Switching from a two-tablet regimen of tenofovir/emtricitabine and efavirenz to a one-tablet regimen may affect patients’ perceptions and drug management*

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Objectives
Simplification of antiretroviral therapy enhances a patient’s adherence but a new formulation could also lead to new adverse events and changes in daily routine. This study compared medication adherence, tolerance and satisfaction among subjects switching from a two-tablet tenofovir/emtricitabine/efavirenz regimen to a one-tablet regimen.

Methods
Clinical and sociodemographic data were collected and three surveys were administered at month 0 (=switch), and then 1 and 4–6 months after the switch: the Beliefs about Medicines Questionnaire, the HIV-symptom index questionnaire, the Short HIV Treatment Satisfaction Questionnaire, the Swiss HIV Cohort Study (SHCS) two-item adherence questionnaire, and a questionnaire on daily combination antiretroviral therapy (cART) management. Medication adherence of a subgroup of subjects was routinely monitored using an electronic device (MEMS™).

Results
Eighty-eight subjects gave informed consent to participate in the study. The subjects’ back-switch rate was 7% (six of 88). Subjects who did not back-switch preferred the one-tablet regimen (median = 2; IQR = 1.3–2.5; on a −3 to 3 scale), but no change in adherence was found (10 of 46 nonadherent subjects; \( P = 1.00 \)). The perception of treatment necessity score decreased \( (P = 0.004) \), the efavirenz blood level increased (14%; \( P = 0.04 \)), and association/dissociation of cART with food intake evolved \( (P = 0.01) \) after the switch. Subjects listed equivalent numbers of symptoms during the three visits.

Conclusions
The one-tablet regimen was preferred but the number of back-switches was not negligible. The perception of treatment necessity score decreased with the simplification of the regimen from a two-tablet to a one-tablet formulation, which could negatively impact adherence. Switching is a sensitive time in a patient’s treatment life and professionals should pay particular attention to patient’s perceptions of treatment during such a transition.

Keywords: combination, drug therapy, medication adherence, medication therapy management, patient beliefs, regimen simplification, HIV, tenofovir, efavirenz

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Introduction

Two or more drugs are often used simultaneously to treat diabetes, hypertension, graft rejection and HIV infection among other chronic conditions. In an effort to reduce pill burden, to improve medication adherence and to ensure better therapeutic outcomes, fixed-dose combinations are made available by the pharmaceutical industry. In the HIV field, the first one-tablet combined antiretroviral regimen containing nucleoside and nonnucleoside reverse transcriptase inhibitors [tenofovir (TDF)/emtricitabine (FTC)/efavirenz (EFV)] became available in the USA in 2006 and in Switzerland in 2010. Since then, additional brands have been approved and others are in the pipeline [1].

A recent meta-analysis showed that a reduction in pill burden improves medication adherence, and other observational cohort studies have shown that fixed-dose combinations tend to improve medication adherence and may have a potentially beneficial impact on cost-utility [2–5]. Moreover, the majority of patients prefer a one-tablet once-a-day regimen [2,6]. The TDF/FTC/EFV one-tablet regimen has been shown to be as effective in maintaining virological suppression as previous combined antiretroviral therapies [2].

The different half-lives of the three components of the one tablet (52 h for EFV, 12–18 h for TDF and 10 h for FTC) differentially impact virological outcomes in the case of discontinuation [7]. For example, sustained treatment interruptions of EFV as well as other nonnucleoside reverse transcriptase inhibitors (NNRTIs) are more predictive of virological failure than are the same number of interspersed missed doses [8]. Moreover, tablet intake management (e.g. fasting or not) influences bioavailability and therefore adverse drug reactions [9].

A few studies have described a switch between identical active molecules: they found better adherence and quality of life and decreased HIV-related symptoms with a combined tablet. The molecules studied were lamivudine and zidovudine, and TDF, emtricitabine and EFV [6,10,11]. Tolerance of a medication depends not only on the active molecules but also on the inactive ingredients. A case of increased side effects was reported when switching from the TDF/FTC/EFV two-tablet formulation to a one-tablet formulation[12].

We aimed to study the switch from a two-tablet TDF/FTC/EFV regimen to a one-tablet regimen. We compared daily medication management, medication adherence, tolerance and satisfaction of subjects during the switch.

Methods

Study design

This prospective one-arm single-centre study was approved by the ethics committee of Canton de Vaud, Switzerland, and is registered at ClinicalTrial.gov (NCT01322932).

