Persistence and adherence to single-tablet regimens in HIV treatment: a cohort study from the French National Healthcare Insurance Database

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Objectives: To compare adherence and persistence (continuous treatment with a prescribed medication) in HIV adult patients who received combination ART (cART) as a once-daily single-tablet regimen (STR) versus other administration schedules.

Methods: A representative random sample of the French National Healthcare Insurance Database was used. Adherence and persistence were compared according to their administration schedules using χ2 and survival analyses. STRs were marketed in France in 2009 and the study period was selected to allow a sufficient number of patients with an STR and a relevant duration of follow-up.

Results: During the period covered (2006–11), 362 HIV-positive adult antiretroviral-naive patients (566 lines of treatments) were selected. The mean rates of adherence were 89.6% for the STR (tenofovir/emtricitabine/efavirenz; n = 76), 86.4% for cART with 1 pill once daily (n = 242) and 77.0% for cART with 1 daily intake (n = 248; P = 0.0001 versus STR). Kaplan–Meier estimations of persistence after 2 years of treatment were 79.1% for the STR, 53.3% for cART with 1 pill once daily and 51.8% for cART with 1 daily intake (P = 0.001; log-rank test). Sensitivity analyses confirmed these results. After excluding treatment sequences showing a switch from tenofovir/emtricitabine plus efavirenz to the similar STR, the rates of persistence were 80.3% for the STR (n = 60), 77.3% for atazanavir-containing cART (n = 96) and 68.3% for darunavir-containing cART (n = 56) at 18 months (global P = 0.006).

Conclusions: These results suggest that persistence is higher in HIV patients treated with an STR compared with other administration schedules. Significant benefit in terms of adherence was observed with the STR in comparison with regimens involving >1 daily intake but no difference was observed when comparing with regimens involving >1 pill once daily.

Keywords: HIV infection, antiretroviral treatment, fixed-dose combinations, ART

Introduction

A high degree of patient adherence and persistence is required for combination ARTs (cARTs) to achieve viral suppression and prevent resistance. Adherence is defined as the degree to which a patient follows a prescribed regimen over a period of time; persistence of the regimen is defined as the duration of treatment from initiation to discontinuation.1 Early studies showed that an adherence to PI therapy of ≥95% optimized the virological outcome for patients with HIV infection.2 With more efficient antiretroviral drugs, viral suppression was obtained with lower levels of adherence.3–6 Nevertheless, the relationship between the level of adherence and the degree of viral suppression has been established in many studies.7–9 Persistence with the regimen in the context of HIV treatment has been less studied than adherence; however, interruption and discontinuation have been associated with drug resistance and increased mortality.10 It must be acknowledged that a lack of persistence can be due to many reasons, such as poor adherence, side effects, toxicity, drug–drug interactions, the individual's choice, simplification, the availability of new combinations, etc. In France, where PI-based therapy was favoured during the period 2000–12, many practitioners used
to undertake a pre-emptive switch once virological suppression had been achieved in order to simplify the regimen as much as possible, facilitate adherence and prevent long-term metabolic toxicities, as has been proposed by some guidelines.\textsuperscript{11,12}

In 1996, the introduction of cART led to complex regimens with up to 20 pills per day. The development of fixed-dose combinations and once-daily antiretroviral drug schedules has reduced the pill burden, but there are still differences between the different regimens that are available. A meta-analysis including 11 randomized controlled trials comparing different cART regimens showed that the adherence rate was significantly increased with a once-daily regimen compared with a twice-daily regimen.\textsuperscript{13} In a cross-sectional survey of US adults with HIV infection, patients taking the single-tablet tenofovir/emtricitabine/efavirenz fixed-dose regimen were significantly more likely to show complete adherence than were patients taking other cART regimens; moreover, a higher daily pill number was associated with lower adherence, thus showing the negative impact of a higher pill burden on adherence.\textsuperscript{14}

Real-life data on the impact of single-tablet regimens (STRs) on adherence and more specifically on persistence remain limited.\textsuperscript{15} In France, all HIV patients benefit from a full coverage of care for HIV infection and all their treatments are recorded in a National Healthcare Insurance Database. In this study, we compared adherence and persistence with STRs and non-STRs in a cohort taken from this database.

