Switching from tenofovir/emtricitabine and nevirapine to a tenofovir/emtricitabine/rilpivirine single-tablet regimen in virologically suppressed, HIV-1-infected subjects

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Objectives: Nevirapine is an inducer of hepatic metabolism. After discontinuation, nevirapine has an inductive effect on cytochrome P450 3A4, which persists for a few weeks and which, after switching to rilpivirine, may reduce rilpivirine exposures and have a negative clinical impact. This study evaluates the virological outcome, pharmacokinetics and safety of switching virologically suppressed, HIV-1-infected patients from nevirapine to rilpivirine.

Patients and methods: This 24 week open-label single-centre study included HIV-1-infected adults with HIV-1 RNA <50 copies/mL for >6 months on tenofovir/emtricitabine and nevirapine, who were willing to simplify their regimen to tenofovir/emtricitabine/rilpivirine. Virological suppression, safety and nevirapine and rilpivirine pharmacokinetics were assessed.

Results: At weeks 12 and 24, all 32 subjects remained virologically suppressed. One subject discontinued at week 1 for rilpivirine-associated insomnia and two patients chose to resume tenofovir/emtricitabine and nevirapine after week 12 because of rilpivirine-associated food constraint. There was no grade 3/4 laboratory abnormality. Rilpivirine trough concentrations were above the mean trough concentrations observed in Phase 3 studies by 1 week post-switch. Twenty-seven out of 32 patients had no measurable levels of nevirapine by 2 weeks post-switch. The meal accompanying tenofovir/emtricitabine/rilpivirine intake satisfied food requirements in 81% of cases. Overall general satisfaction was improved in 90% of the subjects despite food constraints.

Conclusion: Nevirapine has a short and limited inductive effect on rilpivirine metabolism, which is not clinically significant. Tenofovir/emtricitabine/rilpivirine is an efficacious and safe option for virologically suppressed HIV-infected patients on nevirapine wishing to simplify their regimen.

Keywords: non-nucleoside reverse transcriptase inhibitors, antiretroviral therapy, genotypes, pharmacokinetic interactions

Introduction

Combination antiretroviral therapy (ART) has considerably improved in recent years and is associated with a high rate of virological suppression and an improved safety profile.1,2 The main objective is to maintain success in the long term and to improve the quality of life of patients by avoiding long-term toxicities and facilitating convenience.3

Rilpivirine, the latest licensed non-nucleoside reverse transcriptase inhibitor (NNRTI), has demonstrated non-inferior efficacy and better tolerability than efavirenz in first-line therapy at weeks 48 and 96.4,5 Tenofovir/emtricitabine/rilpivirine also has confirmed potent antiviral efficacy and a favourable safety profile for use in virologically suppressed (HIV RNA <50 copies/mL) adult patients on a stable ritonavir-boosted protease inhibitor-based regimen.6

Rilpivirine and tenofovir/emtricitabine/rilpivirine each have the constraint of needing to be taken with a meal to enhance absorption and exposure.7 Rilpivirine shares with nevirapine a good metabolic profile, but has the advantage of its formulation as a single-tablet regimen when combined with tenofovir/emtricitabine. Thus, in patients on long-term nevirapine-containing therapy, switching to rilpivirine as a single-tablet regimen of tenofovir/emtricitabine/rilpivirine might further improve convenience while preserving efficacy, tolerability and lipid profile.
Switching from nevirapine to rilpivirine

However, rilpivirine, like other NNRTIs, is metabolized by cytochrome P450. Given the prolonged inductive effect of nevirapine on the CYP3A4 enzyme after discontinuation, we assessed the clinical implications of potential reduced rilpivirine exposures subsequent to switching virologically suppressed HIV-1-infected patients on tenofovir/emtricitabine and nevirapine to tenofovir/emtricitabine/rilpivirine. In this pilot study we evaluated the efficacy, pharmacokinetics, virological implications, safety, food intake and patient’s satisfaction of switching from tenofovir/emtricitabine and nevirapine to tenofovir/emtricitabine/rilpivirine.

