Detailed Protocol

Study Title: TruTag Aim 2: Development of a silica microparticle taggant system to measure antiretroviral pharmacotherapy adherence
Version Number/Date: V2.0 / June 5, 2024
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1. Background and Significance.

Medication nonadherence is a widespread challenge affecting the health outcomes of communities and patients.[1] Within the United States (U.S.), approximately 75% of Americans struggle to take their medication as directed,[1] and nearly 125,000 deaths per year in the U.S. are directly related to medication nonadherence.[1] Medication adherence challenges are particularly prominent in the context of the HIV epidemic and antiretroviral treatment (ART),[2-3] as a result of various factors ranging from psychosocial stress, form of medication, and patient knowledge and attitudes.[3] Given the importance of strict ART adherence to achieving optimal health outcomes among HIV patients,[4] multiple tools have been created to measure and improve adherence levels, including self-report diaries,[5] smart pill bottles,[6] and ingestible biosensors.[7]

An additional potential system that can indirectly and unobtrusively measure adherence is the use of microparticle taggants. Taggant systems, small particles or drug metabolites, have been previously integrated into xenobiotics to detect their presence in individuals as a marker of adherence, and utilized to track medications from origin (i.e., manufacturing) to dispensing. [8,9] In this proposal, we are collaborating with TruTag, a small business that manufactures silica-based microparticles that are integrated into medications at the point of manufacturing through the normal coating process.. The TruTag system is a digitization platform that utilizes secure spectrally-encoded particles to engage patients.[10] With this highly innovative and scalable system, medication adherence in relation to ART can be measured through a relatively inexpensive, reliable, and feasible method. Despite this potential, there have yet to be structured, hypothesis-driven studies that elicit user feedback and evaluate the clinical promise of the TruTag system as a cost-effective tool for measuring adherence; as such, best practices for implementing this technology in the context of ART adherence management and support remain unclear.

Prior qualitative work among persons living with HIV (PLWH) has demonstrated that the TruTag system is acceptable as a strategy to measure ART adherence. Participants also reported interest in leveraging the app to receive information around HIV, sexual health and their clinical care including appointment times and testing reminders. Importantly, participants described the system as easy to operate and did not report privacy concerns. As an extension of this qualitative work, this proposal seeks to conduct an open label, pilot demonstration trial that tests the feasibility and acceptability of operating the TruTag system to measure ART adherence in real-world settings.

2. Specific Aims and Objectives.

The aim of this study is to conduct an open-label pilot demonstration trial to understand the feasibility and acceptability of the TruTag system to measure ART adherence with N=15 individuals living with HIV who are currently on ART.

3. General Description of Study Design.

This is an open-label pilot demonstration trial. We will enroll N=15 individuals living with HIV who are taking Bictegravir/emtricitabine/tenofovir alafemate (Biktarvy) as ART, who will utilize the TruTag system to measure ART adherence over a 90-day period.

The participant will use the TruTag coated ART for 90 days with the TruTag application on their smartphone. In this study, participants will scan their coated ART medication before swallowing their medication, and this scanning event will link to the TruTag app on their smartphone, which will be used to measure daily adherence for 90 days.

Potential participants will be approached and pre-screened. Those who meet pre-screening criteria will attend a Screening Visit (Visit 1), where the informed consent process will be conducted and study eligibility will be confirmed. Eligible participants will attend four additional visits over the course of the study – the Enrollment Visit (Visit 2), Month 1 Visit (Visit 3), Month 2 Visit (Visit 4), and Month 3 Visit (Visit 5). Participants will take one ART pill per day, for 90 days total, while using the TruTag system and app. The app will facilitate reminders and serve as a two-way text communication platform between participants and the study team. Simple reminders will be sent following detected nonadherence with the aim of improving ART adherence. Timeline followback discussions will be conducted at the Month 1, Month 2, and Month 3 Visits to understand the context of any detected nonadherence. Dried blood spots (DBS) will be conducted at the Screening Visit (Visit 1) and the Month 3 Visit (Visit 5). Qualitative exit interviews will be conducted at the Month 3 Visit (Visit 5).

