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Barriers to HIV Medication Adherence as a Function of Regimen Simplification

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INTRODUCTION

Combination antiretroviral therapy (ART) has substantially improved the life expectancy and the quality of life of people infected with HIV [1, 2]. Early initiation of ART also significantly improves clinical outcomes and reduces sexual transmission of HIV through viral suppression [3]. The benefits of ART, however, are only achieved through long-term medication adherence. Indeed, ART adherence is one of the key determinants of HIV disease progression [4, 5]. Incomplete adherence severely compromises treatment effectiveness, and leads to unsuppressed virus with the potential for developing HIV drug resistance [6, 7]. The level of ART adherence that may lead to viral rebound and drug resistance differs by medication regimens, with a minimum of 85% adherence typically required for most drug combinations to maintain their effectiveness [8].

Regimen simplification is considered a crucial element for improving adherence [9]. With increased potency and the advent of combining multiple drugs in single tablets, people living with HIV are able to take fewer pills per dose with longer intervals between doses. In 2006, efavirenz-emtricitabine-tenofovir (Atripla) became the first approved branded fixed-dose 3-drug single-tablet regimen (STR) [10]. The US Food and Drug Administration subsequently approved other STRs including emtricitabine/rilpivirine/tenofovir (Complera) and elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild) [11, 12]. A central objective of STR is to potentially improve medication adherence [9].

Several studies have assessed the impact of simplified (once-daily) regimens on medication adherence as compared to more complex (twice or more daily) regimens. One meta-analysis of 11 randomized controlled trials (RCTs) found that ART adherence was better with once-daily than twice-daily regimens among treatment naïve patients [13]. The same pattern was found in an updated meta-analysis with 19 trials [14]. In another RCT not included in the meta-analyses, Cooper et al. [15] assessed the effect of a once-daily multi-tablet regimen (single-dose MTR) on adherence compared to a twice daily regimen (multi-dose MTR), and

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Conflicts of Interest and Ethical Adherence

The authors claim no conflict of interests or competing interests. All research procedures were approved by the University of Connecticut Institutional Review Board and adhered to the ethical guidelines for human participants research set forth by the American Psychological Association.

persons taking the once daily regimen were significantly more likely to achieve higher adherence.

Evidence favoring once-daily regimens over twice-daily regimens suggests the importance of regimen simplification for improving ART adherence. However, examination of relevant studies demonstrates mixed results. Adherence is significantly better for persons taking STR as compared to those taking MTR in several observational studies [16–19], as well as in two pre-post design studies in which adherence was significantly increased from baseline after patients switched to STR [20, 21]. However, there is also considerable evidence showing no effect of STR on adherence. In two randomized trials, adherence was not different between persons who switched to STR and those who stayed on their baseline regimens [22, 23]. In two observational studies, no difference was found between STR and other single-dose MTR among patients initiating ART [24] or among those who switched from STR to MTR for cost reasons [25]. Further complicating drawing conclusions from this literature are findings from a recent study by Tennant et al. [26], in which MTR were associated with better adherence than STR based on clinic refill records.

Lack of consistent better adherence for STR over MTR, especially single-dose MTR, may be due to several factors. One reason could be the insignificance of pill burden as an adherence barrier for once-daily regimens as is reflected in the meta-analysis by Nachega et al., where pill burden was associated with lower adherence for twice-daily regimens but not once-daily regimens [14]. Another reason could be due to the initial differences in patients that led to the correspondingly different prescriptions. Person characteristics including preferences, anticipated and actual adherence, as well as treatment response are likely used by clinicians to guide the selection of regimens [27]. If patients with lower anticipated adherence had a higher tendency of being assigned STR, the improvement in adherence brought by STR might have been attenuated. Variations in measures of adherence across studies may also account for discrepancies in the literature [17, 20–22, 24] [16] [26] [18, 19]. Taken together, the inconsistent relationship between STR and adherence obscures inferences that we can draw about the role of treatment simplification on adherence.

Aside from the call for more evidence regarding the relationship between dosing complexity and adherence, another open question concerns the potential reasons for differential adherence observed across regimens of different dosing frequency. Although dosing complexity and pill burden are reduced through the availability of STR, they are by no means the only barriers to adherence. Barriers to adherence not only stem from intrapersonal factors such as personal capacity to adhere, depression, disruptions in daily routine, and substance use, but also from structural factors such as poverty, lack of social support and efforts to conceal medications [28–30]. All of these barriers persist in the face of simplified drug regimens, and may complicate the relationship between ART regimen and adherence. It is expected that individuals taking different ART regimens may experience different adherence barriers which could inform interventions.

