		X	X	X	X
Routine adherence counseling		X			
Dried blood spot for TFV-DP level		X			X
Plasma for TFV level		X	X*	X*	X
Plasma HIV RNA level		X			X
Whole blood CD4 cell count		X			X
Plasma BMP, LFTs, and phosphorous		X			X
Adherence questionnaire by CASI		X	X	X	X

Abbreviations: TFV-DP – tenofovir diphosphate, TFV – tenofovir, BMP – basic metabolic panel, LFTs – liver function tests

**For the secondary analysis, plasma TFV levels will be analyzed from weeks 0 and 12. If additional funding is obtained, we will analyze replicate specimens at weeks 0 and 12 plus weeks 4 and 8.*

Table 2 – Blood volumes

Bodily Fluid	Amount	Frequency	Total
Blood - Plasma TFV	6mL	Weeks 0, 4, 8, and 12	36ml
Blood – TFV-DP blood spot *	4mL	Weeks 0 and 12	12mL
Blood – HIV RNA	6 ml	Weeks 0 and 12	12mL
Blood – CBC and CD4 cell count	6mL	Week 0	6mL
Blood – BMP, phosphorous, LFTs	6ml	Weeks 0 and 12	12mL

Abbreviations: TFV-DP – tenofovir diphosphate, TFV – tenofovir, CBC – complete blood count, BMP basic metabolic panel, LFTs – liver function tests

*All labs will be processed locally at Weill Cornell/NYPH. The TFV-DP dried blood spot and plasma TFV levels will be assayed by the Colorado Antiviral Pharmacology Laboratory at the University of Colorado Denver. Protocol is included in Appendix F.

HIV Therapy:

The ongoing choice of a patient's HIV antiretroviral regimen will be at the discretion of his/her primary provider, who will not be involved directly in this study. In all circumstances, the health and welfare of the patient will take precedence over study participation and as such, they will be provided with sufficient information about alternative treatments that may be offered outside of the study. If a patient's treating provider decides that s/he should no longer be on a tenofovir-based regimen during the course of the study, the reason for this change will be recorded, the adherence intervention will be discontinued, and the patient will remain in the study for the purpose of an intention-to-treat analysis.

Early Withdrawal:

Any patient who wishes to withdraw from the study is able to do so at any stage. These patients will be encouraged to attend a follow-up visit prior to withdrawal in order to discuss reasons for withdrawal, as well as any safety issues that may be relevant. At this visit a follow-up questionnaire and blood samples will be collected (as per a normal follow-up visit).

Discontinuing a Patient:

Patients will be discontinued from the study if, at any time, they are considered by the study investigators to be unlikely to participate in the necessary follow-up (i.e. due to an inpatient hospital admission, change of residence, incarceration, or a severe medical/psychiatric illness that precludes the patient's ability to make clinic visits or comprehend study procedures) and/or if the patient becomes unwilling to provider blood samples while on the study. In such cases, the adherence intervention will be discontinued and the patient will remain in the study for the purpose of an intention-to-treat analysis.

Duration/Length of follow-up:

Each patient will be followed for a total of 12 weeks after enrollment.

STATISTICAL CONSIDERATIONS AND DATA ANALYSIS PLAN:

Sample Size Estimate:

In this pilot study, the sample size calculation is based on the null hypothesis of no difference in tenofovir-diphosphate (TFV-DP) concentrations (by dried blood spots) at baseline versus a demonstrable difference at week 12. From a simulation study (Castillo), we expect to see the same mean concentration (standard deviation) at both groups at baseline: 900 (404) fmol/punch. At 12 weeks, we expect to see a mean concentration (standard deviation) of 1332 (597) fmol/punch in arm A (adherence intervention) vs. 900 (404) fmol/punch in arm B (control). Assuming normal distribution of TFV-DP concentrations, type 1 error = 0.05, power = 80%, a sample size of 32 will be recruited per arm (64 total) based on a two-sided, two-sample t-test with equal variance. Since the data may have missing data at the last visit, we will add ~10% more participants. Therefore, the final sample size of 35 per arm (70 total) will be enrolled.

We intend to screen approximately 100 total subjects, as we assume there will be subjects who may sign the consent form, but ultimately do not participate in the study do to screen failure, not meeting inclusion/exclusion criteria, and personal choice.

Randomization will be provided by the biostatistician from Weill Cornell Medical College. The randomization list will be provided to the principal investigators.

Data Analysis:

For the primary analysis, we will compare the mean change in drug levels of tenofovir diphosphate (TFV-DP) in red blood cells using dried blood spots between week 0 and week 12 in the AdhereTech intervention group compared with the standard of care group via a two-sided t-test. If the data will not meet the normal assumption, non-parametric Wilcoxon Rank Sum test will be used to test medians between two groups.