### Methods

#### Data source

This retrospective study was performed using a sample extracted from the French National Healthcare Insurance Database covering \textasciitilde90\% of the whole French population and known as the \textit{Echantillon Généraliste des Bénéficiaires} (EGB). The EGB is a random sample (1 out of 97) of the entire database and includes \textasciitilde600000 individuals.\textsuperscript{16,17} This database contains for each individual all items of reimbursed medical expenses since 2002 onwards linked through an anonymous number managed by a third party. These items comprise drugs, including the dates of prescription and quantities dispensed. Previous studies have already used this database for analysing drug utilization and exposure.\textsuperscript{18–20}

#### Study population

Patients aged \(\geq\)18 years receiving cART reimbursed from 2006 to 2011 were identified in the EGB. The selection of the study period 2006–11 allowed for a sufficient number of patients and a long enough follow-up after STR marketing to allow for a comparison between the groups for the different regimens. The antiretroviral drugs were identified according to the Anatomical Therapeutic Chemical (ATC) classification of medicines (WHO). The data on ART included the date of dispensing and the number of boxes dispensed during the year for each drug.

Antiretroviral-naive patients were selected based on an absence of ART in the 3 years before inclusion, starting in 2006 because of a lack of information on hospitalization before 2006 and to ensure sufficient perspective. Patients with prophylactic ART treatments (a duration of ART of \(\leq\)1 month) were excluded. The other extracted variables were age, gender, administrative area identified by the zip code, prescription by either a general practitioner, a specialist or a hospital, the number of hospitalizations, whether the patients were covered by CMU-c (free complementary Universal Health Insurance for low-income people), ‘ALD’ (\textit{Affection de Longue Durée}—chronic disease justifying full healthcare coverage), the presence of depression (at least three prescriptions of antidepressants for 1 year, i.e. drugs with an ATC code of N06A), treated hepatitis C (at least one hospitalization with this diagnosis or at least three prescriptions for hepatitis C treatment during the corresponding year), duration of follow-up and death.

Each line of cART has been reconstituted for the selected population using the dates of delivery of the different ARTs.

### Statistical analysis

Adherence was calculated as the percentage of reimbursed pills divided by the theoretical number of pills prescribed for the corresponding period of persistence. The adherence in each cART group was compared using variance analysis when the distribution was normal or a non-parametric test (Kruskal–Wallis).

Persistence was defined as the duration of treatment without a change in any component. The end of the therapeutic strategy was determined by the reimbursement of at least one antiretroviral drug not present in the current combination. Different sensitivity analyses were performed in order to take into account the availability of the different antiretrovirals during the period of analysis. Persistence for each cART group was compared using survival analysis (non-parametric Kaplan–Meier analysis with a log-rank test).

Comparisons of the administration schedule groups in terms of potential covariates (hepatitis C, depression, CMU-c, etc.) to be included in a multivariate analysis were performed but were negative.

The SAS version 9.2 (SAS Institute, Cary, NC, USA) software program was used for the statistical analyses.

### Ethics

No Ethics Committee approval was required for this database analysis. An anonymous number provided by the Sickness Funds allows the files in the database to be linked; therefore, patient informed consent cannot be obtained.

### Privacy

Only aggregated results are provided.

### Results

#### Characteristics of the study population

Overall, 826 patients who received reimbursement for a triple combination of antiretroviral drugs were selected in the EGB database between 2006 and 2011 (Figure 1). Patients below 18 years of age (\(n=20\)), those who had undergone <1 month of treatment (\(n=149\)) and those who had received antiretroviral drugs during the period 2003–05 (\(n=295\)) were excluded. Among the 362 antiretroviral-naive adult patients of the study population who started treatment after 2005, 11.3\% had had treated hepatitis C and 9.4\% had a diagnosis of depression at the initiation of CART. The patients’ characteristics are described in Table 1.

#### ARTs delivered during the study period

Overall, the 362 patients of the study population received 566 lines of ART during the follow-up period (2006–11). The numbers of lines of treatment during this period were one for 211 patients (58.3\%), two for 110 patients (30.4\%) and three or more for 41 patients (11.3\%). The most frequent cART sequences prescribed were an STR of tenofovir/emtricitabine/efavirenz (13.4\%),...
tenofovir/emtricitabine plus boosted atazanavir (11.5%) and tenofovir/emtricitabine plus efavirenz (9.4%) (Table 2).

During the follow-up period, 20.7% of patients received an STR. This treatment was generally delivered as a second-line treatment (in 65.3% of patients who received the STR). When the STR was delivered as a second-line treatment, patients had mostly received tenofovir/emtricitabine plus efavirenz as the first-line treatment (63.3%). Most patients initially treated with tenofovir/emtricitabine plus efavirenz switched during the study period (88.4% of patients); this switch occurred after a mean of 13.1 months after the initiation of treatment and, for a majority of patients (81.6%), tenofovir/emtricitabine plus efavirenz was replaced with the tenofovir/emtricitabine/efavirenz STR. These results are the consequence of the marketing in France during 2009 of tenofovir/emtricitabine/efavirenz STRs.