This study aims to fill a gap in the literature by identifying potential adherence barriers associated with three types of ART regimens of different dosing complexity, namely, STR, single-dose MTR and multi-dose MTR. Given the mixed findings in studies that compare

STR vs. MTR on adherence, we first assessed the prospective effect of regimen types on adherence. We hypothesized that adherence would be highest among individuals taking STR, and lowest among those on multi-dose MTR. We also supplemented the hypothesis by examining the cross-sectional relationship between types of regimen and viral suppression. Regarding barriers to adherence, we examined the differential prevalence of each adherence barrier by types of regimens. Specifically, we tested whether people taking regimens with different dosing complexity would attribute non-adherence to different barriers, and whether there is a dose-response relationship, with more complex regimens being associated with more barriers, or being more strongly associated with each reported barrier.

METHOD

Study Design

The current data were from a run-in study of a randomized controlled ART adherence trial. The run-in study was designed to obtain initial adherence data from participants prior to randomization and intervention. Data were collected over a six-week span through an office baseline assessment, and three follow-up phone assessments. At baseline we collected information on ART regimen, viral load, and other participant characteristics. The follow-up phone calls concentrated on collecting adherence data (i.e. pill counts, barriers to adherence, and side-effects). Three phone assessments over the course of six weeks generated two measures of adherence (the first pill count establishes the initial number of pills and the subsequent two calls yield adherence values), and three measures of adherence barriers and side-effects. Details about assessment procedures and corresponding measures are described below.

Participants

Participants were men and women who were in care and were taking ART to treat their HIV infection. The site of the study was Atlanta, Georgia with an annual incidence of 30.3 per 100,000, exceeding the 19.6 per 100,000 population rate of HIV in major US cities. Eligible participants were age 18 or older, HIV positive and currently taking ART. A total of 764 participants were recruited but for the current study, we excluded 14 (1.8%) participants who had evidenced treatment failure, defined as receiving five or more different ART medications (salvage therapy). These individuals were excluded due to their atypical adherence profiles that result in highly complex ART regimens. Our final sample consisted of 750 participants. No participants were lost during follow-ups.

Measures

Participants provided four sources of data: audio-computer assisted self-interviews (ACASI) to assess demographic and behavioral characteristics [31, 32]; an office-based interview to assess all prescription medications and determine ART regimen; medical records of HIV RNA (viral load) and CD4 cell counts; and prospectively collected phone-based unannounced pill counts and factors associated with ART adherence.

Time-invariant Measures

Audio-Computer Interviews

Demographic and Health Characteristics, Year of Infection and HIV Symptoms: Participants were asked their gender, age, years of education, race and ethnicity. Participants also reported the year that they first tested HIV positive, completed a measure of 14 HIV-related symptoms of 2-weeks duration (indicated as having or not having experienced each symptom, summed to a composite score) [33].

Self-efficacy and Depressive Symptoms: Adherence self-efficacy was assessed using a scale that measures participants' self-rated confidence to take medications and keep up with treatment under 14 different circumstances (e.g. being interrupted with daily routine, being interfered by side-effects, being discouraged by health condition, etc.). Participants responded on an 11-point (0–10) ascending confidence scale for each circumstance (Cronbach's alpha = 0.95). The final measure was generated by calculating the mean score of all the items. Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CESD), which is comprised of 20 items regarding the frequency of depressive symptoms in the past week (Cronbach's alpha = 0.91) [34].

Participant Provided HIV Viral Load and CD4 Cell Counts—We used a participant assisted method for collecting HIV viral load and CD4 cell counts from participants' medical records. Participants were given a form that asks their physician's office to provide the results and dates of their most recent, and not older than 3-months, HIV viral load and CD4 cell counts. These data were therefore obtained directly by the participants from their HIV health care providers. The form included a place for the provider's office stamp and signature to assure data authenticity. HIV RNA below detection was defined as less than 75 copies/mL for uniformity across providers. Each participant was asked to bring in one record of their viral load and CD4 cell counts during the study period.

ART Regimen Determination—An office interview was conducted to collect information on all prescription medications, determine ART regimen, and train participants in the pill counting procedure. No participant changed regimen during the study period.

Time-variant Measures

Unannounced Pill Counts for ART Adherence—Participants consented to three unannounced telephone-based pill counts that occurred over a six-week period. Unannounced pill counts are reliable and valid in assessing medication adherence when conducted in homes [35] and on the telephone. [36, 37] In this study we conducted unannounced cell-phone based pill counts. Participants were provided with a free cell phone for use in the study assessments. An office interview included a full accounting of all prescription medications, determining ART regimen, and systematic training in the pill counting procedure. Participants were subsequently called at three unscheduled times over 12 to 16 day intervals. Pharmacy information from pill bottles was also collected to verify the number of pills dispensed between calls. Adherence was defined as the ratio of pills counted relative to pills prescribed, taking into account the number of pills dispensed. ART

adherence was examined as a clinically defined categorical variable with adherence defined as greater than 85% of medications [38].

