Randomized Pilot Study of an Advanced Smart-Pill Bottle as an Adherence Intervention in Patients With HIV on Antiretroviral Treatment

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Background: Adherence is critical to achieve the benefits of antiretroviral therapy. A smart-pill bottle service that transmits real-time adherence data via cellular networks to a central service and prompts nonadherent patients with phone or text messages may improve adherence.

Methods: Adults with HIV taking a tenofovir-containing regimen with suboptimal adherence were randomized to adherence counseling ± a smart-pill bottle service for 12 weeks. Tenofovir diphosphatase (TFV-DP) levels by dried blood spot, HIV RNA levels, CD4 cell counts, and self-reported adherence were collected.

Results: Sixty-three participants (22% women; 48% black, 25% Latino) were randomized: 30 to the smart-pill bottle (2 of whom were lost to follow-up before the baseline visit), and 33 to control arms. At baseline, 49% of participants had HIV RNA ≤20 copies/mL and 61% reported 100% adherence with ART over 4 days. From baseline to week 12, median TFV-DP levels were +252 and −41 fmol/punch in the bottle and control arms, respectively (P = 0.10). Exploratory exclusion of 3 participants with known or suspected drug–drug interactions found median TFV-DP levels of +278 and −38 fmol/punch, respectively (P = 0.04). There were no differences in study discontinuations, HIV RNA suppression, CD4 cell counts, or self-reported adherence at week 12.

Conclusions: In a diverse group of participants with suboptimal adherence to ART, the smart-pill bottle service was associated with higher TFV-DP levels.

Key Words: HIV, antiretrovirals, medication adherence, tenofovir, drug monitoring, reminder systems

INTRODUCTION

Patient adherence to antiretroviral therapy (ART) is critical to achieve HIV viral suppression. Durable viral suppression prevents emergence of drug resistance, reduces hospitalizations, improves HIV and mortality outcomes, and prevents transmission of HIV to others. Historically, certain ART regimens require ≥95% adherence to ensure complete virologic suppression and 3-fold higher mortality risk was described in persons living with HIV (PLWH) with less than 95% adherence to ART.

Despite the availability and benefit of multiple, potent, well-tolerated, and convenient one-pill once-daily regimens, ART adherence remains a challenge for some PLWH. In a 2011 meta-analysis of 84 studies across 20 countries, only 62% of participants reported ≥90% adherence to ART. In the US, the virologic suppression rate recently varied from an estimated 63% among those with a known diagnosis of HIV and up to 86% in a large clinical cohort in which 82% reported ≥90% adherence to ART. In one cross-sectional study, the most common reasons for ART nonadherence were “simply forgot” (33%), “away from home” (27%), and “busy” (26%).

Given the importance of adherence to ART, multiple adherence interventions have been evaluated including multiple mobile phone and electronic device-based interventions. Systematic reviews and meta-analyses of adherence...
Interventions have shown mixed effects with nominal results\textsuperscript{13,14} which have included randomized trials of a verbal prompting device to provide reminders,\textsuperscript{15} a watch with a reminder timer,\textsuperscript{16} an alarm device,\textsuperscript{17} modified directly observed therapy,\textsuperscript{18} and serial reminder phone calls.\textsuperscript{19} There are 3 recently published systematic reviews that have concluded that short-messaging services (SMS)-based interventions improved reported adherence to ART\textsuperscript{20–22} with one review reporting the odds of adhering to ART was 1.6 times higher in those receiving scheduled SMS messages ($P < 0.0001$).\textsuperscript{20} Researchers in all 3 reviews note a high risk of bias in the included studies and wide variation among interventions used in the studies.