Methods

This prospective, single-arm, open-label, non-comparative, single-centre study enrolled, between September and December 2012, HIV-1–infected adults receiving a stable tenofovir/emtricitabine and nevirapine regimen, who had maintained virological suppression with a plasma HIV-1 RNA <50 copies/mL for >6 months, with no history of virological failure on an NNRTI–including regimen, and were willing to change their current regimen for convenience reasons. Desire to simplify their regimen was based on a patient–provider discussion on current antiretroviral options. Main exclusion criteria were the presence of resistance mutations to rilpivirine, tenofovir or emtricitabine by cumulative plasma RNA genotype testing or, if not available, by recent HIV DNA genotype and concomitant therapy with drugs contraindicated with rilpivirine, including proton pump inhibitors.

As the study used an approved regimen during a routine visit, ethics approval was not sought. However, data collection from NADIS electronic medical records was approved by an ethics committee and every patient provided written consent for additional biological sampling. On day 1, subjects were switched to tenofovir/emtricitabine/rilpivirine once daily to be taken orally with a meal. HIV-1 RNA (Cobas AmpliPrep/Cobas TaqMan HIV-1 V2.0 assay, Roche) was assessed and a CD4 cell count was performed at baseline and weeks 4, 12 and 24; haematology and chemistry were evaluated at each visit (baseline and weeks 1, 2, 4, 12 and 24) and fasting lipids at baseline and weeks 4 and 12. Patients with an HIV-1 RNA >50 copies/mL during follow-up had a second viral load test done within 4 weeks. Data were prospectively collected from NADIS electronic medical records, which include demographic details, clinical events, antiretroviral history and routine biological data.

Blood samples for nevirapine pharmacokinetic analyses were collected at baseline and weeks 1, 2 and 4. For rilpivirine a plasma trough concentration and an additional blood sample any time post-dosing but at least 1 h after the trough measurement was collected at weeks 1, 2, 4 and 12. The plasma drug concentrations were measured using a previously validated liquid chromatography–tandem mass spectrometry assay for nevirapine and adapted for rilpivirine. A patient self-administered questionnaire was completed at weeks 1, 2, 4 and 12 to provide information on food intake at the time of the last drug intake. The HIVTSQc questionnaire was administered to evaluate any change in patient satisfaction at week 4.

The primary endpoint of the study was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 12 by intent-to-treat analysis. The secondary endpoints were proportion of subjects with HIV-1 RNA <50 copies/mL at week 24, safety and tolerability of nevirapine/emtricitabine/rilpivirine, patient satisfaction at week 4 and rilpivirine pharmacokinetics. Calories and lipids from the meal taken with tenofovir/emtricitabine/rilpivirine the day prior to weeks 1, 2, 4 and 12 visits were evaluated from patient questionnaires by a specialized HIV dietician.

PBMC cellular DNA was isolated by QIASymphony gDNA extraction followed by nested PCR amplification of the PR/RT region. The population genotype was determined by Sanger sequencing.

Characteristics of patients were described using either the median with IQR for continuous variables or the frequency for categorical variables. For the population pharmacokinetic analysis, data on rilpivirine pharmacokinetics were analysed by a non-linear mixed-effect modelling method using NONMEM Version VI level 1.0. Comparison of individual apparent clearance of rilpivirine at weeks 1 and 12 was conducted using a paired Student’s t-test (P < 0.05 for significance).

Results

Among the screened subjects, nine were not included in the study because rilpivirine resistance mutations were detected by resistance testing: the E138A mutation in six subjects (RNA genotype in four cases and DNA genotype in two cases), the E138R mutation in one RNA genotype and the M230I mutation in two DNA genotypes. Baseline characteristics of the 32 enrolled patients are presented in Table 1. The historical RNA genotype was available for 18 subjects, of whom 15 had no resistance mutations and 3 harboured reverse transcriptase mutations (M41L + M184V + T215Y, V90I + V179I and V90I + K101R); DNA genotype was determined for 14 subjects, with no resistance mutations in 10 and resistance mutations in 4 (V179V/I in 2 subjects, M184M/I in 1 subject and V106I in 1 subject).