Subjects

Subjects were recruited from among patients routinely seen at the Infectious Disease Service of the University Hospital of Lausanne, Switzerland. Inclusion criteria were the following: subjects > 18 years, included in the Swiss HIV Cohort Study (SHCS), able to give informed consent, on two-tablet FTC/TDF/EFV treatment for > 3 months and ready to switch. Combination antiretroviral therapy (cART) adherence of a few subjects was routinely monitored using an electronic device (MEMSTM WestRock Switzerland Ltd, Sion, Switzerland); these subjects constituted the adherence subgroup.

Procedure

Subjects attended three visits: just before switching (V0), and at 1 month (V1) and 4–6 months (V2) after switching. They were asked to fill in, on the spot or at home, three (at V0 and V1) and four (at V2) questionnaires related to the previous 4 weeks. If subjects did not return questionnaires within 1 month, they were reminded by telephone (twice).

Questionnaires

The Beliefs about Medicines Questionnaire, Highly Active Antiretroviral Therapy version (BMQ-HAART) is a 19-item questionnaire measuring necessity beliefs (eight items; Cronbach’s alpha 0.80) and concerns (11 items; Cronbach’s alpha 0.82) about prescribed cART on a Likert scale [1–5], which was administered at V0 and V2. A low necessity or a high concern score was associated with lower adherence [13]. The questionnaire was translated into French following the first three stages of an adapted model of Brislin [14].

The HIV-symptom index questionnaire, which was administered at each visit, is a 20-item questionnaire evaluating the frequency of, and discomfort associated with the most common physical symptoms in HIV-infected patients [15]. We used the French validated version (Cronbach’s alpha 0.83) [16].
The Short HIV Treatment Satisfaction Questionnaire change version (six items; no Cronbach’s alpha) (HIVTSQc) was administered at V1 and V2 [17,18]. The scale varies between +3 and −3 (−3 more satisfied with old and +3 with new treatment).

The SHCS two-item adherence questionnaire was used to assess adherence [19]. The items were the following: “How often did you miss a dose in the last 4 weeks?” (daily, more than once per week, once per week, once every 2 weeks, once per month or never) and “Did you have a period of no drug intake for > 24 h in the last 4 weeks?” (yes or no).

A questionnaire on daily cART management, developed for the purpose of the study, was administered at each visit. Items were as follows: “How do you usually take your medicine?” (on an empty stomach, with a snack or with a meal); “Have you ever taken your medicine differently?” (yes or no); “If yes, have you experienced unusual symptoms and which ones?” Subjects were also asked about their satisfaction with tablet characteristics (taste, smell, colour, size, shape and easiness to swallow), the timing of medicine intake (morning, afternoon, evening or night) and, at V0, whether both tablets were swallowed together.

Subjects’ demographic and clinical data

The following sociodemographic data were collected at baseline from the SHCS database: gender, ethnicity, level of education, sexual preference, most likely route of infection, time since first positive HIV test and time since introduction of the FTC/TDF/EFV two-tablet regimen. Viral load and CD4 count were assessed at each visit. Baseline EFV therapeutic drug monitoring (TDM) data were collected if available within the previous 2 years or, if not, were measured at V0. TDM was also performed at V1. To characterize plasma EFV concentrations, we used percentile curves as described elsewhere [20].

Statistical analyses

Continuous variables were characterized using medians [with interquartile ranges (IQRs)], means [with standard deviations (SDs)] or percentages. A paired t-test or McNemar and Wilcoxon signed rank test was applied, when appropriate, using STATA statistical software (release 12; StataCorp LP, College Station, TX, USA). Changes over the three visits were characterized using generalized estimating equations (GEEs) for continuous variables (means) and logistic GEEs for dichotomous variables (P < 0.05) in the R system (v.3.1.2; GNU Project, University of Auckland, Auckland, New Zealand; library “gee”).

Results

Ninety-five subjects fulfilled the inclusion criteria and 88 (93%) gave their informed consent to participate in the study. The subjects’ sociodemographic and clinical data are listed in Table 1. Among the 88 subjects, six (7%) switched back to their previous two-tablet regimen (83%) because of adverse drug reactions: dizziness, nausea and vomiting, oesophageal burns, sleep disorder, a feeling of a worsening of general health, and cutaneous pain in the left upper limb, respectively; one patient (17%) could not