4. Participant Selection.

Recruitment. Individuals will be recruited through social media, flyering, and community outreach events in partnership with HIV advocacy groups and organizations serving LGBT populations in the greater Boston area. We will coordinate recruitment efforts with the recruitment team at The Fenway Institute (TFI), a dedicated group that assist research teams with identifying and matching potential participants with ongoing research studies at Fenway Health. The data team at TFI additionally compiles and generates periodic reports using specific inclusion criteria to generate lists of potentially eligible patients interested in participating in research. We will utilize a HIPAA waiver to obtain these reports from the Fenway Health electronic health record, and, following the identification of potentially eligible individuals, will contact primary care providers (PCPs) via email to obtain clearance to contact their patients, as needed per Fenway Health policy. We will contact interested individuals to explain the study in more detail and conduct a brief pre-screening to confirm eligibility.

Pre-screening. All interested individuals will undergo a pre-screening process, conducted via phone or in-person by a study RA, student intern, or other trained study team member, to evaluate preliminary eligibility. A Pre-Screen ID number will be assigned to each individual during this process. Data collected during pre-screening will be recorded in a password-protected spreadsheet or within REDCap hosted at TFI.

Informed Consent. Individuals who meet pre-screening criteria will be scheduled for a Screening Visit (Visit 1), where we will conduct the informed consent discussion and obtain written consent. A trained study RA will review the consent form with the individual in detail, discuss the overall goals of the study, and review all procedures. Individuals will be asked to voice their understanding of the information and will have adequate time to ask questions. If they agree to participate, they will be asked to sign the informed consent form and will be provided with a copy for their records. Informed consent discussions will take place in private consult rooms at TFI.

Inclusion Criteria	Exclusion Criteria
1) Age 18 or older 2) Living with HIV 3) Currently prescribed and taking Biktarvy as ART for at least 3 months 4) Undetectable viral load in prior 6 months 5) Owns iPhone model 11 or higher (non-SE only)	1) Not English-speaking 2) Unwilling to interact with the TruTag app

5. Participant Enrollment.

Once the informed consent form and Medical Release Form have been signed, study staff will confirm eligibility. Individuals will be asked to provide their most recent viral load results to confirm undetectable viral load during the prior 6 months. If they do not have recent viral load results, study staff will obtain an HIV viral load during this visit, or, if preferred, individuals can obtain a viral load from their HIV care provider. Individuals who meet all criteria will be scheduled for an Enrollment Visit (Visit 2).

6. Study Procedures.

Study Visits. There are a total of five visits during the study period: the Screening Visit (Visit 1), Enrollment Visit (Visit 2), Month 1 Visit (Visit 3), Month 2 Visit (Visit 4), and Month 3 Visit (Visit 5).

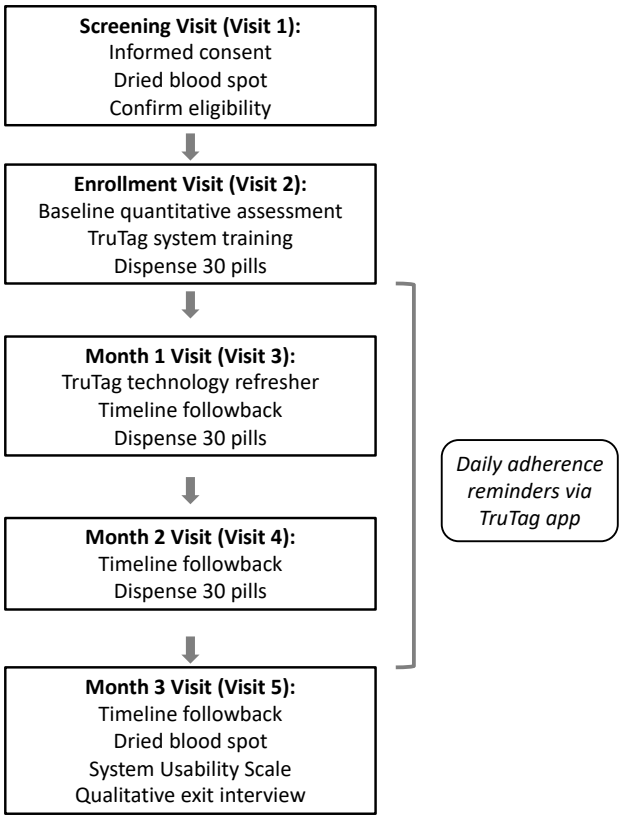
Screening Visit (Visit 1): As described above, potential participants will be approached and pre-screened, either via phone or email, by a trained member of the study team. Individuals who meet the pre-screening criteria will be scheduled to attend an initial Screening Visit (Visit 1), where the informed consent process will be conducted and study eligibility will be confirmed. Following the consent process, individuals will be asked to sign a Medical Release Form and Locator Form. A Screen ID number will be assigned at this visit. Study staff will confirm that individuals have been diagnosed with HIV, have been taking Biktarvy for at least 3 months prior to the Screening Visit, and have an undetectable viral load documented within the past 6 months. Study staff will administer a blood draw for DBS testing, in order to measure baseline ART adherence. All individuals will be enrolled in the ClinCard remuneration system during this visit, and study staff will issue payment following completion of visit procedures. Following this visit, if eligibility has been confirmed, we will notify the Fenway Pharmacy and schedule participants for the Enrollment Visit (Visit 2).

