The Impact of Once-Nightly Versus Twice-Daily Dosing and Baseline Beliefs About HAART on Adherence to Efavirenz-Based HAART Over 48 Weeks: The NOCTE Study

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Objective: To determine the impact of once-nightly versus twice-daily dosing and beliefs about highly active antiretroviral therapy (HAART) on adherence to efavirenz-based HAART in antiretroviral-naive patients.

Methods: A multicenter, open-label, 48-week, randomized controlled trial. Participants were randomized to receive once nightly didanosine plus lamivudine, or twice-daily combivir (zidovudine plus lamivudine) both in combination with efavirenz. Medication Event Monitoring Systems were used to compile drug-dosing histories. Beliefs about HAART (necessity and concerns) were measured at baseline using validated questionnaires. Perceptions of HAART intrusiveness were assessed after 4 weeks.

Results: Eighty-seven patients were randomized (44 once-nightly and 43 twice-daily). Overall adherence was higher among the once-nightly arm ($P = 0.0327$). Eighty-one percent once-nightly and 62% twice-daily patients persisted with treatment for 48 weeks ($P = 0.0559$). Regimen execution was similar between both arms. Participants were significantly less likely to persist with HAART if their initial concerns about HAART were high relative to their perceived need for treatment ($P = 0.025$).

Conclusions: The difference in adherence observed between once-nightly and twice-daily dosing was driven by a difference in persistence with treatment. Psychological preparation for starting HAART should address patients' perceptions of necessity for HAART and concerns about adverse effects to maximize persistence with treatment.

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INTRODUCTION

Early antiretroviral Therapy (HAART) regimens were extremely demanding, frequently involving 3 or 4 daily doses of drugs, a high pill burden and food restrictions, or requirements for different types of drugs. As the importance of adherence for realising the benefits of HAART became evident,[1–3] less complex treatment schedules have become available. There are now several safe and efficacious low pill burden, once-daily treatment regimens.[4–7]

Many patients prefer once-daily therapy,[8] furthermore, the results of a recent meta-analysis of 11 studies including a total of 3029 subjects showed modest but significant benefit [+2.9%, 95% confidence interval (CI): 1.0% to 4.8%] of once versus twice-daily therapy for adherence.[9] This advantage of once-daily dosing for adherence has been shown across a variety of antiretroviral regimens including better pill counts[10] and higher self-reported adherence[11] among those receiving once-daily efavirenz-based regimens.

Even when HAART regimens are relatively simple, nonadherence is likely to remain a problem if patients have perceptual barriers to their treatment. The objective complexity of the treatment regimen (once- versus twice-daily dosing) may not be as influential for adherence as the individual patient's perception of the regimen and the degree to which it fits in or "intrudes" in their daily routine.[12] Other beliefs associated with nonadherence to antiretroviral therapy[13–23] can be grouped under 2 categories as follows: perceptions of personal necessity for treatment and concerns about potential adverse effects.[24,25] Low rates of adherence to medication across a variety of long-term illnesses, including HIV, have been associated with patients' doubts about their personal necessity for treatment, strong concerns about adverse effects, and high concerns relative to perceived need for treatment.[26–29]

The primary objective of this study was to examine the potential benefit of once-nightly versus twice-daily nucleoside reverse transcriptase inhibitor backbone on electronically monitored adherence to efavirenz-containing HAART among previously treatment-naive patients. The secondary objective was to examine associations between beliefs about HAART and adherence to once-nightly and twice-daily HAART regimens.

METHODS

Design and Treatments

NOCTE was a multicenter open-label randomized controlled trial comparing adherence with 2 treatment regimens:

Once Nightly Regimen

1 × Didanosine (DDI) enteric-coated (EC) capsule 400 mg (250 mg if weight <60 kg), 2 × lamivudine (3TC) 150 mg tablet, 1 × efavirenz (Sustiva) 600 mg tablet.

Twice Daily Regimen

Combivir (zidovudine 300 mg + 3TC 150 mg): 1 tablet twice daily, 1 × efavirenz 600 mg tablet taken nightly.

Randomization

Participants were randomized on a one-to-one basis to receive the once-nightly or twice-daily regimen. The sequential allocation of consecutive patients was predetermined by random number tables.