A cellular network based electronic pill box service known as WisePill (Somerset West, South Africa) that generates an SMS message to users when not opened within a set timeframe did not improve self-reported adherence or viral suppression rates after 48 weeks in a randomized control trial (RCT) in a study of PWLH in South Africa.\textsuperscript{23} The same service did improve mean adherence from 86% to 96% in a randomized clinical trial in China but did not improve viral suppression after 5 months of the intervention.\textsuperscript{24} In an Adolescent Trials Network adherence study of tenofovir disoproxil fumarate (TDF)/emtricitabine as HIV pre-exposure prophylaxis (PrEP) in young men who have sex with men ages 15–22 years old in the U.S. 23% (65 of 279) of participants used a WisePill device but among those given the device, usage was low and poorly correlated with clinical and adherence outcomes.\textsuperscript{25}

AdhereTech (New York, NY) has developed a patented smart-pill bottle service that measures and transmits encrypted adherence information to a secure service. In addition to programmable on-device visual and audio reminder cues, the service can send customizable voice and SMS text messages to nonadherent users of the service. Users can reply to triggered messages indicating the cause of nonadherence. The smart-pill bottle itself uses a cellular data network for transmission and does not require frequent battery changing with a 6+ month battery life. The basic function and appearance of the bottle is similar to a standard pill bottle (Fig. 1). The smart-pill bottle service was shown to improve adherence in a RCT of 40 participants with multiple myeloma from 87% to 100% ($P = 0.001$) in a RCT of 40 participants,\textsuperscript{26} and it was shown to increase prescription fill rates and duration on therapy in review of commercial pharmacy data of thousands of patients.\textsuperscript{27}

Tenofovir (TFV) is a nucleotide analogue that is an important part of first-line ART regimens recommended by multiple HIV treatment guidelines.\textsuperscript{28–32} There are 2 FDA-approved formulations of tenofovir for the treatment and prevention of HIV: TDF and tenofovir alafenamide (TAF). Both TDF and TAF are phosphorylated intracellularly to the active moiety, tenofovir diphosphate (TFV-DP), a compound with a long intracellular half-life in red blood cells (RBCs) of about 17 days. TFV-DP drug levels in RBCs measured with dried blood spots can estimate the average drug exposure over the preceding 8 weeks.\textsuperscript{33} Higher TFV-DP levels are associated with greater rates of virologic suppression, and 75% of PLWH taking TDF-based regimens with TFV-DP concentrations in RBCs above 1250 fmol/punch achieve HIV RNA levels below the threshold of detection.\textsuperscript{34} Lower TFV-DP levels are a predictor of future viremia in those currently virologically suppressed.\textsuperscript{35} In the previously mentioned adolescent trials network study of PrEP in adolescents, use of the WisePill device (as measured by device openings) did not increase TFV-DP levels in dried blood spots.\textsuperscript{25}

Our hypothesis was that an advanced smart-pill bottle service may improve suboptimal adherence in PLWH as measured by TFV-DP and was evaluated in the HIV Adherence Bottle Intervention Trial.

**METHODS**

**Participant Recruitment**

Participants living with HIV, ages 18 and older, were required to be receiving a TFV-based ART regimen and have 2 HIV RNA levels $>20$ copies/mL in the prior 52 weeks to be eligible for the study. All subjects provided written consent...
and the study was approved by the institutional review board at Weill Cornell Medicine.

**Study Conduct**

Participants remained on the ART regimens prescribed by their health care providers. Enrolled participants were randomized one-to-one to receive the smart-bottle service and routine adherence counseling versus routine adherence counseling alone for 12 weeks. Those randomized to receive the smart-bottle service received instruction on the operation of the smart-pill bottle. The service was configured to call or send text messages to nonadherent participants reminding them of their dosing schedules. Phone/text messages did not disclose diagnoses nor did they prompt participants to take medication doses to avoid overdosing. TFV-DP measured in dried blood spots (fmol/punch), HIV RNA level, and CD4 count were collected at weeks 0, 4, 8, and 12. Participants also completed a standardized AIDS Clinical Trials Group Adherence Questionnaire and received adherence counseling at weeks 0, 4, 8, and 12.