Barriers to Adherence and Side-effects: At each of the unannounced phone assessments participants whose pill count indicated incomplete adherence (< 100% pills taken) were asked whether they had experienced 15 common barriers to adherence over the previous two-week period. Barriers to adherence were adapted from Catz et al. [39] and included substance use, depression, daily life events, running out of medications prior to getting a refill, side-effects, cost of medications, and transportation (exact barriers are shown in the Results section). Each barrier was indicated as having occurred or not occurred. In addition, all participants regardless of their adherence were asked to respond to a single item measure of current side-effects with a four-point ascending scale that ranges from 0 (no side-effects) to 3 (severe side-effects).

Procedures

Men and women living with HIV were recruited through targeted community sampling with both venue recruitment and snowball sampling techniques. Venue recruitment relied on responses to brochures placed in waiting rooms of HIV service providers and infectious disease clinics throughout Atlanta. Participants were also encouraged to use the study brochures to refer their HIV positive friends to the study. Individuals provided informed consent prior to completing any study activities. Following completion of the ACASI assessment, participants were interviewed regarding their current ART regimen and were trained in unannounced phone-based pill count procedures and provided with a project cell phone. Medication regimens were recorded from ART prescription bottles brought to this appointment. We asked participants to return with their medical information (CD4 count and viral load) within the next five weeks.

Participants were subsequently phoned three times over the next six weeks to obtain two calculations of adherence. Participants were also asked whether they believe they had missed any of their ART in the previous two weeks. Participants were probed regarding their adherence when their report of missed medication doses did not reflect the adherence obtained by pill counts. Participants were then asked about the reasons they had missed their medications in the previous two-weeks. Participants were paid up to US$175 for completing study activities. All procedures were approved by the Institutional Review Board.

Data Analyses

All participants were taking combination highly active antiretroviral therapy. Participants were grouped on the basis of their prescribed ART and dosing schedule. Medication regimens were coded from prescription labels. We categorized medication regimen along two dimensions; number of pills taken per dose and number of doses taken per day. Thus, we formulated the three groups: (a) Individuals taking one pill once per day (STR), (b) individuals taking more than one pill once per day (single-dose MTR); and (c) those taking two or more doses per day (multi-dose MTR). For descriptive analyses, we compared participants who were less than 85% adherent over the six weeks to those who demonstrated 85% or greater adherence. Because two adherence measures were collected from each

participant over the study duration, we used Rao–Scott corrected Pearson X^2 test to control for clustering within participants [40]. Proportions presented are the average of the two adherence points. We also compared participants whose viral load was determined detectable to those whose viral load was undetectable, using Pearson X^2 test. For ease of description, we categorized all continuous variables for the descriptive analyses. The cut-off at 16 for CESD indicates probable depression [41]. Other variables were categorized for descriptive purposes based on arbitrary cut-off points. All the continuous variables were kept in their original forms for regression analyses.

The association between types of ART regimen and status of adherence and viral load were further evaluated in both simple and multiple logistic regressions, adjusting for potential confounders identified in descriptive analyses and previous literature [42, 43]. Given the repeated measures of adherence, we used generalized equation estimation (GEE) for logistic regression with Huber-White standard error estimates, assuming unstructured correlation matrix, to control for within-subject clustering [44]. Viral load was obtained only once, so standard logistic regression was adopted for viral load as the outcome. In all models, individuals taking STR were entered as the reference group.

To assess different adherence barriers in relation to dosing characteristics, we first conducted descriptive analysis, comparing each of the 15 binary-coded barriers by three types of regimens. Because perceived barriers to adherence were evaluated for three times within each individual, Rao-Scott corrected Pearson's X^2 test was used. Proportions reported in the results were averaged across three assessments. Conceptual grouping of the barriers was guided by results of exploratory factor analysis. Two barriers (i.e. got confused with what to take, and did not want someone to see) demonstrated extremely high uniqueness. Among the rest of barriers, a four-factor structure was indicated: scheduling barriers, substance abuse, logistic inconvenience, and ART-induced problems.

The prospective association between types of ART regimen and perceived barriers to adherence was further examined by regression. We used logistic regression with GEE and robust variance estimation to account for correlations within the repeated measures in barriers. One regression model was fit for each barrier, with the three-level regimen type as the predictor, adjusting for time of assessment, depressive symptoms, adherence self-efficacy and side-effects. Adjusted covariates were chosen based on their relevance to dosing complexity and barriers to adherence based on exploratory analyses and previous literature [42, 45]. A dose-response relationship was also tested between regimen type and each perceived barrier. Statistical significance was defined as $p < .05$, therefore controlling for the false discovery rate (FDR) of multiple comparisons at 8.6%, estimated using the method of Benjamini and Hochberg [46]. All analyses were performed in STATA ver.14 [47].