Population

Patients were recruited from 9 sites across the United Kingdom. Inclusion criteria were being HIV positive, age >18 years, able to give informed consent, being antiretroviral naive, with CD4 lymphocyte count <350 cells per cubic millimeter and/or HIV viral load >20,000 copies per milliliter and/or AIDS-defining illness, and likely to live more than 2 years with antiviral therapy. Exclusion criteria were alkaline phosphatase or hepatic transaminases >5 times upper limit of normal, neutrophil count of $<0.5 \times 10^9$/L, medical history of pancreatitis, prior exposure to any antiretroviral agent, pregnancy or female patient trying to become pregnant, patients who do not self-medicate, those unwilling or unable to use Medication Event Monitoring Systems (MEMS) monitors, patients who are unable to comprehend the written questionnaires with the help of a clinician or interpreter, and those needing medication other than their proposed antiretrovirals that is either more than 3 additional tablets or capsules per day, that cannot be taken at the same time as their antiretrovirals, or that may have a significant pharmacological interaction with their proposed antiretrovirals.

Endpoints and Their Measures

Adherence

Patient adherence to prescribed therapy was defined as the extent to which patients' drug-dosing histories conformed, or not, to their corresponding prescribed drug-dosing regimen.[30] The concept of patient adherence can be broken into 2 main components as follows[31,32]: persistence with treatment and execution of the dosing regimen.

Persistence With HAART

Defined as the length of time during which the medication is taken, that is, the time from the first-taken dose to the last-taken dose, measured using MEMS, as described below.

Execution of the Dosing Regimen

Measures how closely the patient's dosing history corresponds to the prescribed drug-dosing regimen when he/she is still engaged with the therapy. Regimen execution was summarized by reporting the proportion of prescribed doses taken. In addition, regimen execution was summarized as a binary time series where for each consecutive day that the patient was still engaged with the treatment, the variable indicated whether or not the patient had taken at least the prescribed number of doses.

MEMS 6 (child-resistant) monitors (AARDEX Ltd, CH-6302 Zug; Switzerland) were used to collect 3TC drug-dosing histories. All monitored medications were dispensed in specific MEMS compatible bottles. The MEMS monitor contains a liquid crystal display (LCD) indicating to the patient the number of times the drug container has been opened that day and the time since last intake. Data from the MEMS monitor was downloaded 4, 12, 24, 36, and 48 weeks after each patient initiated treatment to a centralized secured database. Adherence data were not available to the clinician or patient until after the patient had completed the study.

Patients were not excluded from the study in the event of regimen change. In this case, the nearest equivalent to the 3TC component was subjected to electronic monitoring for adherence.

Beliefs About HAART

Beliefs about HAART were measured using the Beliefs about Medicines Questionnaire–HAART specific version.[25,28] The Beliefs about Medicines Questionnaire–HAART comprises 2 scales: a HAART necessity scale and a HAART concerns scale. The HAART necessity scale consists of 8 items assessing individuals' beliefs about their personal need for HAART for controlling their HIV, maintaining their health, and preventing illness, whereas the HAART concerns scale consists of 11 items which bring together a range of separate concerns about the potential adverse effects of HAART that have been identified across studies (eg, concerns about side effects, beliefs that using the medication is disruptive, embarrassment about taking treatment, concerns about potential long-term effects, and dependence).[28,29,33] Participants were presented with a series of statements about which they were told "these are statements that other people have made about combination therapy." They were then asked to rate their level of agreement with each item on a scale, where responses ranged from strongly agree (scored 5) to strongly disagree (scored 1). Scores for the individual items within each scale were summed to give a total scale score. A mean scale score was computed by dividing each scale by the number of items, giving a range of 1–5 for both necessity and concerns scales. This was done to facilitate comparison of scores between scales and to calculate a necessity–concerns differential (NCD) by subtracting concerns scores from necessity scores (scores range from −4 to 4). The NCD score can be thought of as a crude indicator of the way the individual rates their perceived need for the treatment relative to their concerns about taking it.