**Statistical Considerations**

The sample size calculation was based on the null hypothesis of no difference in the mean difference in TFV-DP levels between study arms from baseline to week 12. Based on prior work by Castillo, et al.\(^3\) we expected a mean baseline TFV-DP level of 900 fmol/punch in both study arms, which corresponds to the median of about 4 daily 300 mg doses of TDF per week. At week 12, the mean (SD) TFV-DP levels were anticipated to be 1332 (597) fmol/punch (about 2 additional daily doses per week) in the smart-bottle group and 900 (404) fmol/punch. Assuming a normal distribution of TFV-DP levels, type I error rate of 0.05, power of 0.8, a sample size of 32 participants in each arm was needed based on a 2-sided \(t\) test with equal variance. The recruitment goal was set to account for anticipated 10% missing data was increased to 35 participants per arm (70 overall).

TFV-DP levels were compared between arms using a Kruskal–Wallis test or 2-sided \(t\) test depending on normality. The effects of age, gender, race, and ethnicity on TFV-DP levels were evaluated using linear regression. The proportions of participants completing the 12 weeks of follow-up, with HIV RNA \(\leq 20\) copies/mL at week 12, and reporting perfect adherence during the prior 4 days at week 12 were compared between arms using \(z\)-tests. HIV RNA levels \(\leq 20\) copies/mL were recoded to 19 copies/mL. Log changes in quantitative HIV RNA levels from baseline to week 12 between arms were compared using a Kruskal–Wallis test or 2-sided \(t\) test.

TAF-based ART became available commercially at the start of the recruitment period and during the course of the study. If TAF usage was confirmed more than 12 weeks before obtaining a specific TFV-DP level, the TDF level was considered to have reached steady state and this level was attributable to TAF. The TFV-DP value was then multiplied by a factor of 10.5, which enabled adherence interpretations similar to those for TDF.\(^37\) This approach was validated in a previous study of directly observed dosing with TAF. The analytical method for TFV-DP was also validated previously.\(^37,38\)

**RESULTS**

**Study Participants**

Recruitment occurred primarily from the population receiving care for HIV at the Weill Cornell Medicine—New York Presbyterian Hospital Center for Special Studies located at 2 locations in New York City. A total of 67 participants were recruited (25 and 42 participants at the East Side and Chelsea locations, respectively) between May 2015 and August 2018. Sixty-seven potential participants were screened for the study, and 4 ultimately did not enroll (Fig. 2, modified CONSORT diagram).

Sixty-three participants were randomized with 30 assigned to the smart bottle arm and 33 to the control arm. Baseline characteristics of the participants are listed in Table 1 and are notably diverse (22% women; 48% black, 25% Latino) and differed significantly only by age; the median age in the smart-bottle arm was 3 years older than the control arm (52 vs. 49 years, \(P = 0.03\)). Two participants assigned to the smart bottle arm were lost to follow-up before the baseline visit and are missing baseline ART regimen information.

**Changes in TFV-DP Levels**

The difference of TFV-DP from baseline to week 12 was not normally distributed because of 2 outliers that were orders of magnitude different from the mean. The change in median TFV-DP from baseline to week 12 was +252 fmol/punch (IQR: −167; +946) in the smart-bottle arm and −41 fmol/punch (IQR: −327; +214) in the control arm (\(P = 0.101\)) in an intention-to-treat analysis (Table 2; Fig. 3). There was no significant change in the difference of TFV-DP levels from baseline to week 12 associated with age, gender, race, and/or ethnicity in multivariable analysis.

Three participants had baseline TFV-DP levels greater than an order of magnitude higher than that of the median level. Two, one in each study arm, reported concurrent or recent use of combination ledipasvir/sofosbuvir (LDV/SOF) for treatment of hepatitis C infection known to increase TFV-DP levels.\(^39\) A third, in the smart bottle arm, had a suspected, but unidentified, drug interaction, which was suspected to be by the same mechanism. Excluding these 3 participants in an exploratory analysis demonstrated the change in TFV-DP levels from baseline to week 12 was +278 fmol/punch in the smart-bottle arm and −38 fmol/punch in the control arm (\(P = 0.038\), Table 2).