RESULTS

Sample Characteristics

Table 1 displays the dosing categories and relevant characteristics by participants' adherence and viral load. Among the 750 HIV patients who were in care and met the current study criteria of taking four or less ART drugs, 166 (22%) were receiving STR, 300 (40%) were

taking single-dose MTR, and 284 (38%) were taking multi-dose MTR. Two thirds of the participants were male and a majority were African American. Participants represented a wide-range of ages and years since testing HIV positive. Around 40% of participants had been diagnosed with HIV for 10–20 years, and a lower proportion of participants were diagnosed for less than 10 years (30%) or for more than 20 years (29%). The mean number of HIV symptoms reported by participants was 3.8 (SD=3.4), and over half of the participants (54%) reported less than four symptoms. An average of 69% of the participants reported no side-effects from their HIV regimen across three assessment calls (62% at baseline, 71% two weeks later, and 74% four weeks later).

Sample Characteristics by Adherence Status

Valid pill-count data of ART adherence were available for 744 (99%) participants by the end of the study. Adherence greater than or equal to 85% of pills taken was achieved among 518 (70%) participants. A higher proportion of participants taking STR (76%) achieved ≥85% adherence compared to both the group taking single-dose MTR (68%) and the group taking multi-dose MTR (66%). Across the four age categories, there was an increase in the proportion of people adherent, with over 70% of participants adherent in two older age groups. No gender difference in adherence was found. The proportion of people adherent decreased as the number of reported HIV symptoms increased; 74% of participants with less than three HIV symptoms were adherent, whereas this proportion dropped to 63% among those with more than six symptoms. Comparatively, the proportion of adherent participants also decreased as the severity of side-effects increased. Over 72% participants who reported no side-effects were adherent, whereas the proportion declined to 50% among those who reported severe side-effects (see Table 1).

Sample Characteristics by Viral-load Status

Viral loads were provided by 712 (95%) participants. As shown in Table 1, a total of 549 (77%) participants had an undetectable viral load. Over 91% of participants taking STR regimens demonstrated viral suppression, while this proportion dropped to 70% for those taking single-dose MTR and 75% for those taking multi-dose MTR. As age increased, the proportion of people with undetectable viral loads also increased, with the highest proportion (84%) appearing in the oldest group. Overall more female participants (82%) had an undetectable viral load than male participants (74%). Additionally, a decrease in undetectable viral load was shown as HIV symptoms increased; undetectable viral load declined from 80% to 69% as the number of reported HIV symptoms increased from 0–3 symptoms to 7–14 symptoms.

Associations of Regimen Type with Adherence or Viral Load Outcomes

Table 2 presents both the unadjusted and adjusted associations between regimen type and HIV-related outcomes, with those taking STR serving as the reference group. Given that the proportion of missing cases is relatively small (1% and 5%), no special handling procedure was adopted except for the default mechanism of case-wise deletion. Individuals with missing data did not differ from those with complete data on regimen type and adjusted covariates.

Both single-dose MTR and multi-dose MTR were associated with lower odds of ≥85% adherence in the unadjusted analysis. Intra-class correlation for the adherence measure was 56% (95%CI: 46.9%–66.2%), indicating significant within participant correlation of the data. Adjustment of covariates significantly improved model fit (X^2=30.61, p<0.001). After adjusting for relevant characteristics shown in Table 2, multi-dose MTR was associated with 37% lower odds of adherence (OR: 0.62, 95%CI: 0.43, 0.90) as compared to STR. Among the adjusted characteristics, age was positively associated with adherence; a one-year increase in age was associated with a 2% higher odds of ≥85% adherence (OR: 1.02, 95%CI: 1.01, 1.04).

Participants taking single-dose MTR and multi-dose MTR were less likely to have an undetectable viral load in both unadjusted and adjusted analyses. Single-dose MTR was correlated with a 77% reduced likelihood of undetectable viral load as compared to STR (OR: 0.23, 95%CI: 0.12, 0.42). Similarly, multi-dose MTR was correlated with a 70% reduced odds of undetectable viral load (OR: 0.30, 95%CI: 0.16, 0.57). No significant difference was found between single-dose MTR and multi-dose MTR. Additionally, age and gender were associated with undetectable viral load. One-year increases in age were associated with a 5% increase in the odds of undetectable viral load (OR: 1.05, 95%CI: 1.02, 1.07), and female participants were more likely than male to have an undetectable viral load (OR: 1.61, 95%CI: 1.04, 2.49).

Associations of Regimen Type with Perceived Barriers to Adherence

Descriptive statistics in Table 3 show the frequency that each barrier was reported as reasons for missing doses by the three types of regimen. Participants on the three types of regimens had different frequencies of reporting the following barriers: scheduling barriers (i.e. “forgot”, “too busy”, and “something unexpected came up”), ART-induced barriers (i.e. “making me sick” and “felt depressed and overwhelmed”), and the barrier of “being confused with what to take”. The frequency of reporting each barrier increased with the level of regimen complexity. Overall the “scheduling barriers” were more frequently cited as reasons for missing doses, while the “substance-induced barriers” were relatively less often reported.