**Adherence by administration schedule**

To compare the persistence and adherence according to the administration schedule used (the number of pills and number of daily intakes), the cARTs were classified into three groups: (i) STR (tenofovir/emtricitabine/efavirenz); (ii) cART with >1 pill once daily; and (iii) cART with >1 daily intake. During the period 2006–11, 13.4% of the initial regimens were an STR, 42.8% had an administration schedule with >1 pill once daily and 43.8% had an administration schedule with >1 daily intake.

The mean rate of adherence was 89.6% for the STR group, 86.4% for cART with >1 pill once daily and 77.0% for cART with >1 daily intake ($P < 0.0001$) (Table 3). The rates of adherence for the STR and cART with >1 pill once daily were comparable.

**Persistence by administration schedule**

In a first approach, any treatment change was considered as a discontinuation and all lines of treatment were analysed. No significant difference in mean persistence in terms of the schedule was identified despite a trend in favour of the STR: the median duration of treatment was 21.9 months for the STR versus 15.8 and 15.1 months for the other two groups (Table 4). The rates of discontinuation were significantly different: 19.7% for the STR and cART with >1 pill once daily were comparable.

### Table 1. Baseline characteristics of the population and of the treatment schedule groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients included, n = 362</th>
<th>STR, n = 76</th>
<th>&gt;1 pill once daily, n = 242</th>
<th>&gt;1 daily intakea, n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up (months), mean (SD)</td>
<td>32.8 (17.3)</td>
<td>33.0 (15.9)</td>
<td>34.8 (17.9)</td>
<td>37.5 (16.9)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>242 (66.9)</td>
<td>53 (69.7)</td>
<td>165 (68.2)</td>
<td>158 (63.7)</td>
</tr>
<tr>
<td>female</td>
<td>120 (33.1)</td>
<td>23 (30.3)</td>
<td>77 (31.8)</td>
<td>90 (36.3)</td>
</tr>
<tr>
<td>Age at initiation of cART (years), mean (SD)</td>
<td>44.7 (11.3)</td>
<td>43.4 (9.8)</td>
<td>44.2 (10.2)</td>
<td>44.8 (11.2)</td>
</tr>
<tr>
<td>Patients with CMU-c, n (%)</td>
<td>116 (32.0)</td>
<td>26 (34.2)</td>
<td>79 (32.6)</td>
<td>79 (31.9)</td>
</tr>
<tr>
<td>Patients with ALD, n (%)</td>
<td>332 (91.7)</td>
<td>75 (98.7)</td>
<td>230 (95.0)</td>
<td>225 (90.7)</td>
</tr>
<tr>
<td>Death during the period, n (%)</td>
<td>13 (3.6)</td>
<td>—</td>
<td>4 (1.7)</td>
<td>10 (4.0)</td>
</tr>
<tr>
<td>Year of start of cART, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>44 (12.2)</td>
<td>7 (9.2)</td>
<td>34 (14.0)</td>
<td>37 (14.9)</td>
</tr>
<tr>
<td>2007</td>
<td>37 (10.2)</td>
<td>8 (10.5)</td>
<td>28 (11.6)</td>
<td>39 (15.7)</td>
</tr>
<tr>
<td>2008</td>
<td>35 (9.7)</td>
<td>8 (10.5)</td>
<td>26 (10.7)</td>
<td>26 (10.5)</td>
</tr>
<tr>
<td>2009</td>
<td>167 (46.1)</td>
<td>34 (44.7)</td>
<td>101 (41.7)</td>
<td>122 (49.2)</td>
</tr>
<tr>
<td>2010</td>
<td>45 (12.4)</td>
<td>13 (17.1)</td>
<td>29 (12.0)</td>
<td>17 (6.9)</td>
</tr>
<tr>
<td>2011</td>
<td>34 (9.4)</td>
<td>6 (7.9)</td>
<td>24 (9.9)</td>
<td>7 (2.8)</td>
</tr>
</tbody>
</table>

a>1 daily intake is taking pills at least twice daily.

bCMU-c, free complementary Universal Health Insurance for low-income patients, used in the analysis as a surrogate for poverty.