Table 1 Subjects’ (n = 88) sociodemographic and clinical data at inclusion

| Gender [n (%)] | Male 70 (79) |
| Age [years] [median (IQR)] | 47 (37, 54) |
| Ethnicity [n (%)] | White 70 (79) |
| Sexual preference [n (%)] | Heterosexual 61 (69) |
| | Men who have sex with men 24 (27) |
| | Bisexual 3 (3) |
| Most likely source of HIV infection [n (%)] | Sexual contacts 73 (83) |
| | Injecting drug use 7 (8) |
| | Time since the first HIV-positive test (years) [median (IQR)] | 7 (4.1, 11.6) [n = 76; 86%] |
| | Unknown [n (%)] | 12 (14) |
| | Mean time under emtricitabine/tenofovir/efavirenz regimen/year [median (IQR)] | 3 (1.8, 3.4) [n = 78; 89%] |
| | Unknown [n (%)] | 10 (11) |
| Highest level of education completed [n (%)] | Medium/advanced 60 (68) |
| | Basic 23 (26) |
| | Unknown 5 (6) |
| CD4 count [cells/µL] [median (IQR)] | At switch time (n = 86) 606.5 (421, 781) |
| | After 6 months (n = 65) 562.0 (460, 787)* |
| | Subjects with viral load < 20 copies/mL [n (%)] | At switch time (n = 87) 73 (83) |
| | 6 months post-switch (n = 64) 56 (67)* |
| | Viral load in subjects with detectable load [copies/mL] | At switch time (n = 14)* | 8 (23, 33) |
| | 1 month post-switch (n = 5) | 41 (40, 43) |
| | 6 months post-switch (n = 8) | 31 (26, 41) |
| | Number of subjects with continuous electronic monitoring of cART adherence | (adherence subgroup) | 14 (16) |

*One subject had repeated blips at switch and 1 month post-switch, another at switch and 6 months post-switch and two at 1 and 6 months post-switch; all other subjects had a single blip during the 6-month study.

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swallow the tablets because of their large size. Furthermore, three subjects (3%) dropped out and three (3%) withdrew because cART was changed (see Fig. 1). V1 and V2 occurred a median of 58 (IQR 45, 87; n = 70) and 189 (IQR 166, 223; n = 65) days after V0, respectively.

The BMQ-HAART showed a significant decrease in the necessity score between V0 and V2 [mean (± SD) 1.96 ± 0.58 vs. 1.79 ± 0.52, respectively; n = 53; P = 0.004] but no significant change in the concern score [mean (± SD) 3.32 ± 0.62 vs. 3.32 ± 0.68, respectively; n = 53; P = 0.93]. In the HIV-symptom index questionnaire, subjects listed equivalent numbers of symptoms at V0, V1 and V2 [median (IQR) 5.5 (2.0, 10.0), 5.5 (2.0, 10.0) and 6.5 (4.0, 9.0), respectively; n = 50], with fatigue and sleep disorders being the most frequently cited symptoms. According to the Short HIV Treatment Satisfaction Questionnaire, the subjects consistently preferred the one-tablet regimen at V1 [median (IQR) score 2.0 (1.3, 2.5); n = 44] and at V2 [median (IQR) score 2.0 (1.1, 2.6); n = 52; P < 0.05 for the comparison between the two-tablet and one-tablet regimens]. Such a preference could not be inferred from the tablet’s characteristics (taste, smell, size, shape, colour and ease of swallowing), as more than 85% of subjects were satisfied or very satisfied with both drug formulations.

When the subjects were asked about their daily cART management, 61 of 69 (88%) stated that they were swallowing the two tablets at the same time at V0. Regarding the association with food, more subjects took their regimen on an empty stomach at V1 compared with V0.

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**Fig. 1** Flow chart of the study: from subject enrolment to follow-up.
and V2 (32% vs. 20% and 18%, respectively; n = 44; *P* = 0.01). Concerning medication adherence, the number of subjects self-reporting at least one missed dose during the last 4 weeks was similar at the three visits (n = 10; 22%). Adherence as measured by electronic monitors in the adherence subgroup (n = 12) was high before and after the switch (95%, 95 CI 90–97%), and no difference related to the switch was detected. Median (IQR) EFV concentrations were at the 39th (29th, 56th) percentile at V0 and at the 47th (29th, 53th) percentile at V1 (*P* = 0.04; n = 45). This 8 percentile increase corresponds to a 14% increase in EFV concentration. No significant change in clinical data was noticed after the switch.