There were few ART changes and all participants remained on a TFV-based regimen through week 12. Three participants were prescribed TAF-containing ART during the study. 2 participants reported a switch from TDF to TAF within 12 weeks before the baseline or week 12 visit with TFV-DP levels attributable to prior use of TDF that may not have reached steady state, which prevented attributing TFV-DP levels to TAF dosing.\(^37\) Excluding these 2 participants with unstable TFV-DP levels, both randomized to the smart-bottle arm, results in a median change in TFV-DP levels from baseline to week 12 of +252 and −41 fmol/punch in the smart bottle and control arms, respectively (\(P = 0.081\)) in exploratory analysis.
In further exploratory analysis, excluding the 3 participants with suspected or known drug–drug interactions and the 2 participants with unpredictable TFV-DP levels because of TDF to TAF switches, yields a median change in TFV-DP levels from baseline to week 12 of +278 and 238 fmol/punch in the smart bottle and control arms, respectively (P = 0.025).

Secondary Outcomes
Loss to follow-up rates were 5 of 30 (17%) in the smart-bottle arm versus 7 of 33 (22%) in the control arm (P = 0.89). At week 12, 23 of 24 (96%) in the smart bottle arm reported that the bottle and service were easy to use, the service helped them miss fewer doses, and they were interested in future use of the smart bottle service.

The proportions of participants with HIV RNA levels ≤20 copies/mL at week 12 were 14 of 24 (58%) in the smart-bottle service arm compared with 12 of 26 (46%) in the control arm (P = 0.563, Table 2). There were no differences in log change of HIV RNA levels (P = 0.328).

The change in CD4 cell counts from baseline to week 12 were +14 cells/μL in the smart-bottle arm vs. −16 cells/μL in the control arm (P = 0.328, Table 2).

Six (25%) participants self-reported at least one missed dose of ART during the 4 days before the week 12 visit compared with 6 (23%) in the control arm. Overall, 24 (39%) participants self-reported nonadherence during the 4 days before the baseline visit vs. 12 (24%) reporting nonadherence at week 12 (P = 0.130).

DISCUSSION
This randomized controlled pilot study demonstrated that in a group of diverse participants with documented prior suboptimal adherence on a tenofovir-containing ART regimen, an advanced smart-pill bottle service was associated with increased levels of TFV-DP measured in dried blood spots, particularly in exploratory analyses. TFV-DP is a surrogate for adherence and is thereby associated with persistent virologic suppression for those taking TFV-containing ART.34,35 The smart bottle service appeared acceptable because it was not associated with greater loss-to-follow-up among those randomized to receive it and 96% of participants randomized to the smart bottle service reported satisfaction with its use. There were no changes in HIV RNA levels, CD4 cell counts or self-reported adherence at the end of the 12-week intervention period.

Proven strategies to improve ART adherence leading to virologic suppression are critical to ending the HIV epidemic,4,5 particularly in black populations that have the lowest rates of suppression10 and the highest incidence of HIV infection.40 In our pilot study conducted in a predominantly minority cohort, this smart-pill bottle service led to higher TFV-DP levels an objective marker of adherence, particularly when potential confounders were removed in exploratory analyses. The magnitude of effect (increase of about 240 fmol/punch) is commensurate with taking approximately one additional dose of TDF per week on average.33