HAART Intrusiveness Scale

Perceived intrusiveness of the HAART regimen was assessed using the HAART intrusiveness scale.[34] This scale consists of 10 items addressing the degree to which HAART is perceived to interfere with 10 aspects of daily life (eg, social life, ability to work, and relationships). Participants indicate the degree to which HAART interferes with each area on a scale from 1 to 5, where 1 indicates low interference and 5 indicates high interference. A total score was computed by adding up responses to each item. For comparison with other scales, an average score was computed by dividing the total score by the number of items. Possible responses ranged from 1 to 5 with higher scores indicating higher perceived intrusiveness.

Clinical and Demographic Data

Demographic data were collected by questionnaire at the screening visit. This included gender, date of birth, self-assigned ethnicity, country of birth, level of education, employment status, living situation (alone or with others), and the most likely way in which the participant contracted HIV. Clinical data [AIDS-defining illness, CD4 count (cells/mm^3), and viral load (copies/mL)] were recorded at baseline (day 0) and each follow-up assessment.

Clinical Outcomes Assessment

Viral load was assessed at 4, 12, 24, 36, and 48 weeks after each patient initiated treatment. This used the locally available method in each case. Viral load failure was defined as viral load $>$50 copies per milliliter at 48 weeks.

Procedure

Questionnaires were completed in the clinic before patients initiated treatment (baseline) and each subsequent time point (4, 12, 24, 36, and 48 weeks). For this primary analysis of the study, only baseline scores (4 week scores for the HAART intrusiveness scale) were used. Any changes to the regimen and adverse events experienced were also recorded. Drug-dosing histories were electronically compiled over the entire course of the study.

Power and Statistical Analysis Plan

The study was originally powered to show a difference in percentage of patients with viral load control, resulting in a sample size of 320 patients. Due to poor recruitment, it was curtailed and redesigned for an adherence primary endpoint based on longitudinal assessment of the drug-dosing history as compiled by MEMS monitors. Using the longitudinal approach to analyze the adherence data, a sample size of 43 patients per group achieves a power of 80% to detect a difference of minimum 16% in adherence (intracluster correlation between daily binary adherence outcome is assumed to be 0.3).

Analysis was planned to be primarily on an intention to treat basis. Where patients needed to change medication because of adverse events, drug substitution was within the principle of their randomization, that is, once or twice daily if possible. Substitution of drugs was at the treating physician's discretion. Drugs were dispensed from routine commercial supplies.

Statistical Methods

Persistence was defined as the time, in days, between the first dose intake until the day of treatment discontinuation. Kaplan–Meier curves were used to display persistence over time. Persistence was censored if there was no evidence of a treatment discontinuation at the end of the observation period. The log-rank test was used to compare persistence between randomized groups. A Cox regression model was used to evaluate the relationship between persistence and explanatory variables. Patients without MEMS data available were considered nonpersistent from day 1.

Quality of drug regimen execution was defined as a binary time series where, for each consecutive day that the patient was still engaged with the treatment, the variable indicated whether or not the patient had taken at least the prescribed number of doses. Marginal longitudinal logistic models (Generalized Estimating Equations) were used to investigate the relationship between execution of the drug-dosing history and explanatory variables.

Adherence to treatment, the combination of persistence with treatment and execution of the dosing regimen, was summarized by plotting, for each consecutive day, the percentage of patients who were still persistent and had taken at least the prescribed number of doses. Marginal longitudinal logistic models (Generalized Estimating Equations) were used to compare percentages of patients between groups over time.

The prevalence of adverse events was compared between groups using a χ^2 test.

All statistical tests were considered significant at the 5% level.

RESULTS

Eighty-seven patients from 9 sites [Brighton: 26 (29.9%), Birmingham Heartlands: 17 (19.5%), Kings College London: 4 (4.6%), Birmingham Whittall Street: 8 (9.2%), Newcastle General: 14 (16.1%), Leicester 12 (13.8%), St. Mary's London 3 (3.4%), Oxford 2 (2.3%), Newham 1 (1.1%)] were enrolled in the study and randomly assigned to receive once-nightly (n = 44) or twice-daily (n = 43) HAART. Adherence was monitored for 336 days (48 weeks).

Sample Characteristics

Table 1 displays the characteristics of the full sample (n = 87) and among each randomized group. There were no significant differences between those in once-nightly and twice-daily groups in terms of any baseline characteristic.