At week 12, all the subjects maintained plasma HIV-1 RNA <50 copies/mL. By intent-to-treat analysis, discontinuation = failure, the success rate was 31/32 (97%), with a lower limit of the 95% CI of 84%. At week 24, one patient had a dip at 91 copies/mL, and was retested at <50 copies/mL 4 weeks later without any change of therapy.

Tenofovir/emtricitabine/rilpivirine was well tolerated overall, with no serious adverse event. Three subjects discontinued the treatment, one subject for rilpivirine-related insomnia at week 1 and two subjects after week 12 because of food constraint. There was no grade 3/4 laboratory abnormality. Changes over 12 weeks in the fasting lipid parameters were statistically significant (P < 0.05), with a decrease in total cholesterol (mean −0.35 mg/dL), LDL-cholesterol (mean −0.25 mg/dL) and HDL-cholesterol (mean −0.11 mg/dL) and an increase in triglycerides (mean +0.15 mg/dL), while the change in total HDL-cholesterol was statistically significant (P = 0.02).

Table 1. Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Median (IQR)</th>
</tr>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td></td>
<td>51 (44–61)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>26 (81)</td>
<td></td>
</tr>
<tr>
<td>HBV coinfection, n (%)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>HIV subtype B/CRF02/unknown, n/n</td>
<td>17/14</td>
<td></td>
</tr>
<tr>
<td>Time since first HIV+ test (years), median (IQR)</td>
<td>10 (8–12)</td>
<td></td>
</tr>
<tr>
<td>Time since first antiretroviral therapy (years), median (IQR)</td>
<td>8 (6–11)</td>
<td></td>
</tr>
<tr>
<td>Time on tenofovir/emtricitabine–nevirapine (years), median (IQR)</td>
<td>4 (3–5)</td>
<td></td>
</tr>
<tr>
<td>Time of HIV-1 RNA &lt;50 copies/mL (years)</td>
<td>6 (5–8)</td>
<td></td>
</tr>
<tr>
<td>CD4 count (cells/mm³), median (IQR)</td>
<td>698 (493–825)</td>
<td></td>
</tr>
<tr>
<td>CD4 nadir (cells/mm³), median (IQR)</td>
<td>189 (111–272)</td>
<td></td>
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<tr>
<td>Creatinine clearance (mL/min), using the MDRD formula, median (IQR)</td>
<td>74 (68–80)</td>
<td></td>
</tr>
<tr>
<td>Nevirapine once a day, n (%)</td>
<td>26 (81)</td>
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clearance decreased between weeks 1 and 12 (7.98 ± 27 patients by 2 weeks post-switch. Mean rilpivirine concentration (3 mg/L) in all the subjects at week 1, and undetectable in 16.1% of patients at week 1, 3.2% at week 4 and no patient after week 12 because of food constraint were among the five unsatisfied patients at week 4.

Mean rilpivirine trough plasma concentration and nevirapine plasma concentration over time are presented in Figure 1. Rilpivirine trough plasma concentration <50 µg/L was seen in 16.1% of patients at week 1, 3.2% at week 4 and no patient at week 12. Nevirapine concentration was below the therapeutic range (3 mg/L) in all the subjects at week 1, and undetectable in 27 patients by 2 weeks post-switch. Mean rilpivirine individual clearance decreased between weeks 1 and 12 (7.98 ± 1.13 versus 7.75 ± 1.10 L/h; P < 0.01).

Meal composition, analysed from 118 questionnaires during the first four visits, was 750 ± 368 kcal with 33 ± 20 g of fat; meal composition was below the recommendation of at least 390 kcal and 12 g of fat in 19% of the meals (37% of breakfasts, 8% of dinners and 0% of lunches). No correlation was found between rilpivirine C_{trough}, and kcal (r = −0.07; P = 0.51) and fat (r = 0.05; P = 0.64).

**Discussion**

In this study, switching from tenofovir/emtricitabine and nevirapine to tenofovir/emtricitabine/rilpivirine was an effective strategy. It was reasonably safe as there was only one drug-related adverse event leading to discontinuation, an early rilpivirine-associated insomnia, which is one of the most frequent adverse events in the Phase 3 studies of rilpivirine in first-line therapy. The switch of nevirapine to rilpivirine was associated with absence of significant change in lipid levels, as expected based on the favourable profile of both nevirapine and rilpivirine.