There were unanticipated factors that complicated the interpretation of the strict intent-to-treat analysis of TFV-DP levels: significant drug–drug interactions because of direct-acting hepatitis C antivirals and the use of the newer TAF formulation of TFV instead of the TDF formulation. Investigators in the AIDS Clinical Trials Group study 5327 showed that combination LDV/SOF led to TFV-DP levels 17.8 fold-higher after 8 weeks of treatment versus study entry likely due to inhibition of carboxylesterase.39 In
addition, those taking TDF-containing regimens had median TFV-DP levels approximately 11-fold higher than the levels in the participants that reported taking TAF-containing regimens, as previous studies have identiﬁed.37 This is because red blood cells lack cathepsin A, which frees TFV from TAF, leading to poor red blood cell loading, in contrast to high levels of cathepsin A in peripheral blood mononuclear cells and high TFV loading in those cells.37 By excluding 5 participants with these factors (and corresponding outlier data), we demonstrated, in exploratory analysis, that the smart-pill bottle service was associated with signiﬁcant increases in TFV-DP compared with controls. One of the excluded participants had TFV-DP levels a magnitude of order higher than the median presumably because of an unknown drug–drug interaction and was not receiving treatment for hepatitis C but taking 9 different medications (combination TDF/emtricitabine/cobicistat/elvitegravir, atomoxetine, clonazepam, dronabinol, duloxetine, and olanzapine). Further research is needed to verify our exploratory analyses and any future study using TFV-DP measurements should plan and account for TDF versus TAF-based therapy and potential concomitant use of LDV/SOF.

Prior device-based interventions did not reliably improve adherence to ART. SMS text-based interventions seemed to show promise to improve adherence in systematic reviews, but prior studies used subjective adherence measures that may increase the risk of bias, and the SMS interventions varied in message length, content, and frequency and included studies that took place in various parts of the world.20–22 A cellular-based pill box service did not improve objective markers of adherence in prior studies.23,24 Our pilot study beneﬁted from use of a quantitative novel marker of antiretroviral drug adherence, intracellular TFV-DP by dried blood spot and the results support further exploration of this device as an adherence intervention for ART in randomized studies.

There are limitations with this pilot study. Research activity was conducted only at a single site, and there was familiarity with some participants that either had enrolled in other studies at our site and/or received care at our HIV clinic. Although we nearly achieved our recruitment goal, sample sizes remained small, particularly when participants were excluded in exploratory analyses. Study follow-up was short and limited to 12 weeks. A relatively low viral load threshold (HIV RNA >20 copies/mL) to determine nonadherence may have resulted in about half of our participants having viral suppression at entry; this complicated the demonstration of any difference attributable to the intervention in HIV RNA levels through week 12. Because

| TABLE 1. Baseline characteristics |
|----------------------------------|
|                                  |
| Smart Bottle (n = 30)            |
| Control (n = 33)                 |
| All (n = 63)                     |
| P                                |
| Age, median (IQR)               | 52 (48–56) | 49 (42–52) | 51 (43–55) | 0.036 |
| Gender, n (%)                   |            |            |            | 0.906 |
| Male                            | 23 (77)    | 23 (70)    | 46 (73)    |        |
| Female                          | 6 (20)     | 8 (24)     | 14 (22)    |        |
| Transgender                     | 1 (3)      | 2 (6)      | 3 (5)      |        |
| Race, n (%)                     |            |            |            | 0.345 |
| Black or African American       | 16 (53)    | 14 (42)    | 30 (48)    |        |
| White                           | 8 (27)     | 12 (36)    | 20 (32)    |        |
| More than one race              | 2 (7)      | 0 (0)      | 2 (3)      |        |
| Unknown or not reported         | 4 (13)     | 7 (21)     | 11 (17)    |        |
| Ethnicity, n (%)                |            |            |            | 0.688 |
| Hispanic or Latino              | 6 (20)     | 10 (30)    | 16 (25)    |        |
| Not Hispanic or Latino          | 21 (70)    | 20 (61)    | 41 (65)    |        |
| Unknown or not reported         | 3 (10)     | 3 (9)      | 6 (10)     |        |
| HIV RNA ≤20 copies/mL, n (%)    | 16 (53)    | 15 (45)    | 31 (49)    | 0.710 |
| CD4 (cells/µL), median (IQR)    | 380 (227–580) | 428 (306–616) | 409 (242–612) | 0.312 |
| No. of pills in daily ART regimen, median (IQR) | 2 (1–3)* | 3 (1–3)† | 2 (1–3)† | 0.245 |
| Participants missing ≥1 dose in the prior 4 days, n (%) | 10 (36)* | 14 (42) | 24 (39)† | 0.786 |
| On tenofovir, n (%)             | 28 (100)* | 33 (100) | 61 (100)† | 1.000 |
| On tenofovir disproxil fumarate, n (%) | 27 (96)* | 32 (97) | 59 (97)† | 1.000 |
| On TAF, n (%)                   | 1 (4)*     | 1 (3)      | 2 (3)†     | 1.000 |
| On NNRTI, n (%)                 | 28 (100)* | 33 (100) | 61 (100)† | 1.000 |
| On NRTI, n (%)                  | 6 (20)*    | 7 (21)     | 13 (21)†   | 1.000 |
| On protease inhibitor, n (%)    | 10 (36)*   | 15 (45)    | 25 (41)†   | 0.610 |
| On integrase inhibitor, n (%)   | 14 (50)*   | 17 (52)    | 31 (51)†   | 1.000 |