Adverse Events

The majority of participants [83 of 87 (95.4%)] experienced at least 1 recorded adverse event during the course of the study [41 of 44 (93.2%) once-nightly and 42 of 43 (97.7%) twice-daily]. In total, 624 adverse events were recorded. Two hundred and three (32.5%) adverse events were deemed to be possibly, probably, or definitely linked to the drug regimen. Of the 624 recorded adverse events, 36 (5.8%) were coded as serious adverse events. Eleven of 44 (25.0%) of

TABLE 1. Baseline Characteristics of the Sample

Variable	Full Sample (n = 87)	Once-nightly (n = 44)	Twice-daily (n = 43)
Gender n (%)			
Male	71 (81.6)	38 (86.4)	33 (76.7)
Female	16 (18.4)	6 (13.6)	10 (23.3)
UK born n (%)			
Yes	46 (52.9)	23 (52.3)	23 (53.5)
No	41 (47.1)	21 (47.7)	20 (46.5)
Ethnicity n (%)			
African	31 (35.6)	14 (31.8)	17 (39.5)
White British/Irish	49 (56.3)	25 (56.8)	24 (55.8)
Other	7 (8.1)	5 (11.4)	2 (4.7)
Employed n (%)			
Yes	61 (70.1)	30 (68.2)	31 (72.1)
No	26 (29.9)	14 (31.8)	12 (27.9)
Education n (%)			
Beyond secondary school	46 (52.9)	22 (50.0)	24 (55.8)
Primary or secondary school	40 (46.0)	21 (47.7)	19 (44.2)
Missing data	1 (1.1)	1 (2.3)	0 (0.0)
Living alone n (%)			
Yes	31 (35.6)	16 (36.4)	15 (34.9)
No	56 (64.4)	28 (63.6)	28 (65.1)
MSM n (%)			
Yes	38 (43.7)	18 (40.9)	20 (46.5)
No	47 (54.0)	24 (54.5)	23 (53.5)
Missing data	2 (2.3)	2 (4.5)	0 (0.0)
AIDS diagnosis n (%)			
Yes	19 (21.8)	6 (13.6)	13 (30.2)
No	68 (78.2)	38 (86.4)	30 (69.8)
Age, mean (SD)	40.9 (9.4)	41.3 (10.5)	40.6 (8.2)
CD4 count (cells/mm^3), median (range)	180 (10–611)	184 (10–611)	180 (0–348)
Viral load (copies/mL, $\log_{10}$), median (range)	5.1 (2.9–6.0)	5.1 (4.0–6.0)	5.0 (2.9–6.0)
HAART necessity score, median (range)	4.2 (2.7–5.0)	4.2 (2.7–5.0)	4.2 (2.7–5.0)
HAART concerns score, median (range)	2.7 (1.4–4.14)	2.7 (1.4–3.7)	2.7 (1.6–4.14)
HAART necessity–concerns differential score, median (range)	1.4 (−0.6 to 3.4)	1.5 (−0.5 to 3.4)	1.4 (−0.6 to 3.1)
HAART intrusiveness scale score, median (range)	1.8 (1.0–3.6)	1.8 (1.0–2.8)	1.7 (1.0–3.6)

the once-nightly group and 11 of 43 (25.6%) of the twice-daily group experienced at least 1 serious adverse events (P = 0.960). Two patients (1 in each group) died over the course of the study: the cause of death was Burkitts lymphoma in the twice-daily group and multiorgan failure in the once-nightly group. Both the Burkitts lymphoma and multiorgan failure were deemed unlikely to be related to the treatment regimen.

Regimen Changes

Changes to the drug regimen were made for 15 participants [5 changed DDI (to tenofovir (3), abacavir (1), and an unspecified drug (1)], 7 changed efavirenz to nevirapine, 3 changed combivir to 3TC and abacavir (1), 3TC and stavudine (1), and 3TC and tenofovir (1)]. Four patients swapped from one trial arm to the other: 2 swapped from once daily to twice daily, and two from twice daily to once daily. One participant later swapped again, from twice daily to once daily. These participants were included in the adherence analysis on an intention to treat basis.