Enrollment Visit (Visit 2): At the Enrollment Visit (Visit 2), participants will be formally enrolled in the study. Participants will complete a baseline quantitative assessment (e.g., sociodemographics, sexual history, attitudes about technology). Participants will be informed that they may skip any questions they do not feel comfortable answering. The study team will introduce participants to the TruTag technology via a brief PowerPoint presentation, which will cover its functionality and structure, and provide answers to common questions. Participants will receive a standardized training on operation of the TruTag system, and will be assisted with downloading the TruTag app onto their phone. We will assist participants in registering the app, and we will program in standardized reminders (see *In-Study Messaging* section). Study staff will bring a completed Prescription Card to the Fenway Pharmacy, which will dispense 30 ART pills for the first month of the study. Participants will be provided with the 30-day supply of pills and will be instructed to take one pill once daily. Their first dose will be observed by the study team during this visit. We will then issue a ClinCard payment and schedule the Month 1 Visit (Visit 3).

Month 1 Visit (Visit 3): Participants will attend the Month 1 Visit (Visit 3) approximately 30 days after the Enrollment Visit (Visit 2). This visit can be conducted remotely via Zoom. During this visit, study staff will conduct a timeline followback discussion in order to better understand the context of any nonadherence events detected by the TruTag system during the prior 30 days. Participants will also receive a technology refresher training at this visit, if needed, around the operation of the TruTag system and app. Participants will return any unused pills from the prior 30 days, which will be counted by study staff. Participants will be dispensed an additional 30-day supply of pills for the second month of the study. We will then issue a ClinCard payment and schedule the Month 2 Visit (Visit 4).

Month 2 Visit (Visit 4): Participants will attend the Month 2 Visit (Visit 4) approximately 30 days after the Month 1 Visit (Visit 3). This visit can be conducted remotely via Zoom. During this visit, we will conduct a timeline followback discussion regarding any nonadherence detected by the TruTag system during the prior 30 days. Participant will return any unused pills from the prior 30 days, which will be counted by study staff. Participants will be dispensed a final 30-day supply of pills for the third month of the study. We will then issue a ClinCard payment and schedule the Month 3 Visit (Visit 5).

Month 3 Visit (Visit 5): Participants will attend the Month 3 Visit (Visit 5) approximately 30 days after the Month 2 Visit (Visit 4).This is the final study visit. During this visit, we will conduct a timeline followback discussion regarding any nonadherence detected by the TruTag system during the prior 30 days. Participant will return any unused pills from the prior 30 days, which will be counted by study staff. Participants will complete the System Usability Scale. We will administer a blood draw for DBS testing as a measure of ART adherence, to be compared to TruTag-detected adherence. A study team member trained in qualitative methods will then conduct a digitally recorded, semi-structured qualitative exit interview in order to gauge user experiences operating the TruTag system during the 90-day study period. Participants will delete the TruTag app from their phone. We will then issue the final ClinCard payment.



Remuneration. Participants will be remunerated a total of $275 via the ClinCard system, according to the following payment schedule, upon completion of all study visit procedures.

Study Visit	Compensation
Screening Visit (Visit 1)	$40
Enrollment Visit (Visit 2)	$40
Month 1 Visit (Visit 3)	$65
Month 2 Visit (Visit 4)	$65
Month 3 Visit (Visit 5)	$65
Total	**$275**

TruTag System. The TruTag system leverages a silica-based FDA generally regarded as safe (GRAS) microparticle that is incorporated into the coating of B/F/TAF. When light shines from a smartphone camera onto the coated drug, the reflected optical image is interpreted as B/F/TAF. A corresponding app records each scan as an adherence event and patients using the TruTag system are coached to scan their medication prior to ingesting it. Dissolution of B/F/TAF when overcoated with the TruTag system was tested by Gilead Sciences, demonstrating that there is no change in dissolution. Specialty coated B/F/TAF will be provided through a cooperative agreement between Gilead Sciences and TruTag. In brief, B/F/TAF from the Gilead manufacturing supply chain will be overcoated with the TruTag system by ThermoFisher, the Gilead contract coating manufacturer. Drug will then be shipped in bottles of 30 to the Fenway Health Pharmacy.