Randomized groups differed only by age.
* n = 28 (2 not available).
† n = 61.
participants reported their adherence, this outcome is subject to bias, and self-reported adherence notably improved in both arms.

Based on our pilot study, the smart-bottle service warrants validation in larger clinical and research cohorts as an adherence intervention to ART. There also is potential for use of this smart-bottle service in promoting adherence in those taking PrEP, because adherence is key to the efficacy of oral combination tenofovir/emtricitabine to prevent the acquisition of HIV.41 U.S. Centers for Disease Control and Prevention estimates that PrEP reduces the risk of getting HIV from sex by about 99% when taken daily.42 Prior evaluation of an online device-based intervention for PrEP occurred in a portion of study

### TABLE 2. Study Results

|                              | Smart Bottle | Control | P     |
|------------------------------|--------------|---------|-------|
| Baseline TFV-DP, median (IQR), fmol/punch* | 1230 (923 to 2066) | 1108 (553 to 1886) | 0.400 |
| Week 12 TFV-DP, median (IQR), fmol/punch† | 1887 (816 to 2794) | 1048 (504 to 1775) | 0.035 |
| Change in TFV-DP levels from baseline to wk 12, median (IQR), fmol/punch‡ |                       |                     |       |
| Intention to treat           | 252 (−167 to 946) | −41 (−327 to 214) | 0.101 |
| Excluding suspected drug–drug interactions (n = 3) | 278 (−38 to 955) | −38 (−285 to 214) | 0.038 |
| Excluding unstable TFV-DP levels because of change to TAF (n = 2) | 252 (−106 to 880) | −41 (−327 to 214) | 0.081 |
| Excluding drug–drug interactions and unstable TFV-DP levels (n = 5) | 278 (−32 to 946) | −38 (−285 to 214) | 0.025 |
| Secondary outcomes           |              |         |       |
| Participants lost to follow up, n (%) | 5 (17) | 7 (22) | 0.890 |
| HIV RNA <20 copies/mL at wk 12, n (%)‡ | 14 (58) | 12 (46) | 0.563 |
| CD4 count, change from baseline to wk 12, median (IQR), cells/μL§ | 14 (−52 to 91) | −16 (−141 to 53) | 0.356 |
| Participants reporting missing ≥1 dose during the 4 days prior at wk 12, n (%)|| 6 (25) | 6 (23) | 1.000 |

TFV-DP baseline and week 12 results including post-hoc analyses. Secondary outcomes including loss to follow-up rates, HIV RNA levels, CD4 levels, and self-reported adherence outcomes.
*Four participants in the control arm are baseline missing dried blood spots therefore TFV-DP levels. Five participants in the smart bottle arm are missing baseline TFV-DP levels: 2 were lost to follow-up prior obtaining dried blood spots and 3 participants are missing blood spots.
†At week 12 and change in TFV-DP levels: all missing dried blood spots are because of study discontinuation (or loss to follow-up) in both arms.
‡HIV RNA levels are missing for a participant in the smart-bottle arm at week 12.
§CD4 counts were missed for one participant in the smart-bottle arm and 3 participants in the control arm.
||One and 3 participants in the smart-bottle and control arm respectively did not complete the week 12 adherence survey.