cALD, chronic disease justifying full healthcare coverage.
Table 2. Most frequent triple combinations of antiretroviral drugs in the population study (global and first line of treatment in antiretroviral-naive patients); total number = 566 sequences (100%)

<table>
<thead>
<tr>
<th>Combinations of antiretroviral drugs (international non-proprietary names; ritonavir not included)</th>
<th>Global, n (%)</th>
<th>First line, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC/EFV in STR</td>
<td>76 (13.4)</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td>TDF/FTC plus atazanavir</td>
<td>65 (11.5)</td>
<td>47 (13.0)</td>
</tr>
<tr>
<td>TDF/FTC plus EFV</td>
<td>53 (9.4)</td>
<td>43 (11.9)</td>
</tr>
<tr>
<td>TDF/FTC plus lopinavir/ritonavir</td>
<td>44 (7.8)</td>
<td>34 (9.4)</td>
</tr>
<tr>
<td>TDF/FTC plus darunavir</td>
<td>44 (7.8)</td>
<td>30 (8.3)</td>
</tr>
<tr>
<td>ABC/3TC plus atazanavir</td>
<td>31 (5.5)</td>
<td>21 (5.8)</td>
</tr>
<tr>
<td>ZDV/3TC plus lopinavir/ritonavir</td>
<td>22 (3.9)</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>TDF/FTC plus nevirapine</td>
<td>22 (3.9)</td>
<td>14 (3.9)</td>
</tr>
<tr>
<td>ABC/3TC plus lopinavir/ritonavir</td>
<td>20 (3.5)</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td>TDF/FTC plus raltegravir</td>
<td>19 (3.4)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>ZDV/3TC/ABC</td>
<td>16 (2.8)</td>
<td>15 (4.1)</td>
</tr>
<tr>
<td>ABC/3TC plus darunavir</td>
<td>12 (2.1)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>TDF/FTC plus fosamprenavir</td>
<td>12 (2.1)</td>
<td>9 (2.5)</td>
</tr>
</tbody>
</table>

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; ABC, abacavir; 3TC, lamivudine; ZDV, zidovudine.

Persistence by type of combination

Persistence with the STR (tenofovir/emtricitabine/efavirenz) was compared with the persistence with a limited number of cARTs representative of the current therapeutic strategies for HIV. Four groups of cARTs were analysed: (i) STR (n = 60); (ii) atazanavir/ritonavir (with tenofovir/emtricitabine or abacavir/lamivudine as the backbone; n = 96); (iii) darunavir/ritonavir (with tenofovir/emtricitabine or abacavir/lamivudine; n = 56); and (iv) raltegravir (n = 41). In order to achieve sufficient statistical power, all the cARTs containing raltegravir (whatever the backbone) were taken into account (only 26 patients received raltegravir with tenofovir/emtricitabine or abacavir/lamivudine as the backbone). We excluded patients who started cART before 1 January 2009 and received STR as a second-line treatment (i.e. after an

Table 3. Rates of adherence according to administration schedule of cART

<table>
<thead>
<tr>
<th>Adherence (%)</th>
<th>STR, n = 76</th>
<th>&gt;1 pill once daily, n = 242</th>
<th>&gt;1 daily intake, n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (SD)</td>
<td>89.6 (12.5)</td>
<td>86.4 (22.2)</td>
<td>77.0 (25.9)</td>
</tr>
<tr>
<td>median</td>
<td>94.2</td>
<td>100</td>
<td>87.5</td>
</tr>
<tr>
<td>Cut-off adherence value, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>47 (61.8)</td>
<td>158 (65.3)</td>
<td>121 (48.8)</td>
</tr>
<tr>
<td>&gt;80%</td>
<td>58 (76.3)</td>
<td>179 (74.0)</td>
<td>143 (57.7)</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>69 (90.8)</td>
<td>202 (83.5)</td>
<td>163 (65.7)</td>
</tr>
</tbody>
</table>

P<0.0001 a

aANOVA. bX² test.