In addition to recording adherence events, the TruTag app also provides a calendar for participants to review their adherence on-demand, as well as reminder systems that are triggered if no adherence event is detected by the TruTag system during a 24-hour period. Finally, the app

provides a secure platform to facilitate two-way text message communication between participants and the study team. This platform will be used to provide study-related reminders and communication in the setting of detected nonadherence.

In-Study Messaging. Participants will receive communications via the TruTag app during their participation in the study. Messaging will include: (1) daily adherence reminders, (2) reminders following detected nonadherence, (3) study-related reminders of upcoming visits, and (4) responses to technology-related questions.

Daily Adherence Reminders. During installation of the TruTag app, study staff will ask participants what time of day they expect to take their daily B/F/TAF dose. We will set up daily adherence reminders in the app for 10 minutes prior to their expected dosing period.

Detected Nonadherence Reminders. The TruTag app will also be programmed to provide adherence reminders 60 minutes after the end of a dosing period, in the event that no ingestion has been detected. Additionally, if 48 hours of nonadherence is detected (i.e., 2 days of missed ingestions), study staff will utilize the two-way texting in the app to check in with participants. If participants do not respond to these nonadherence reminders, the study team will call or message participants to ensure that recorded nonadherence is not related to technological issues (i.e., related to operation of the TruTag system).

Study-Related Reminders. The TruTag app will be programmed to send reminders to participants in advance of each upcoming study visit. Reminders will be sent at 48 and 24 hours prior to the scheduled visit date.

Technology-Related Questions. We will encourage participants to report any technology-related questions and/or challenges to the study team via the TruTag app. We anticipate that these may include questions about how to operate the TruTag app, scan medication, or possible updates or reinstallations of the app. We will attempt to address technology-related issues through in-app messaging. If unsuccessful, we will contact participants by phone to troubleshoot technological concerns. if further assistance is required, we will schedule a study visit to assist participants with technology-related issues.

Data Collection. Quantitative data will be collected via the baseline quantitative assessment at the Enrollment Visit (Visit 2), and via the System Usability Scale at the Month 3 Visit (Visit 5). Study staff will collect participant monthly adherence via the TruTag application and create timeline followback discussions at the Month 1 Visit (Visit 3), Month 2 Visit (Visit 4), and Month 3 Visit (Visit 5) to identify and contextualize adherence events of interest across the study period. Qualitative data will be collected via individual qualitative interviews at the Month 3 Visit (Visit 5). Dried blood spot testing will be conducted at the Screening Visit (Visit 1) and the Month 3 Visit (Visit 5). Lastly, general participant TruTag application usage will be collected to better understand participant engagement with the application. This will include: app engagement, including time spent in the app and which screens of the application participants access along with the frequency and time in which they spend on each screen on the application, as well as reminder data, including number of reminders delivered, timing of reminders, dosing window around which reminders will be sent, and conversion rate (days in which a reminder is delivered and adherence event recorded afterwards in the TruTag app).

Baseline Quantitative Assessment. Quantitative data, including questions related to sociodemographics, use of ART, sexual history, mental health, attitudes about technology, medical mistrust, and substance use will be collected via a quantitative assessment. Quantitative data will be stored and managed on the REDCap platform hosted at TFI.

System Usability Scale. Participants will complete the System Usability Scale (SUS)[11] at the Month 3 Visit (Visit 5). The SUS is a 10-item Likert scale which will assess participants' perceptions of the usability of TruTag technology.

Qualitative Interview. Qualitative data will be collected via individual, qualitative interviews. Interviews will follow a semi-structured guide, which contains key content areas, including overall perceptions of the TruTag technology, perspectives about this technology in the context of ART treatment, potential applications for the technology and associated adherence data, privacy and health-related concerns, and future recommendations. The interview guide will be semi-structured and will allow for interviews to be adapted based on participants' responses. Qualitative interviews will be conducted until thematic saturation is reached.