Patterns and Predictors of Adherence Over 48-Week Follow-Up

Adherence

There was a significant effect of regimen on overall adherence, with greater adherence among patients randomized to the once-nightly arm (P = 0.0327; Fig. 1).

Persistence

The percentage of patients persisting with treatment to 48 weeks (336 days) was 81% in the once-nightly arm and 62% in the twice-daily group (Fig. 2) (log-rank test: P = 0.0559). There was a significant association between persistence and virologic outcome, with patients defined as nonpersistent being less likely to achieve undetectable viral load at 48 weeks ($P < 0.001$). Nonpersistent patients had significantly lower NCD scores (P = 0.025), suggesting that their initial concerns about HAART tended to outweigh their perceived need for treatment. There was a trend for higher

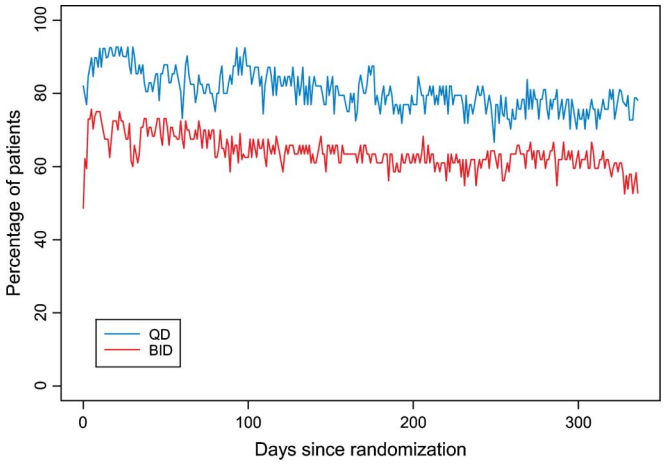

FIGURE 1. Primary outcome: adherence to HAART treatment summarized, on each consecutive day, as the percentage of patients who persist with HAART treatment and take at least the prescribed number of doses.

initial concerns about HAART among patients who were subsequently nonpersistent ($P = 0.066$). Nonpersistence was associated with younger age ($P = 0.012$), African ethnicity ($P = 0.013$), and female gender ($P = 0.0084$). Table 2 shows Hazard ratios and 95% CI.

Quality of Execution

A mean (SD) of 94.6% (10.2%) and 95.7% (11.1%) of prescribed doses were taken in once-nightly and twice-daily groups, respectively. Over time, of the percentage of participants who opened their MEMS monitors, at least the prescribed number of times each day (once for patients randomized to once-nightly and twice for twice-daily regimens), was stable over 48 weeks. There was a significant "weekend effect" [odds ratio (OR) = 0.79; 95% CI = 0.72 to 0.87, $P = 0.0002$], with doses being more likely to be missed on Fridays, Saturdays, and Sundays compared with Monday to Thursday. This effect was not moderated by regimen frequency. On average, of the patients who were still engaged with the dosing regimen, 92% took at least the prescribed number of doses.

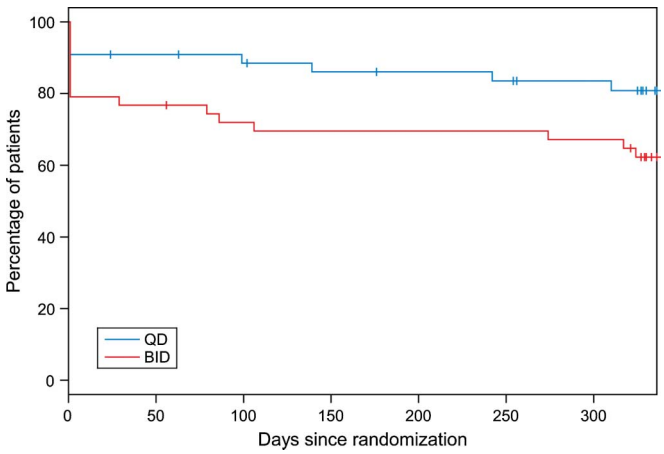

FIGURE 2. Persistence with HAART treatment: Kaplan–Meier estimates of the percentage of patients who persist with HAART treatment more than 48 weeks.