Results from multivariate analyses were consistent with those from the descriptive analyses. Table 4 presents adherence barriers that were differentially distributed across the types of regimen. Compared to participants taking STR, those taking single-dose MTR or multi-dose MTR were two to three times more likely to attribute missed doses to the scheduling barriers, and the experience of side-effects (i.e. “making me sick”), holding constant the level of self-efficacy at baseline, and the level of self-reported side-effects at each assessment. Participants taking multi-dose MTR were also more likely than those on STR to report feeling depressed (OR: 2.22, 95%CI: 1.03, 4.82) and confusion (OR: 6.10, 95%CI: 1.43, 26.13) as reasons for missing ART. No difference was found between STR and single-dose MTR regarding these two barriers. The confidence interval of confusion was relatively wide due to the small number of people on STR who reported confusion as a barrier. Trend analyses revealed significant gradient associations, in which increasing level of dosing complexity was associated with increasing likelihood of reporting each of the three

scheduling barriers ($p<0.001$). In contrast, a curvilinear relationship was found for side-effects as a barrier ($p=0.01$). The odds of attributing missed doses to side-effects was higher for people taking single-dose MTR than those taking STR or multi-dose MTR. This pattern of association was not apparent in the descriptive statistics averaged over time shown in Table 3, possibly because it was only manifested at time 1 and 2 but not at time 0. The reported frequency of each barrier tended to decline over the study period.

DISCUSSION

In this study we examined the prospective association between three types of ART dosing regimens and adherence among people living with HIV who were receiving care and taking 4 or less ART drugs. We further evaluated the differential patterns of adherence barriers in relation to the three types of regimens. Participants taking MTR reported more barriers than those taking STR in general. Specifically, people taking MTRs were more likely to report scheduling barriers, side-effect-induced barriers, and confusion over their prescription as reasons for missing a dose than those taking STR. These adherence barriers would be expected to be less common with a simpler medication regimen. Although individuals taking STR were least likely to attribute non-adherence to barriers related to scheduling and confusion as compared to those taking MTR, they were equally likely to attribute missed medications to logistical and life-style-related barriers. As one of the first studies to examine adherence barriers in the context of regimen simplification, these results have implications for developing adherence interventions.

We found that patients taking the simplest regimen (STR) were most likely to adhere, followed by single-dose MTR and multi-dose MTR, with no difference between the latter two. The lack of difference in adherence and viral suppression between single-dose MTR and multi-dose MTR counters the expectations that better adherence results from less frequent doses. The recent meta-analysis by Nachega et al. provided some evidence along the lines of ours as they found that adherence and viral suppression were both better for patients with lower pill burden, but adherence was only slightly higher for persons taking once-daily regimens than those taking twice-daily regimens, with no difference in viral suppression between the two [14]. It is however premature to claim that pill burden is more relevant to adherence than dosage frequency. At least one previous study provides the opposite evidence with once daily regimens being associated with better adherence than twice daily regimens, whereas no difference in adherence was found between STR and single-dose MTR [24]. The difference in measurement (visual analogue scale vs. pill counts) and study populations (treatment naïve vs. all) may partially account for the contradictory findings between Buscher's study and ours, because there has been evidence showing that the effect of dosage frequency on adherence is more pronounced in treatment-naïve patients [48]. Additional evidence is needed to sort out the relative importance of pill burden and dosage frequency in patients with different treatment profiles.

As one of the key strategies to improve adherence, regimen simplification alone does not completely resolve non-adherence. Even among patients taking the simplest regimen (STR), non-adherence still persists for some patients, typically around 20–25% across different studies [49, 50]. In fact Langebeek and colleagues have shown that among different

predictors for non-adherence, daily dosing frequency and pill burden only have small to very small effect sizes compared with other adherence barriers [51].

In the current study we have attempted to identify adherence barriers keyed to dosing features in order to specify what adherence barriers are associated with regimen types. It was found that people taking STR were less likely to attribute their missed medication to scheduling barriers. These barriers include things like forgetfulness and being tied up with unexpected events, etc. Forgetting to take pills and being away from medicine during dose time are two of the commonly cited reasons for missing medications. As Senkomago and colleagues have pointed out, addressing these two barriers would be an effective intervention in enhancing adherence for a subset of patients [52]. Additionally, the significant gradient relationship further implies the role of regimen simplification in overcoming scheduling barriers to adherence. These findings suggest that reducing dose frequencies may be a promising approach to improve adherence among patients who experience multiple competing demands.

Apart from scheduling barriers, people taking STR were also less likely to report side-effects as a barrier, even after controlling for self-reported side-effects at each assessment. Experience of side-effects may not be the most prevalent barrier, but it is not negligible [53]. Our findings imply that STR may be a potential solution for patients who have trouble adhering to ART due to severe drug reactions. A counter-intuitive finding is the curvilinear relationship where single-dose MTR was most strongly associated with attributing non-adherence to side-effects. It might be assumed that the intensity of side-effects was alleviated by the pharmacology of multi-dose MTR versus single-dose MTR. Yet we cannot rule out the possibility of a spurious association, especially given that this pattern was not consistent across time. We encourage more studies to validate this finding, and to explore patterns of association between dosing complexity and barriers to adherence.