Subgroup analyses showed that more men who have sex with men (MSM) tended to take their pill on an empty stomach than heterosexuals (28% vs. 6%, respectively (*P* = 0.02), at V0 and 30% vs. 6%, respectively (*P* = 0.04), at V2) and that self-reported suboptimal adherence was more frequent in women than in men (46% vs. 18%, respectively (*P* = 0.03), at V0; 27% vs. 18%, respectively (not significant), at V1; 55% vs. 15%, respectively (*P* = 0.01, at V2), with suboptimal adherence defined as ≥1 day without intake in the last 4 weeks. However, EFV concentrations were higher in women than in men (percentile 51 vs. 42, respectively (not significant), at V0 and 57 vs. 41, respectively (*P* < 0.01, at V1). Outcomes as measured by questionnaires were not different in subjects in the adherence subgroup (n = 14) vs. all other subjects, or in subjects with detectable viral load at V0 (n = 14) vs. subjects with undetectable viral load.

**Discussion**

Our results show that, although subjects were satisfied with the tablet characteristics of both regimens, the one-tablet regimen was preferred. However, we noted a 7% back-switch rate (vs. 2–3% in other studies) [4]. Five of six subjects back-switched because of perceived side effects before the 1-month EFV drug concentration measurement. Increased EFV concentration may have played a role in this. Indeed, other authors have noted an increase in EFV concentration associated with side effect complaints, and high concentrations have been associated with more frequent central nervous system side effects [12,21]. In our subjects who did not back-switch, we observed a 14% increase in EFV concentration at 1 month post-switch. The clinical relevance of such an increase in plasma EFV concentrations is difficult to establish; Burger et al. consider changes in concentration smaller than 25% as irrelevant because such changes are within the reported intrasubject variability [12]. Although it was not measured, the concentration of EFV could have further increased at 6 months post-switch as a result of the increased number of subjects swallowing EFV in fed conditions. Interestingly, three subjects withdrew from the study because they changed cART. Unfortunately, because of the single-arm observational design of the study, the imputability of the switch to the withdrawal rate could not be established.

The score for the perception of treatment necessity decreased after the switch, which could be considered a red flag in terms of risk of medication nonadherence. Indeed, in the literature, a low necessity/concern score has been associated with lower medication adherence in cross-sectional and longitudinal studies [13]. However, to our knowledge, the impact of a change in the perception of necessity is not well explored and we encourage professionals to be vigilant in long-term follow-up and to remind patients of the importance of treatment, even if the regimen dosing frequency decreases to a one-tablet daily regimen.

Self-reported medication adherence was stable during our 6-month study. The rate of self-reported nonadherence (the percentage of subjects with at least one missed dose during the last 4 weeks) was 22%, which is lower than the 31% of subjects with self-reported nonadherence in another study also nested within the SHCS but with all types of HIV regimens represented [19]. According to some reviews, treatment simplification, especially a reduction in pill burden and dosing frequency, tends to increase adherence [4–6].

Changes in drug intake habits are interesting to study. Official recommendations state that the TDF/FTC combination should be swallowed with a meal, and EFV should be taken under fasting conditions [4]. Yet, the majority of our subjects swallowed both tablets together with a meal. Just after switching, a greater proportion of subjects swallowed the one-tablet regimen under fasting conditions, as recommended for the one-tablet regimen, but after 6 months, this proportion had decreased and most subjects were again taking the medication under fed conditions. The reason for this change is not known, but it is probably attributable to a better adequacy with the patients’ daily routines or the patients adapting their behaviour in order to control for the presence of residual, inconvenient central side effects in the morning (the most frequently cited side effect being fatigue), by increasing the length of time between drug intake and waking up in the morning. This possibility should be discussed with patients, as professionals know that swallowing EFV in fed conditions increases exposure and thus side effects [4,7].

This study has some limitations. First, the use of electronic monitoring of cART adherence in the entire group instead of the questionnaire would have increased the
sensitivity of the measure. However, it would have meant
that we had to postpone the switch by at least 10–
12 weeks (to avoid the Hawthorne effect), which was eth-
ically questionable. Secondly, subjects who switched back
did not answer questionnaires at V1 and/or V2, as such a
high back-switch rate was not expected. In further stud-
ies, the number and perception of side effects should also
be monitored after back-switch. Finally, our sample is
representative of the SHCS enrollees in terms of basic
sociodemographic data (age, sex, ethnicity and sexual
preference) [22]. In Switzerland, 75% of HIV-infected
patients are enrolled in the SHCS, which ensures its rep-
resentativeness [22]. Although the number of MSM may
be considered low in our study in comparison to other
cohort studies in resource-rich settings, they represent
about 40% of cases of HIV transmission in Switzerland
for the time period analysed.

In conclusion, switching is a sensitive time in a
patient’s treatment life. Professionals should pay particu-
lar attention to treatment management during such a
transition to prevent patients becoming discouraged and
experiencing treatment interruptions because of emerging
side effects.

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