![FIGURE 3. Median TFV-DP (IQR) over time by study arm in (A) the intention to treat analysis. B, Exploratory analysis excluding those with drug–drug interactions and those with unstable (or unpredictable) TFV-DP levels because of ART changes (TDF-based to TAF-based) within 12 weeks of the baseline or week 12 visit.](Image)
participants with over half (56%) of those surveyed reporting that they were “not at all likely” to use the device outside the study and it did not lead to improved outcomes in the subcohort.\textsuperscript{25} An evaluation of the effects of the smart-pill bottle service on adherence to oral daily PrEP is warranted.

In summary, our pilot study showed in a diverse group of persons living with HIV with demonstrated suboptimal adherence to their antiretroviral regimen, a smart-pill bottle service was associated with a significant increase in antiretroviral drug levels that would be expected to improve virologic suppression rates over time. This device-based intervention shows promise to improve adherence to ART and deserves further exploration in randomized clinical trials. ART adherence is a key strategy for both long-term virologic control and reduction of HIV transmission, important components to end the HIV epidemic.

ACKNOWLEDGMENTS

AdhereTech provided the smart-pill bottles and service to the study. Acknowledgement is due to the tireless staff of the Cornell HIV Clinical Trials Unit and Weill Cornell Medicine Division of Infectious Diseases as well to the willing participants of the HIV Adherence Bottle Intervention Trial study.