In a post-hoc analysis of suppressed patients switching from a boosted protease inhibitor-based regimen to tenofovir/emtricitabine/rilpivirine, baseline mutations with low-level resistance to rilpivirine (E138A/G/K/Q) in proviral HIV-1 DNA from PBMCs did not affect virological success. In our study, the three patients with the presence of the V179I mutation in RNA genotype (n = 1) or in DNA genotypes (n = 2) prior to the switch to tenofovir/emtricitabine/rilpivirine maintained virological suppression over 24 weeks. Even if the subjects enrolled in our study had no prior virological failure on the NNRTI-containing regimen and were fully suppressed on a current nevirapine-based regimen for >4 years, rilpivirine resistance mutations were found at screening in nine subjects, in four cases in the DNA genotype, leading to exclusion of patients from the study. Therefore, a historical genotype generated prior to antiretroviral therapy should be consulted (if available) and re-interpreted with the latest algorithm to rule out archived resistance mutations, prior to switching from a virologically suppressive regimen to a rilpivirine-containing regimen.

If no historical genotype is available, circulating PBMC DNA genotyping can act as a record of transmitted or previously emergent drug resistance and may have utility in detecting drug resistance mutations. This makes it possible to provide the best chance of success to patients with current full virological suppression who desire to switch from their current regimen to decrease pill burden or reduce side effects.

Rilpivirine concentration was >50 µg/L, the lower limit of rilpivirine Phase 3 mean trough, 1 week after switching from nevirapine to rilpivirine in most of the patients. The limited inductive effect of nevirapine on rilpivirine metabolism, illustrated by the small decrease in rilpivirine clearance between weeks 1 and 12, had no clinical relevance in the setting of virologically suppressed...
patients. When switching from efavirenz to rilpivirine, the mean values of rilpivirine trough concentrations were above the lower limit of Phase 3 trials at 2 weeks, indicating that the inductive effect on rilpivirine metabolism seems to be more pronounced with efavirenz than with nevirapine.18

Even in the few patients who had taken theoretically insufficient meals with their tablet, no virological failure occurred. Interestingly, there was no correlation between kcal or fat and rilpivirine trough concentrations, a calorie intake even lower than that recommended being in fact sufficient. Treatment satisfaction was overall better with the regimen of one pill once a day compared with the previous treatment with three pills a day in a once daily or twice daily dosage. The main reason for worse satisfaction was the food constraint. The high saturation upon tenofovir/emtricitabine/rilpivirine switch is biased, as patients enrolled in the study were those willing to switch an already simple and easy regimen to an even simpler regimen. Our study has other limitations, including its open-label nature, the limited sample size and the highly selected population with prolonged virological suppression, with exclusion of patients with archived genotypic rilpivirine-associated resistance mutations.

In summary, switching from tenofovir/emtricitabine and nevirapine to a tenofovir/emtricitabine/rilpivirine single-tablet regimen is an effective strategy. Nevirapine has a short and limited inductive effect on rilpivirine metabolism, which is not clinically relevant. Of note, 9% of patients did not continue the new regimen, highlighting the importance of strict selection of candidates who were already asymptomatic and virologically suppressed, when trying to switch the current antiretroviral regimen for a more convenient one.

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Transparency declarations

C. A. is a board member of and has received travel grants from Gilead and Janssen. E. D. has received speaking honoraria from Janssen. E. B. is a board member of Gilead and has received travel grants from Gilead and Janssen. F. R. is a consultant for and has received speaking honoraria and research grants from Gilead and Janssen. V. R., B. B., S. P., E. A.-G., D. B., R. B., A. R. and S. B.: none to declare.

Author contributions

C. A., E. D. and F. R. conceived the protocol design and analysis plan, and interpreted data. C. A. wrote the first draft of the article with critical review and approval of the submitted version by all the authors. E. D. and R. B. performed the pharmacokinetic analysis. S. P. provided statistical expertise. E. A.-G. analysed the resistance testing. A. R. analysed the food questionnaire. C. A., V. R., B. B., D. B., E. B., S. B. and F. R. enrolled patients in the study, reviewed the study data reports and approved the final manuscript.

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