It was also found that patients taking STR were less likely to attribute their missed doses to “feeling overwhelmed or depressed”. This association persisted after controlling for baseline level of depressive symptoms. Previous research has suggested that complex ART regimens may increase the level of patients’ anxiety and subsequent lack of consistent adherence [54]. The current findings lend partial support to this claim by showing that more complicated regimens were associated with higher frequency of reporting anxious feelings as the cause for missed medication, irrespective of pre-existing depression. Like most of the perceived barriers to adherence included in this study, the association may only imply prescription of simpler regimens to patients experiencing certain barriers.

Despite having advantages in adherence, patients taking STR were equally as likely to attribute missed doses to fear of disclosure, logistic barriers and substance use. Both quantitative and qualitative studies have found that fears of inadvertent disclosure of HIV status have prevented patients from taking medications in the presence of other people [55, 56]. The current study once again found evidence consistent with these findings. It was not surprising that dosing complexity cannot reduce the frequency of disclosure concerns as the barrier because it is essentially a stigma-related problem. As Van Tam and colleagues pointed out, some patients skip medicine not because they forget, but because they simply

cannot afford the consequence of disclosing HIV status to others [55]. HIV-related stigma acts on both inter and intra-personal levels and may detrimentally affect multiple aspects of HIV care, including disclosing HIV status, gaining social support, accessing resources, and attaining mental well-being [57–59]. Impairment in any of these aspects could lower HIV adherence. Although reduced dosing frequency may have the potential to lower the risk of identity exposure, additional strategies are needed to counter the broader impact of stigma on HIV treatment and adherence. Effective strategies may include community mobilization to integrate stigma reduction in health sectors, promotion of social support in local communities, and social advocacy to foster positive changes in laws and policies [54, 60].

In contrast to stigma, logistical barriers such as being unable to get to the pharmacy and not having the right pill may be less complex. It is not known if our participants failed to get to the pharmacy due to any specific reason. But a common logistical barrier to successful adherence is lack of transportation to a pharmacy [61]. If this was the case, strategies such as home-delivery of medicine and improved community support might overcome this barrier [55]. Also of note is that substance use, including alcohol and drug use, constitutes another barrier beyond the domain of dosing complexity. As one of the strongest predictors for non-adherence [51], substance use was identified as a barrier to adherence across patients on different regimens to a similar extent. Previous evidence has showed that treating addictions could significantly improve ART adherence and HIV viral suppression [62].

The current study demonstrates that regimens with different dosing complexity may be associated with different adherence barriers. Yet it is unclear, given the observational design, which causal direction is implied by this association, or whether a bidirectional association might be operating. The bi-directionality of the adherence-regimen-relationship is compatible with the flow of adherence management in a clinical setting. Patients' adherence and reported barriers to adherence may influence prescribing decisions regarding the choice of ART regimen. For example, patients who complain that they forget their medications or are confused over when to take their medications may be prescribed simpler regimens [63]. We believe further analysis of the dynamic interaction between barriers associated with regimens and clinicians' decisions of which regimens to prescribe would be informative to the development of tailored adherence interventions. Examination of the alternative direction can be achieved by collecting prospective data on changes in regimens given initial adherence level, or retrospective data related to previous adherence characteristics that have affected current regimen selection.

This study was not conducted without limitations. Firstly, a convenience sample limits the generalizability of the findings. Secondly, self-reported measures of adherence barriers may be subject to recall and social desirability bias. Thirdly, the list of barriers provided in the study is not open-ended and thus cannot be considered comprehensive. Lastly, despite the temporal ordering of our measures, causal inference based on results from the current study should be avoided. With these caveats in mind, the findings from the current study provide implications to the design of adherence interventions.

A known relationship between dosing complexity and certain barriers might provide a rapid assessment of a patient's potential of being adherent. Moreover, with an established profile

of regimen and associated barriers, clinicians could generate more proactive adherence interventions and assemble packages of adherence strategies for patients with higher efficiency. On the other hand, barriers that still persist in the face of regimen simplification deserve attention across all patients regardless of dosing complexity. In conclusion, regimen simplification should be encompassed within a broader array of strategies that address personal, social and structural barriers to adherence in order to maximize its potential benefits.