Table 4. Rates of persistence (time to discontinuation) according to administration schedule of cART

<table>
<thead>
<tr>
<th>Persistence (months)</th>
<th>STR, n = 76</th>
<th>&gt;1 pill once daily, n = 242</th>
<th>&gt;1 daily uptake, n = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (SD)</td>
<td>18.3 (9.5)</td>
<td>18.3 (13.5)</td>
<td>19.4 (15.9)</td>
</tr>
<tr>
<td>median</td>
<td>21.9</td>
<td>15.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Discontinuation, n (%)</td>
<td>15 (19.7)</td>
<td>96 (39.7)</td>
<td>93 (37.5)</td>
</tr>
<tr>
<td>Persistence with discontinuation (months), mean (SD)</td>
<td>9.2 (8.9)</td>
<td>13.3 (11.3)</td>
<td>15.1 (11.8)</td>
</tr>
<tr>
<td>Persistence without discontinuation (months), mean (SD)</td>
<td>21.2 (8.1)</td>
<td>21.6 (13.8)</td>
<td>22.0 (17.4)</td>
</tr>
</tbody>
</table>

P<0.0056 a

aANOVA. bX² test.
automatic switch from tenofovir/emtricitabine plus efavirenz to an STR of tenofovir/emtricitabine/efavirenz. Any modification of the treatment was considered as a discontinuation.

After 18 months of treatment, the rate of persistence was 80.3% with an STR, 77.3% with an atazanavir-containing cART and 68.3% with a darunavir-containing cART (global \( P = 0.006 \); log-rank test). The results in Figure 3 suggested that discontinuations of STRs were observed during the early months of treatment whereas discontinuations of atazanavir-containing cARTs and darunavir-containing cARTs occurred gradually over time; the rate of persistence of raltegravir-containing cART decreased rapidly and was 39.3% after 12 months of treatment. This finding should be interpreted with caution as 15/41 raltegravir-based regimens were NRTI-sparing with PI/ritonavir and/or NNRTI.

Finally, no statistical relationship was observed between adherence and persistence.

**Discussion**

High rates of adherence and persistence are of critical importance for the long-term therapy of HIV patients, who are now treated for many decades. Indeed, the 2013 French guidelines...
recommended treating all patients whatever the number of CD4 cells measured, thus increasing the duration of exposure to ART.\textsuperscript{21} The discontinuation of antiretroviral drugs because of poor tolerability, poor adherence or complexity carries risks of the development of resistance, toxicity and resistance being associated with compromised future treatment options. New drugs and regimens have better tolerability but variable complexity. With STRs and once-daily intakes, patients are more likely to take their pills more consistently. The fixed-dose combination of tenofovir/emtricitabine/efavirenz was the first STR that provided complete therapy for HIV infection and this was the STR available during the period covered by the present analysis (2006–11).\textsuperscript{22}

Other once-daily STRs are now being marketed, with tenofovir/emtricitabine/rilpivirine STRs available in France since September 2012, and tenofovir/emtricitabine/elvitegravir/cobicistat available in France since March 2014.\textsuperscript{23–26} Available data on STRs come mainly from clinical trials, which are not primarily designed to assess adherence and persistence and take place in settings that are not representative of real life. Moreover, randomized clinical trials frequently use a double-dummy design (with two placebo(s), thus increasing the number of pills to be taken. The present analysis provides an insight into adherence and persistence with STRs in real life in France. Based on the random sampling and the database analysed, our results are representative of the overall HIV-treated population in France. A total of 826 HIV patients receiving cART were obtained from the database and the results are consistent with those for the overall population of patients managed for HIV in France. In 2010, it was estimated that 149900 people were living with HIV in France; among these, 81% had been diagnosed and 60% had been taking antiretroviral drugs for at least 6 months (i.e. 89940 HIV patients were receiving cART).\textsuperscript{21} In our sample, there was an increase in the number of patients who started cART in the year 2009. This transient increase is most probably related to the 2009 guidelines that for the first time recommended starting ART for all HIV patients with a CD4 count <350 cells/mm\textsuperscript{3} (and not <200 cells/mm\textsuperscript{3} as before).\textsuperscript{27}

Overall, for the entire period (2006–11), the most frequent first-line cARTs were the STRs (13.4%), tenofovir/emtricitabine plus atazanavir/ritonavir (11.5%) and tenofovir/emtricitabine plus efavirenz (9.4%). The STR was usually prescribed as second-line treatment according to the Summary of Product Characteristics for Atripla (market authorization for patients with HIV RNA <50 copies/mL). The benefit in terms of adherence was observed as soon as the number of intakes was reduced to once daily, whatever the total number of pills to be taken daily. As outlined in a recent meta-analysis, randomized studies evaluating the impact of regimen type on adherence and persistence compared once-daily and twice-daily regimens but none compared the STR with twice-daily or once-daily regimens involving three or four pills, as occurs for most PI/ritonavir-based regimens.\textsuperscript{28} Observational studies have found either better adherence with an STR compared with all other regimens, whether once daily or twice daily,\textsuperscript{29} or no difference between STRs and other once-daily regimens.\textsuperscript{25}