Missing a single once-nightly or twice-daily dose could however have different clinical consequences.[35,36] Figure 3 shows the frequency of delayed doses within (X axis) and between patients (Y axis). Almost 50% of the patients missed a single dose at least once a month (12 in 48 weeks); that is, had an interval since last dose of over 18 hours in twice-daily or over 30 hours in once-nightly. However, among twice-daily subjects, an interval of more than 30 hours since the last dose is reached after missing at least 2 consecutive doses. This happened at least once a month in only 14% of the patients. The difference in the percentage of patients who increased their interdose intervals by missing 1 or 2 consecutive doses could result in different clinical outcomes, especially for drugs with limited forgiveness.[37] The percentage of patients with drug holidays (treatment interruptions >78 hours) was similar between both groups.

There was no significant effect of regimen (once-nightly versus twice-daily) on treatment execution (OR = 1.03; 95% CI: 0.47 to 2.27; $P = 0.93$) (Fig. 4). The single predictor of regimen execution in the study was the patient's living situation, with those who lived alone significantly less likely to execute their treatment correctly than those who lived with at least 1 other person ($P = 0.0223$). The quality of regimen execution was not associated with beliefs about HAART [necessity ($P = 0.28$), concerns ($P = 0.16$), or the NCD score ($P = 0.15$)] or the degree to which HAART was perceived to interfere with daily activities ($P = 0.65$). Treatment execution was not associated with viral load suppression at 48 weeks ($P = 0.82$). Table 2 shows OR and 95% CI.

DISCUSSION

We found a significant benefit of once-nightly over twice-daily dosing for adherence to the nucleoside reverse transcriptase inhibitor component of efavirenz-based HAART among previously antiretroviral-naive individuals. This finding corroborates those of other studies showing greater adherence to once-daily versus twice-daily efavirenz-based regimens both among antiretroviral-naive individuals[10] and those randomized to switch from twice-daily to once-daily regimens.[11,38,39] The effect of regimen on adherence was mainly driven by a difference in persistence, with 81% of the once-nightly group persisting with treatment to 48 weeks compared with 62% of the twice-daily group. This is in line with the results of larger study demonstrating the increased durability of once-daily regimens among previously antiretroviral-naive patients.[40]

The absence of a significant association between dosing frequency and regimen execution is in contrast to the findings of previous studies.[38,39,41] There are several possible reasons for this. First, the once-nightly group were required to take 4 pills per day, whereas the twice-daily group were required to take only 3 pills per day. Previous studies have shown an inverse relationship between the number of pills per day and adherence.[42] Second, the once-daily regimen included DDI

TABLE 2. Associations Between Adherence (Treatment Persistence and Regimen Execution), Baseline Clinical, and Demographic Variables and Beliefs About HAART

	Persistence With Treatment			Execution of the Dosing Regimen		
	HR	95% CI	*P*	OR	95% CI	*P*
Regimen (once-nightly)	0.99	0.98 to 1.00	0.0536	1.03	0.47 to 2.27	0.93
Age	0.93	0.88 to 0.98	0.0120	1.03	0.99 to 1.07	0.17
Gender (female)	3.14	1.34 to 7.38	0.0084	1.31	0.62 to 2.78	0.47
Ethnicity (white British/Irish)	—	—	—	—	—	—
Ethnicity (African)	2.85	1.24 to 6.53	0.013	0.85	0.39 to 1.83	0.67
Education (beyond secondary school)	0.53	0.24 to 1.20	0.13	0.85	0.36 to 1.99	0.71
Employment (employed)	1.34	0.53 to 3.38	0.53	1.56	0.69 to 3.52	0.28
MSM (yes)	0.61	0.26 to 1.46	0.27	0.87	0.41 to 1.85	0.71
Living alone (yes)	0.64	0.26 to 1.52	0.32	0.43	0.21 to 0.89	0.0223
AIDS diagnosis (no)	0.99	0.37 to 2.66	0.99	1.20	0.42 to 3.47	0.73
Viral load ≤50 copies/mL (yes)	0.76	0.67 to 0.86	0.0001	0.87	0.27 to 2.83	0.82
CD4 count (cells/mm^3)	1.00	1.00 to 1.01	0.46	0.99	0.99 to 1.00	0.23
Viral load ($\log_{10}$)	0.94	0.52 to 1.67	0.82	0.93	0.60 to 1.46	0.76
HAART necessity score*	0.58	0.30 to 1.12	0.11	1.37	0.77 to 2.43	0.28
HAART concerns score†	2.03	0.95 to 4.31	0.066	0.60	0.30 to 1.21	0.16
HAART necessity–concerns differential score‡	0.57	0.35 to 0.93	0.025	1.42	0.88 to 2.28	0.15
HAART intrusiveness scale score (4 wks)§	1.81	0.80 to 4.07	0.15	1.18	0.57 to 2.47	0.65