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Table 1

Sample characteristics by adherence and viral load status

	Total (N=750)	Adherence[a]			Viral load		
		<85% (n=226)	≥85% (n=518)	*p*[b]	Undetectable (n=549)	Detectable(n=163)	*p*[c]
Regimen type (n,%)				*0.043*			*<0.001*
Single Tablet Regimen	166(22.13)	39(23.49)	127(76.51)		143(91.08)	14(8.92)	
Single-dose Multi-Tablet Regimen	300(40.00)	92(31.08)	204(68.92)		200(70.67)	83(29.33)	
Multi-dose Multi-Tablet Regimen	284(37.87)	95(33.69)	187(66.31)		206(75.74)	66(24.26)	
Other characteristics (n,%)							
Age [21–72 yrs]				*0.011*			*<0.001*
21–30 yrs	51(6.81)	23(46.94)	26(53.06)		25(56.82)	19(43.18)	
31–40 yrs	95(12.68)	35(36.84)	60(63.16)		66(72.53)	25(27.47)	
41–50 yrs	328(43.79)	89927.38)	236(72.62)		235(75.56)	76(24.44)	
51–72 yrs	275(36.72)	78(28.47)	196(71.53)		223(84.15)	42(15.85)	
Gender (female)				*0.560*			*0.033*
Male	531(70.99)	161(30.61)	365(69.39)		379(74.90)	127(25.10)	
Female	217(29.01)	65(30.09)	151(69.91)		168(82.35)	36(17.65)	
Ethnicity				*0.219*			*0.334*
African American	679(90.53)	207(30.76)	466(69.24)		499(77.60)	144(22.40)	
Other	71(9.47)	19(26.76)	52(73.24)		50(72.46)	19(27.54)	
Years since infection				*0.963*			*0.162*
≤10 years	228(30.60)	68(30.09)	158(69.91)		156(72.56)	59(27.44)	
10–20 years	300(40.27)	95(31.77)	204(68.23)		226(79.02)	60(20.98)	
≥20 years	217(29.13)	63(29.30)	152(70.70)		164(79.23)	43(20.77)	
HIV symptoms				*0.002*			*0.014*
0–3 symptoms	403(53.73)	104(26.00)	300(74.00)		303(79.74)	77(20.26)	
4–6 symptoms	183(24.40)	62(33.88)	123(66.12)		137(79.19)	36(20.81)	
7–14 symptoms	164(21.87)	60(37.27)	100(62.73)		109(68.55)	50(31.45)	
Depressive symptoms				*0.002*			*0.111*
CESD(≤16)	406(54.13)	103(25.50)	301(74.50)		305(79.43)	79(20.57)	
CESD(>16)	344(45.87)	123(36.18)	217(63.82)		244(74.39)	84(25.61)	

	Total (N=750)	Adherence[a]			Viral load		
		<85% (n=226)	≥85% (n=518)	p[b]	Undetectable (n=549)	Detectable(n=163)	p[c]
Self-efficacy [0–10]				*0.086*			*0.355*
Low (<6)	161(21.50)	59(37.34)	99(62.66)		118(75.64)	38(24.36)	
Medium (6–8)	204(27.24)	65(31.86)	139(68.14)		144(74.23)	50(25.77)	
High (>8)	384(51.27)	102(26.70)	280(73.30)		287(79.28)	75(20.72)	
Side effects				*0.003*			*0.055*
None	513(69.22)	143(27.29)	381(72.71)		394(72.29)	106(21.20)	
Mild	151(20.46)	50(36.23)	88(63.77)		107(80.45)	26(19.55)	
Moderate	56(7.53)	18(33.33)	36(66.67)		34(64.15)	19(35.85)	
Severe	21(2.79)	9(50.00)	9(50.00)		10(66.67)	5(33.33)	

Note:

[a] Data presented are the average of two adherence assessments

[b] *p*-value from Rao–Scott corrected Pearson χ^2 test;

[c] *p*-value from Pearson Chi-square test; CESD is the Center for Epidemiologic Studies Depression Scale

Table 2

Association of regimen characteristics with adherence or viral load

	≥85% Adherence		Undetectable viral load	
	OR(95%CI)	**AOR (95%CI)**	**OR(95%CI)**	**AOR(95%CI)**
Dosing complexity				
Single Tablet Regimen	1.00	1.00	1.00	1.00
Single-dose Multi-Tablet Regimen	0.69(0.48,0.99) *	0.73(0.50,1.05)	0.24(0.13,0.43) ***	0.23(0.12,0.42) ***
Multi-dose Multi-Tablet Regimen	0.62(0.44,0.89) **	0.62(0.43,0.90) *	0.31(0.17,0.57) ***	0.30(0.16,0.57) ***
Time-invariant covariates				
Age	---	1.02(1.01,1.04) **	---	1.05(1.02,1.07) ***
Female	---	1.11(0.82,1.49)	---	1.61(1.04,2.49) *
HIV symptoms	---	0.95(0.91,0.99)	---	0.99(0.93,1.05)
CESD	---	0.99(0.98,1.01)	---	0.99(0.98,1.01)
Self-efficacy		1.05(0.98,1.13)		1.04(0.94,1.15)
Time-variant covariates				
First assessment	1.00	1.00	---	---
Second assessment	0.92(0.77,1.10)	0.90(0.75,1.08)	---	---
Side effects	---	0.87(0.74,1.03)	---	0.89(0.70,1.14)

Note:

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$;

OR: odds ratio; AOR: adjusted odds ratio; CESD is the Center for Epidemiologic Studies Depression Scale.