A benefit in terms of persistence was also observed for STRs. This difference was more important after 2 years of treatment, which could be a consequence of French practitioners' initial use of PI regimens with a switch of the PI to prevent or improve metabolic abnormalities, fat redistribution, gastrointestinal toxicities or hyperbilirubinaemia. Various sensitivity analyses confirmed these results. Our study compared different administration schedules over a long period of time (2006–11). As a consequence, the inclusion of cARTs that are nowadays less frequently used (due to poor persistence, for example) could bias the results. Therefore, the persistence with the STR was compared with the persistence of a limited number of cARTs representative of the current therapeutic strategies for HIV. We observed that, after excluding patients who had undergone an automatic switch from tenofovir/emtricitabine plus efavirenz to the tenofovir/emtricitabine/efavirenz STR, the rates of persistence were 80.3% for the STR, 77.3% for the atazanavir-containing CART and 68.3% for the darunavir-containing cART at 18 months; the rate of persistence for raltegravir-containing CART decreased rapidly and dramatically, but the sample size was small, with only 41 patients. Of interest, the discontinuations with the STR, when they occurred, were observed earlier than with the other cARTs. The increase in adherence and persistence seen with STRs might be related not only to the STR per se, but also to its components, such as an NNRTI. In a retrospective comparison of first-line tenofovir/emtricitabine plus efavirenz given as two pills, versus tenofovir/emtricitabine/efavirenz as an STR, there was no evaluation of adherence and persistence.\textsuperscript{30}

Future studies looking at adherence and persistence for STRs with different components (rilpivirine, elvitegravir/cobicistat, dolutegravir and, in the near future, darunavir/cobicistat) will allow an evaluation of whether adherence and persistence are related to the component(s) of the STR or to the STR itself. Indeed, a recent retrospective Canadian study, with many potential biases, suggested that a tenofovir/emtricitabine/efavirenz STR was no more durable than a very well tolerated, more complex non-STR based on raltegravir given twice daily.\textsuperscript{31} Another advantage of an STR is the potential decrease in cost through reductions in pharmacy and hospitalization costs.\textsuperscript{32}

The strengths of the current study are the representativeness of the sample for France, the retrospective design of the analysis and the long duration of the observation period allowing relevant analyses in a real-life setting. Another strength is that the free coverage of care and therapy for all HIV-infected patients decreases the risk of lack of adherence or low persistence from issues of administration or cost.

Overall, our data are consistent with a study that assessed antiretroviral persistence in a commercially insured population in the USA.\textsuperscript{33} Persistence was longer with NNRTI-based regimens than PI-based regimens, and fixed-dose regimens of once-daily tenofovir/emtricitabine/efavirenz were associated with the lowest risk of discontinuation. In a retrospective study of an HIV cohort in a single centre, where 472 patients received an STR of tenofovir/emtricitabine/efavirenz as first-line therapy, persistence was 81% after a median duration of 294 days.\textsuperscript{31} In a recent retrospective study of 7381 US Medicaid patients receiving treatment for HIV infection (1797 treated with an STR and 5584 with ≥2 pills per day), the patients receiving the STR were significantly more likely to reach 95% adherence.\textsuperscript{33}

Our study has a number of limitations. First, health insurance data collected by Sickness Funds have no medical or scientific purposes. The information on patients is limited; biological data such as CD4 counts or viral loads are not recorded. Therefore, we could not correlate the benefit of STRs in terms of adherence/persistence with virological suppression. Many subjects could have switched for convenience rather than issues related to toxicity. Adherence may be overestimated in this study as it relied only
on the medical delivery to the subject, which may not fully reflect
the true adherence. Another limitation of the database is the
absence of data for drugs that were prescribed but not delivered.
In addition, the number of patients treated with some cARTs
(e.g. raltegravir) was limited, thus affecting the statistical power.
The time period over which the study was conducted (2006–11)
was marked by therapeutic advances and a decline in use of some
therapeutic agents. Therefore, the mean rates of persistence
could have been affected by the availability of each different anti-
retroviral drug, which varied with time. The survival analysis never-
theless allowed this limitation to be partially overcome. Finally,
patients were not randomized according to the different treat-
ments and some confounding factors could not be controlled.

In conclusion, these results based on data from the French
National Healthcare Insurance Database suggest that higher
rates of adherence and persistence were achieved in HIV patients
with a once-daily intake, whatever the number of pills
given, compared with other administration schedules.

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