Study Outcomes. The primary outcomes will be the feasibility and acceptability of the TruTag system during the 90-day study period, which will be assessed through participant recruitment and engagement with the technology via adherence data, qualitative interviews at the end of the study, and quantitative assessments (i.e. SUS survey). We will additionally collect biological (HIV viral load) and pharmacologic (dried blood spot) data for a secondary outcome, which will be to correlate TruTag-recorded adherence with other traditional ART adherence measures.

Data Storage and Transfer. Secure Business Dropbox, hosted at Mass General Brigham (MGB), will be used for file storage in this study. Quantitative data will be stored and managed on the REDCap platform hosted at TFI. Quantitative assessments and qualitative interview transcripts will not be made publicly available. De-identified data may be shared with the study sponsor (TruTag). Audio files from qualitative interviews will be sent to Landmark Associates, Inc., a HIPAA-compliant external transcription company, via their online portal. Audio files will be removed from recording devices and from the Landmark portal when transcripts are available for download. Transcript files will be stored in access-protected folders behind the TFI firewall, accessible only to approved members of the study team. A secure Excel spreadsheet linking Study ID numbers to participants' names will be maintained in the same fashion.

7. Risks and Discomforts.

We anticipate that the potential risks or discomforts associated with this research fall into five categories: (1); risk of loss of privacy; (2) risk of ingesting pills with TruTag coating; (3) risks associated with taking B/F/TAF (Biktarvy); (4) risks of psychological discomfort while completing assessments; and (5) risks associated with blood draws.

Risk of Loss of Privacy. There is a risk of discoverability of ART use and/or participation in the study should someone acquire a participant's smartphone and access the TruTag app, which could imply study participation. To mitigate this, we will ensure that participants' smartphones are enabled with password protection (or Touch ID and/or Face ID). All protected health information will be stored on secure servers at TFI, and all consent forms will be kept in locked file cabinets at TFI. The link between participants' Study ID numbers and names will be password-protected in Excel, and accessible only to approved members of the study team.

Risk of TruTag Coating. The TruTag system uses a silica material incorporated into the outer coating of B/F/TAF. Silica is known to be safe for ingestion and is designated by the FDA as Generally Recognized As Safe (GRAS). The TruTag materials are similar to silica materials that have been used for decades in the production of tablets. Formal internal studies have confirmed that these materials have no impact on the effectiveness of Biktarvy.

Risk of taking Biktarvy. All participants will be monitored for side effects that may be related to taking Biktarvy as ART. The most common side effect of taking Biktarvy are nausea, diarrhea, fatigue, headache, dizziness, insomnia, muscle pain, and abnormal heartbeat. Rare side effects from Biktarvy can include worsening kidney function, liver problems, and lactic acidosis (an abnormal amount of lactic acid in your blood). Participants will be informed during the informed consent process about all possible side effects and allergic reactions that may result from taking Biktarvy. They will be instructed to call the study doctor if they suspect they are having an allergic reaction, and to call 911 if they are having trouble breathing.

Risks of Psychological Discomfort while Completing Assessments. Study questionnaires and interviews may include questions that individuals do not feel comfortable answering, or that may cause psychological discomfort. Individuals will be informed during the consent process that they may choose to skip any questions that they do not want to answer. They will also be reminded that they may withdraw from the study at any time, for any reason, without penalty.

Risks of Blood Draws. Participants will be informed during the consent process that they may have a bruise or pain from the site where blood samples are drawn. There is also a small risk of infection, lightheadedness, and/or fainting. To mitigate this risk, all study staff will be trained in phlebotomy at Fenway Health. We will ask participants who have a history of vasovagal syncope from blood draws to lie flat or sit in a recliner prior to blood draw. We will also have oral fluids available for participants at visits where blood draws are required.

8. Benefits.

Individuals may not benefit directly from participation in this study. They may indirectly benefit from learning about the TruTag system as a tool for measuring their ART adherence behaviors.

9. Statistical Analysis.

We will calculate basic descriptive statistics for key demographic variables. SUS scores will be summed and a mean score will be calculated for each participant. Overall SUS will be measured at each month during study participation. We will measure adherence via three strategies: (1) TruTag recorded adherence, (2) pill count at each monthly study visit, and (3) dried blood spot tenofovir alafenamide concentration. Correlation coefficients will be calculated between each of these adherence metrics. To measure if correlation of measures degrades over time (e.g., if individuals disengage from the TruTag system and stop using it over time), we will use a point biserial correlation.