HRs larger than 1 express an increase in hazard for treatment discontinuation (nonpersistence). ORs larger than 1 indicate an increased probability of executing appropriately (at least 1 intake in once-nightly and at least two intakes in twice-daily) the dosing regimen on each consecutive day.

*Higher score indicates greater perceived necessity.

†Higher score indicates stronger concerns.

‡Higher score indicates stronger necessity beliefs relative to concerns.

§Higher score indicates greater intrusiveness.

HR, hazard ratio.

which needed to be taken on an empty stomach, thereby adding a further barrier to the regimen execution.[12] Third, the MEMS containers in both arms of the study contained an LCD showing the number of dose taken, which could have improved execution and thus reduced the potential difference between the groups. Fourth, both arms of the study required a dose of medication to be taken at night. Previous studies have shown the evening dose to be particularly problematic[36] and, in this case, both arms of the study were similarly affected. The nonsignificant difference in regimen execution between once-nightly and twice-daily arms was unlikely to be a problem related to the power of the study because the estimates in each group were very close.

Patients' perceptions of HAART, elicited before they initiated treatment, were associated with nonpersistence over 48 weeks. Those who reported strong concerns about potential adverse effects relative to their perceived necessity for HAART were less likely to persist with treatment. Similar results were found in a previous study, where patients' initial doubts about their personal necessity and concerns about adverse effects predicted nonadherence (taking <95% as prescribed or having stopped treatment altogether) a year later.[29] In contrast with previous studies,[28,43] there was no significant relationship between patients' initial beliefs about HAART and the quality of regimen execution among those who remained on treatment. Moreover, in contrast with previous studies,[11,34] HAART intrusiveness was not significantly associated with adherence. The lack of association between persistence and intrusiveness may be explained by the fact that over half of the nonpersistent group did not complete the assessment of intrusiveness at the 4-week visit.

For individuals who persisted with treatment, the quality of execution was 92% and thus, on each consecutive day, 8% of people did not take the correct number of doses of HAART

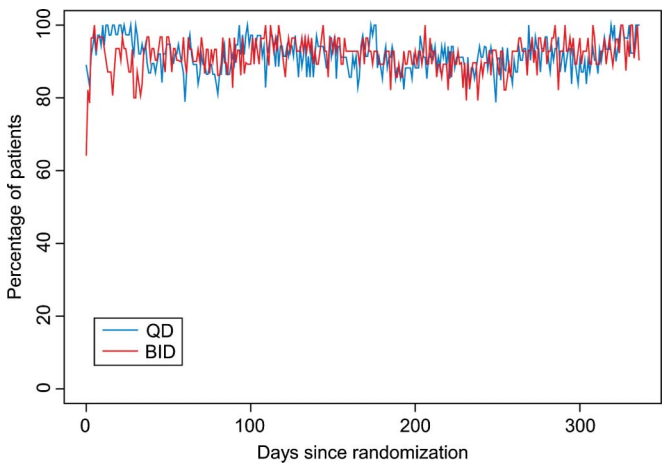

FIGURE 3. Execution of the dosing regimen summarized, on each consecutive day, as the percentage of patients who take at least the prescribed number of doses while they are still engaged (persistent) with the HAART treatment.