Table 3

Frequency of Reporting Each Barrier to Adherence among People on Regimens with Different Level of Complexity

	Scheduling barriers					*Substance-induced barriers*			*Logistic barriers*			*ART-induced barriers*		*Other barriers*	
	Forgot	**Did not have the right pill with me**	**Too busy**	**Something unexpected came up**	**Slept through dose time**	**Too drunk or high**	**Have been drinking**	**Have been using drugs**	**Ran out of pills**	**Couldn't get to the pharmacy**	**Couldn't afford**	**Making me sick**	**Felt depressed and overwhelmed**	**Got confused with what to take**	**Did not want someone to see me take them**
	n(%)[a]	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**	**n(%)[a]**
Single Tablet Regimen	45(15.36)	30(20.69)	33(14.67)	33(15.21)	28(19.71)	7(20.00)	8(18.18)	2(18.18)	12(16.44)	5(12.50)	3(10.71)	6(9.06)	9(12.86)	2(5.13)	8(15.69)
Single-dose Multi-Tablet Regimen	113(38.57)	51(35.17)	85(37.78)	90(41.47)	47(33.10)	17(48.57)	22(50.00)	5(45.45)	33(45.21)	18(45.00)	15(53.57)	29(43.94)	30(42.86)	14(35.90)	22(43.14)
Multi-dose Multi-Tablet Regimen	135(46.08)	64(44.14)	107(47.56)	94(43.32)	67(47.18)	11(31.43)	14(31.82)	4(36.36)	28(38.36)	17(42.50)	10(35.71)	31(46.97)	31(44.29)	23(58.97)	21(41.18)
p[b]	*<0.001*	*0.20*	*<0.001*	*0.01*	*0.06*	*0.32*	*0.45*	*0.48*	*0.51*	*0.63*	*0.23*	*0.02*	*0.06*	*0.02*	*0.38*

Note:

[a]Number of people reporting each barrier was averaged across three assessments and column percentages were reported for each barrier;

[b]*p*-value from Rao Scott corrected Pearson test.

Table 4

Associations of Reported Barriers to Adherence by Regimen Complexity among People on Non-salvage Treatment

	Scheduling barriers			ART-induced barriers		Other barrier
	Forgot	**Too busy**	**Something unexpected came up**	**Making me sick**	**Felt depressed and overwhelmed**	**Got confused with what to take**
	OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Dosing complexity						
STR	1.00	1.00	1.00	1.00	1.00	1.00
Single-dose MTR	1.66(1.14, 2.42)**	1.86(1.21, 2.88)**	1.70(1.10, 2.63)*	3.49(1.38, 8.79)**	2.11(0.98, 4.54)	4.26(0.93, 19.63)
Multi-dose MTR	2.13(1.47, 3.08)***	2.46(1.61, 3.74)***	1.78(1.16, 2.74)**	2.82(1.15, 6.92)*	2.22(1.03, 4.82)*	6.10(1.43, 26.13)*
***P*-value for Trend**[1]	*<0.001*	*<0.001*	*0.013*	*0.010*	*0.062*	*0.005*
Time-invariant covariates						
CES-D	1.01(1.00, 1.02)*	1.00(0.99, 1.01)	1.01(0.99, 1.02)	1.01(0.98, 1.03)	1.05(1.03, 1.07)***	1.01(0.98, 1.04)
Self-efficacy	0.89(0.83, 0.95)***	0.86(0.80, 0.93)***	1.33(1.13, 1.56)**	0.85(0.75, 0.96)*	0.89(0.78, 1.00)	0.99(0.83, 1.20)
Time-variant covariates						
Time 0	1.00	1.00	1.00	1.00	1.00	1.00
Time 1	0.84(0.66, 1.07)	0.75(0.58, 0.98)*	0.80(0.60, 1.05)	0.72(0.45, 1.13)	0.73(0.45, 1.21)	0.62(0.32, 1.23)
Time 2	0.89(0.70, 1.13)	0.81(0.62, 1.04)	0.85(0.65, 1.10)	0.56(0.34, 0.90)*	0.77(0.46, 1.28)	0.84(0.44, 1.64)
Side-effect	1.23(1.07, 1.41)**	0.86(0.80, 0.93)*	1.3(1.13, 1.56)***	2.52(2.01, 3.17)***	1.52(1.15, 2.01)**	1.85(1.33, 2.57)***

[1] Testing gradient or curvilinear relationship between dosing complexity and barriers;

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$;

STR: single-tablet regimen; MTR: multi-tablet regimen; CES-D: Center for Epidemiologic Studies Depression Scale.