Qualitative data will be analyzed using an applied thematic analysis approach. As part of this analytical approach, digitally recorded interviews will be professionally transcribed and scrubbed of identifiers. The study team will develop an initial qualitative codebook based on the interview guide and an initial review of interview transcripts. Transcripts will then be coded in duplicate, with coders reviewing and comparing their coding following N=5 transcripts for completeness and inter-rater reliability. If the Kappa statistic >0.8, all remaining interviews will be independently coded. Any discrepancies in coding will be reviewed and resolved by the coders, and an audit trail of computerized coding will be maintained to maximize the validity of the process. All coding will be facilitated using NVivo software.[13] A framework matrix analysis will be created based on the results to organize codes by common themes.

10. Monitoring and Quality Assurance.

Data Monitoring and Quality Assurance. All quantitative data will be collected by the research team and entered into the REDCap platform[14] hosted at TFI. A study team member not directly involved in the quantitative data entry process will conduct data verification procedures in REDCap to ensure the accuracy of all manually entered data. Study tracking logs, including those containing contact information, screening information, enrollment link information, and visit attendance, will be maintained in a password-protected Excel spreadsheet stored behind the TFI firewall, and accessible only to approved members of the study team. Qualitative interview transcripts will be manually reviewed by study staff to ensure that all potentially identifying information has been appropriately redacted during transcription.

Adverse Event Monitoring. No adverse events are expected in this study. However, the PI will monitor for any adverse events, defined as undesirable experiences or unanticipated injury. The PI will assess whether any occurrences should be considered adverse events and will record the details of all adverse events on a case report form. All adverse events and serious adverse events will simultaneously be reported within 24 hours to the Fenway Health. Reports will include the event date and description; whether the event is related to the study procedures; event severity; steps taken to address the issue; whether the event provides emerging knowledge about study risks that should be conveyed to current and future participants; and whether the study fact sheet should be revised accordingly. This information will also be documented in a password-protected adverse event log stored behind the TFI firewall. The PI will additionally abide by all TFI regulations with respect to monitoring of safety events; all events will be evaluated by the PI on a case-by-case basis and reported to the IRB within 24 hours.

11. Privacy and Confidentiality.

All study procedures will be conducted in a private setting. Only data necessary for the conduct of the study will be collected. Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas). Data will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this protocol. Data requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g., encrypted files, password protection, using chain-of-custody procedures, etc.). All electronic communication with participants will comply with TFI's secure communication policies. Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research. All staff are trained on and will follow TFI policies and procedures for maintaining appropriate confidentiality of research data and specimens.

References.

1. Benjamin RM. Medication Adherence: Helping Patients Take Their Medicines as Directed. *Public Health Rep*. 2012;127(1):2-3. doi:10.1177/003335491212700102

2. Van Wyk BE, Davids LAC. Challenges to HIV treatment adherence amongst adolescents in a low socio-economic setting in Cape Town. *South Afr J HIV Med*. 2019;20(1). doi:10.4102/sajhivmed.v20i1.1002

3. Mehta S, Richard Moore, Neil Graham. Potential factors affecting adherence with HIV therapy. 1997;11(14):1665-1670.

4. Schaecher KL. The importance of treatment adherence in HIV. *Am J Manag Care*. 2013;19(12 Suppl):s231-237.

5. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10(3):227-245. doi:10.1007/s10461-006-9078-6

6. Ellsworth GB, Burke LA, Wells MT, et al. Randomized Pilot Study of an Advanced Smart-Pill Bottle as an Adherence Intervention in Patients With HIV on Antiretroviral Treatment. *JAIDS J Acquir Immune Defic Syndr*. 2021;86(1):73-80. doi:10.1097/QAI.0000000000002519

7. Chai PR, Rosen RK, Boyer EW. Ingestible Biosensors for Real-Time Medical Adherence Monitoring: MyTMed. In: *2016 49th Hawaii International Conference on System Sciences (HICSS)*. IEEE; 2016:3416-3423. doi:10.1109/HICSS.2016.426

8. Deisingh AK. Pharmaceutical counterfeiting. *The Analyst*. 2005;130(3):271. doi:10.1039/b407759h

9. Fayazpour F, Lucas B, Huyghebaert N, et al. Digitally Encoded Drug Tablets to Combat Counterfeiting. *Adv Mater*. 2007;19(22):3854-3858. doi:10.1002/adma.200602800

10. TruTag Technologies. https://trutags.com

11. Brooke J. SUS: A quick and dirty usability scale. *Usability Eval Ind*. 1995;189.