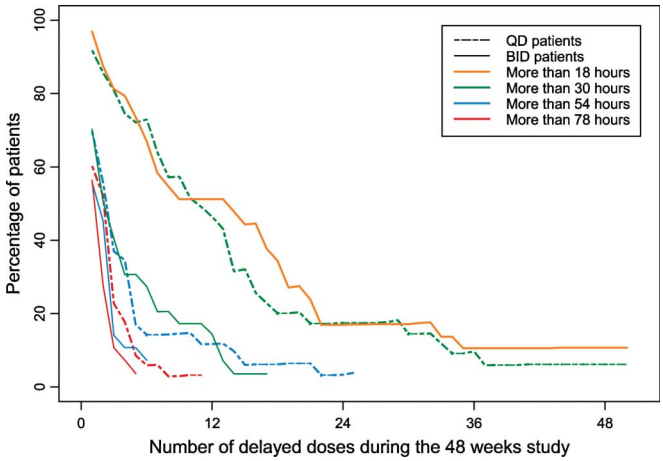

FIGURE 4. Frequency of delaying a dose by more than 18, 30, 54, and 78 hours within (*X*-axis) and between patients (*Y*-axis).

medicines. Missing doses was significantly more frequent over weekends. Although the quality of execution was not associated with viral outcome in this study, there is evidence that missing doses on a regular basis precedes nonpersistence with medicines.[32] The problem of poor execution therefore still needs to be addressed. This analysis explored only the influence of patients' beliefs about HAART *before* they initiated HAART on subsequent adherence. A previous study in HIV showed that beliefs changed over time associated with a decrease in perceived need for HAART over time associated with low adherence.[44] We did not explore relationships between patients' experiences of symptoms on adherence, yet these have previously been shown to influence regimen execution.[45,46]

The finding of increased nonadherence over weekends concurs with those of a recent study,[47] where a greater trend for 100% adherence was found when a self-report questionnaire measuring 3-day recall was used, compared with a questionnaire measuring 7-day recall. These findings emphasise the need to assess adherence over at least the past 7 days to ensure that a weekend is included.

People who were born outside the United Kingdom, those of African ethnicity, and women were more likely to stop their treatment. These relationships warrant further investigation. Possible explanations include stigma surrounding HIV in African communities[48] and fear that treatment would lead to the disclosure of the individual's HIV status.[49] Younger age was also associated with nonpersistence. This is in accordance with the adherence literature across long-term conditions including HIV.[29,50] Living with at least one other person was associated with better regimen execution, perhaps due to the availability of social support for adherence.[51]

Interpretation of the results of this study should take account of its limitations. Recruitment was slow and the study was stopped early for this reason. We were not powered to detect an effect of once versus twice-daily dosing on viral load nor questionnaire-based adherence data. The once-nightly regimen contained 4 pills per dose in contrast with the twice-daily regimen which contained 3 pills per day and with current recommended efaverenz-based regimens which are given as 1 or 2 pills once daily. Lower adherence has previously been associated with a greater number of pills per dose.[42] The study did not use identical once-nightly and twice-daily regimens, therefore, the influence of side effects or other considerations not picked up in the analysis cannot be excluded. Since the trial was conducted there have been changes to standard of care for the treatment of antiretroviral-naive HIV-positive patients. Although efavirenz remains the nonnucleoside reverse transcriptase inhibitor of choice, zidovudine and DDI are now used less often in first-line treatment because of their toxicity profiles.[52] DDI EC also has dietary restrictions that may have impeded adherence in the once-nightly group. Once-daily treatment is now common place in first-line treatments. Patients who sign up to a clinical trial may have fewer concerns about HAART and higher adherence than those receiving standard care. As a result, the relationships between beliefs and nonadherence may have been underestimated in this study.

Our findings have important implications for clinical practice, particularly in view of the current recommendation of life-long uninterrupted HAART.[53,54] The results of this study and others[40] suggest that once-daily HAART may enhance the duration of time spent on treatment, with ultimate implications for improving morbidity and mortality for HIV-positive people.[55] Efforts to support patients to remain on treatment over the long term may benefit from addressing both practical and perceptual barriers to adherence.[56] Practical barriers may be minimised by once-daily treatment, whereas perceptual barriers (doubts about necessity for treatment and concerns about potential adverse effect) should be elicited and addressed before patients initiate treatment. Poor quality of execution also remains a problem for a minority of patients, indicating that tools that reduce the likelihood of forgetting and the development of strategies to avoid missing doses of HAART over the weekend may be useful. Interventions to improve adherence to HAART should be based on needs assessment of each patient.

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