For the secondary analyses, we will:

- Calculate the mean percentage of patients who complete the 12 week AdhereTech intervention and compare that with the percent that complete 12 weeks of follow-up in the standard of care group.
- Compare the mean change in TFV-DP blood spot level with TFV plasma level and self-reported medication adherence from weeks 0 and 12 between the AdhereTech intervention and standard of care groups.
- Compare the mean change in HIV level and median percent of patients with an HIV RNA below the level of detection from weeks 0 and 12 between the AdhereTech intervention and standard of care group.

These analyses will be performed via two-sided t-tests.

Initial analysis will be performed based on an intent-to-treat basis. An additional secondary per-protocol analysis will also be performed, including only those patients who completed the intervention originally allocated and excluding patients who discontinued the AdhereTech study intervention early for reasons clearly not related to the intervention (i.e. HIV regimen changed by primary provider, imprisonment, or relocation).

HUMAN SUBJECTS CONCERNS:

Recruitment:

Recruitment will occur via various means. First, physicians and nurse practitioners caring for people with HIV within the Weill Cornell Center for Special Studies and Primary Care clinics will be notified of the study and asked to identify potentially eligible patients who meet the inclusion criteria from a review of their case records. These providers: (1) will ask potential participants: if they are interested in participating in the study, and if so, to call one of the investigators, or the research coordinators, or (2) will identify patients who would be suitable for the study and contact the patients via mail. He/she will mail a letter and a study flyer describing the study to the patients inviting them to call the research team for more information. Samples of the letter and study flyer are provided in Appendices G-J. Patients will be approached only by their clinical care providers and not by any members of the research team. Second, the IRB-approved recruitment fliers will be posted in the Weill Cornell Center for Special Studies and Primary Care clinics. Third, potential participants will be identified via current use of tenofovir and this protocol's inclusion/exclusion criteria by a search of Weill Cornell/NYPH medical records. Potential study participants will be

approached for participation in this study only by their primary medical providers and not by the study investigators. Prior to obtaining informed consent, potential participants will be screened for eligibility according to the inclusion and exclusion criteria specified. Once it is determined that participants meet these criteria and have provided informed consent, additional screening as specified in the Study Time Line will be conducted between weeks -2 and 0.

Consent Process:

The study investigators or research coordinators will obtain written informed consent from each potential participant prior to enrollment in the study during their initial screening visit at the Cornell Clinical Trials Unit. S/he will administer the informed consent (Appendix A) and HIPAA authorization form (Appendix K) by reading them through with the study participant or providing the potential participant with time to read the informed consent and HIPAA authorization form. After all of the study participant's questions have been answered, the participant will be asked to sign and date the consent and HIPAA authorization form. A copy of the signed consent and HIPAA authorization form will be given to the study participant for his/her records. A subject can withdraw from the study at any time s/he desires.

Safety Concerns:

Risk associated with participation this study is related to blood drawing. This is of minimal risk compared with the standard of care for patients currently undergoing medical treatment for HIV. The risk of blood draws includes: hematoma, arterial puncture, pain or rash at the blood collection site, phlebitis, peripheral nerve damage, vasovagal reaction (including syncope).

Although we will take precautions to protect participant privacy, a breach of confidentiality is possible (for example, if a patient loses the AdhereTech bottle or a person not participating in the study answers the patient's cell phone). All patients will be educated on ways to avoid these situations. In the unlikely event of a breach of confidentiality, the nature of the research data should not negatively affect employment status, lead to civil/criminal liability, incur financial risks to the study participants, or other risks. Risks associated with a potential invasion of privacy include psychological distress and discrimination. The risk associated with telephone calls is inconvenience to the patient or anyone who lives with them.

Information for the novel pill bottle will be transmitted via telephone call or text message (per the subject's preference) using secure, encrypted, HIPAA-compliant wireless methods to the vendor's server (AdherTech). AdhereTech will not have access to any additional patient identifiers. The language used during phone/text reminders will not mention the patients name, disease, drug, or treatment.

Reporting of Adverse Events:

We anticipate no adverse events related specifically to the study intervention of AdhereTech bottles with phone call or text message reminders. However, the patient could suffer an adverse event from either frequent blood draws or the use of a tenofovir-based antiretroviral regimen as outlined above.

The principal investigator (PI), within one working day, will report all serious adverse events (SAE) occurring in enrolled participants to the Weill Cornell Institutional Review Board (IRB). This will be accomplished by submitting an adverse event report memorandum to the IRB. Serious adverse

events will be reported even if the PI believes that the adverse events are unrelated to the protocol. Unexpected (but not serious) adverse events occurring in participants enrolled which, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 10 (ten) working days to the IRB using the same procedure

Banking of Human Biological Specimens or Tissues (HSB/Tissue):
Blood specimens will be collected as part of this study. No specimen obtained in this study will be used or banked for any purpose other than what is stated in this protocol.

Confidentiality of Data and Privacy of Subjects:

We are intending to collect data on the following personal health identifiers:

- Subject names
- Street address, city, county, 5-digit zip code
- Months and dates and ages >89 (if applicable for the latter)
- Telephone numbers
- Email addresses
- Social security number (the study team will use the SSN to review the medical records)
- Medical record number
- Health plan beneficiary number

In an effort to protect identifiers, data will be recorded electronically and in paper format and kept in the PIs locked office on a password-protected computer and password-protected, encrypted database. At the completion of the study, paper identifiers will be shredded and electronic identifiers will be deleted from the database.