REFERENCES

1. Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virologic fitness. AIDS. 2006;20:223–231.
2. Sax PE, Meyers JL, Mugavero M, et al. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. PLoS One. 2012;7:e31591.
3. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. New Engl J Med. 2015;373:795–807.
4. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493–505.
5. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375:830–839.
6. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133:21–30.
7. 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;7:185–193.
8. 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;50:529–536.
9. Ortego C, Huedo-Medina TB, Llorea J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav. 2011;15:1381–1396.
10. Harris NS, Johnson AS, Huang YA, et al. Vital signs: status of human immunodeficiency virus testing, viral suppression, and HIV preexposure prophylaxis—United States, 2013–2018. MMWR Morb Mortal Wkly Rep. 2019;68:1117–1123.
11. Nance RM, Delaney JA, Simoni JM, et al. HIV viral suppression trends over time among HIV-infected patients receiving care in the United States, 1997 to 2015: a cohort study. Ann Intern Med. 2018;169:376–384.
12. Reynolds NR, Testa MA, Marc LG, et al. Factors influencing medication adherence beliefs and self-efficacy in persons naïve to antiretroviral therapy: a multicenter, cross-sectional study. AIDS Behav. 2004;8:141–150.
13. Simon JM, Pearson CR, Pantalone DW, et al. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. J Acquir Immune Defic Syndr. 2006;43(suppl 1):S23–S35.
14. Bärnighausen T, Chaiyachati K, Chimbindi N, et al. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. Lancet Infect Dis. 2011;11:942–951.
15. Andrade AS, McGruer 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;41:875–882.
16. 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;10:83–93.
17. Chung MH, Richardson BA, Tapia K, et al. A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes. PLoS Med. 2011;8:e1000422.
18. 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;169:1224–1232.
19. Collier AC, Ribaudo H, Mukherjee LA, et al. A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons initiating antiretroviral therapy. J Infect Dis. 2009;199:1398–1406.
20. Amankwaa I, Boateng D, Quansah DY, et al. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: a systematic review and meta-analysis. PLoS One. 2018;13:e0204091.
21. Shah R, Watson J, Free C. A systematic review and meta-analysis in the effectiveness of mobile phone interventions used to improve adherence to antiretroviral therapy in HIV infection. BMC Public Health. 2019;19:915.
22. Quintana Y, Gonzalez Martorell EA, Fahy D, et al. A systematic review on promoting adherence to antiretroviral therapy in HIV-infected patients using mobile phone technology. Appl Clin Inform. 2018;9:450–466.
23. Orrell C, Cohen K, Mauff K, et al. A randomized controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy. J Acquir Immune Defic Syndr. 2015;70:495–502.
24. Sabin LL, Bachman DeSilva M, Gill CJ, et al. Improving adherence to antiretroviral therapy with triggered real-time text message reminders: the China adherence through technology study. J Acquir Immune Defic Syndr. 2015;69:551–559.
25. Koss CA, Hosek SG, Bacchetti P, et al. Comparison of measures of adherence to human immunodeficiency virus preexposure prophylaxis among adolescent and young men who have sex with men in the United States. Clin Infect Dis. 2018;66:213–219.
26. Mauro J, Mathews KB, Sredniwitz ES. Effect of a smart pill bottle and pharmacist intervention on medication adherence in patients with multiple myeloma new to lenalidomide therapy. J Manag Care Spec Pharm. 2019;25:1244–1254.
27. AdhereTech. Evidence: Proven Results Published by Top Healthcare Companies. Available at: https://www.adheretech.com/evidence. Accessed February 5, 2020.
28. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed January 2, 2020.
29. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in Adults: 2018 recommendations of the international antiretroviral society-USA panel. JAMA. 2018;320:379–396.
30. European AIDS Clinical Society. EACS Guidelines Version 10.0. Available at: https://www.eacsociety.org/files/2019_guidelines-10.0_.final.pdf. Accessed January 2, 2020.
31. British HIV Association. BHIVA Guidelines for the Treatment of HIV-1 Positive Adults With Antiretroviral Therapy 2015 (2016 Update).
32. World Health Organization (WHO). Update of Recommendations on First- and Second-Line Antiretroviral Regimens. Available at: https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1. Accessed January 2, 2020.

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

34. Castillo-Mancilla JR, Morrow M, Coyle RP, et al. Tenofovir diphosphate in dried blood spots is strongly associated with viral suppression in individuals with human immunodeficiency virus infections. *Clin Infect Dis*. 2019;68:1335–1342.

35. Morrow M, MaWhinney S, Coyle RP, et al. Predictive value of tenofovir diphosphate in dried blood spots for future viremia in persons living with HIV. *J Infect Dis*. 2019;220:635–642.

36. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient care committee and adherence working group of the outcomes committee of the adult AIDS clinical trials group (AACTG). *AIDS Care*. 2000;12:255–266.

37. Yager J, Castillo-Mancilla J, Ibrahim ME, et al. Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following tenofovir alafenamide: the TAF-DBS study. *J Acquir Immune Defic Syndr*. 2020;84:323–330.

38. Zheng JH, Rower C, McAllister K, et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. *J Pharm Biomed Anal*. 2016;122:16–20.

39. MacBrayne CE, Marks KM, Fierer DS, et al. Effects of sofosbuvir-based hepatitis C treatment on the pharmacokinetics of tenofovir in HIV/HCV-coinfected individuals receiving tenofovir disoproxil fumarate. *J Antimicrob Chemother*. 2018;73:2112–2119.

40. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2016. *HIV Surveill Supplmental Rep*. 2019;24:19.

41. Donnell D, Baeten JM, Bumpus NN, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. *J Acquir Immune Defic Synd*. 2014;66:340–348.

42. Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention. Pre-exposure Prophylaxis (PrEP), HIV Risk and Prevention, HIV/AIDS, CDC. Available at: https://www.cdc.gov/hiv/risk/prep/index.html. Accessed January 6, 2020.