The following details AdhereTech's data management and privacy procedures:

- *Data Storage*: The bottle itself contains no stored patient data. It contains only a unique Bottle ID, which is mapped to the patient's information in AdhereTech's secure backend server only. The only identifying piece of information AdhereTech stores about patients is the phone number they have requested to be contacted in the event of a dosage reminder event. Even this is optional. AdhereTech follows all measures of the HIPAA security rule to ensure that patient data is properly secured and encrypted while at rest. All data is stored in the United States.
- *Data Transmission*: AdhereTech does not transmit any patient information over the cellular connection, only encoded measurements taken from the bottle and its unique bottle ID. AdhereTech utilizes a cryptographic hashing protocol to authenticate bottle connections to the AdhereTech backend server. This ensures that all bottle data received comes only from AdhereTech bottles. AdhereTech uses the GSM network for its cellular connectivity (AT&T in the United States), in order to secure the bottle connections against eavesdropping attacks. Once connected to the cellular network, the bottle communicates using an HTTP post. AdhereTech supports an additional layer of security by utilizing HTTPS for Bottle to Server communication. AdhereTech's infrastructure machines communicate with one another on a private access-list controlled intranet using TLS/SSL.
- *Data Access for Customers*: Access to patient data is protected by a unique User ID and password assigned to our Users by an AdhereTech Administrator. This password fits requirements defined in the AdhereTech Password Policy.

- *Internal Data Access*: AdhereTech tightly guards sensitive passwords, system access mechanisms, and databases. Patient data is only available to those providing support for the system in a read-only audited way, and full unaudited system access is granted only to the System Administrator. The System Administrator is John Langhauser, CTO and Cofounder of AdhereTech.
- *Overview*: The entire process is managed by AdhereTech. The bottle measurements are analyzed and linked to patients when the measurements are gathered and stored on physical computers in our secured datacenter, which AdhereTech rents from SoftLayer in Texas, an IBM subsidiary hosting company.

STUDY TIMELINE:

The study duration is estimated to be 12 months from approximately March 2015 to April 2016.

REFERENCES/LITERATURE REVIEW:

Andrade AS, McGruder HF, Wu AW, et al. A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. Clin Infect Dis. 2005 Sep 15;41(6):875-82. Epub 2005 Aug 5.

Castillo-Mancilla JR, Zheng J-H, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retorviruses 2013;29:384-390.

Collier AC, Ribaudo H, Mukherjee AL, et al. A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons intiating antiretroviral therapy. J Infect Dis 2005;192:1398-1406.

Gross R, Tierney C, Andrade A, et al. Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naive HIV-1-infected patients: a randomized trial. Arch Intern Med 2009;169:1224-32.

Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. Antivir Ther 2002;7:185-93.

Lima VD, Harrigan R, Bangsberg DR, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquir Immune Defic Syndr 2009;50:529-36.

Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): A meta-analysis. AIDS Behav 2011;15:1381-1396

Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 200;133:21-30.

Reynolds NR, Testa MA, Marc LG, et al. Factors influencing medication adherence beliefs and self-efficacy in persons naive to antiretroviral therapy: a multicenter, cross-sectional study. AIDS Behav 2004;8:141-50.

Safren SA, Hendriksen ES, Desousa N, Boswell SL, Mayer KH. Use of an on-line pager system to increase adherence to antiretroviral medications. AIDS Care. 2003 Dec;15(6):787-93.
Samet JH, Horton NJ, Meli S, et al. A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems. Antivir Ther. 2005;10(1):83-93.

Simoni JM, Pearson Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials. JAIDS 2006;43:S23-S35.

U.S. Department of Health and Human Service, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 2/12/13, available at www.aidsinfo.nih.gov

Watson A. Vitality GlowCaps Trials with Mass General Hospital and Harvard Center for Connected Health. 2008, available at http://www.connected-health.org/events/past-events/symposium-2008/presentations.aspx

Protocol Addendum (09-30-2016):

Addendum to Data Analysis Plan:
Due to enrollment being slower than anticipated as of August 2016 (40 of 70 total participants enrolled), we will perform an interim analysis of the tenofovir dried blood spot data for the primary endpoint. The statistician will be blinded to the participants[1] study group assignments. The statistician will notify us if there is a significant difference detected in the tenofovir dried blood spot levels between the two groups, but the study investigators will be blinded as to the detailed results. Such information will help us determine whether further enrollment into the study is justified. If the difference seen is </= 5% at the 5% level of significance, study enrollment will be terminated due to futility of the intervention. If the difference seen is >/= 20% at the 5% level of significance, the study will be terminated due to a significant difference demonstrating efficacy of the Intervention. If the difference is between 6-19%, study enrollment will continue as previously planned until the target sample size of 70 subjects is achieved.