A randomized clinical trial comparing ritonavir-boosted lopinavir versus maraviroc each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection

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Objectives: The objective of this study was to assess post-exposure prophylaxis (PEP) non-completion at day 28, comparing ritonavir-boosted lopinavir versus maraviroc, both with tenofovir disoproxil/emtricitabine as the backbone.

Methods: We conducted a prospective, open, randomized clinical trial. Individuals attending the emergency room because of potential sexual exposure to HIV and who met criteria for receiving PEP were randomized to one of two groups: tenofovir disoproxil/emtricitabine (245/200 mg) once daily plus either ritonavir-boosted lopinavir (400/100 mg) or maraviroc (300 mg) twice daily. Five follow-up visits were scheduled for days 1, 10, 28, 90 and 180. The primary endpoint was PEP non-completion at day 28. Secondary endpoints were adherence, adverse events and rate of seroconversions. This study was registered in ClinicalTrials.gov: NCT01533272.

Results: One-hundred-and-seventeen individuals were randomized to receive ritonavir-boosted lopinavir and 120 to maraviroc (n = 237). PEP non-completion at day 28 was 38% (n = 89), with significant differences between arms [ritonavir-boosted lopinavir 44% (n = 51) versus maraviroc 32% (n = 38), P = 0.05]. We performed a modified ITT analysis including only those patients who attended on day 1 (n = 182). PEP non-completion in this subgroup was also significantly higher in the ritonavir-boosted lopinavir arm (27% versus 13%, P = 0.004). The proportion of patients with low adherence was similar between arms (52% versus 47%, P = 0.56). Adverse events were reported by 111 patients and were significantly more common in the ritonavir-boosted lopinavir arm (72% versus 51%, P = 0.003). No seroconversions were observed during the study.

Conclusions: PEP non-completion and adverse events were both significantly higher in patients allocated to ritonavir-boosted lopinavir. These data suggest that maraviroc is a well-tolerated antiretroviral that can be used in this setting.

Introduction

Considerable emphasis is now placed on prevention strategies involving ART.1 Post-exposure prophylaxis (PEP) is a 28 day course of ART recommended for persons who have had a potential exposure to HIV. Results from animal studies2 indicate that adequate compliance is necessary for PEP to be effective; however, compliance is often limited by frequent drop-outs and the toxicity of antiretroviral drugs such as PIs.3-5 The search for better tolerated regimens is a priority.

Maraviroc has been shown to be well-tolerated and may be considered as a candidate for PEP.6 In animal models maraviroc has demonstrated preventive effectiveness as a microbicide,7 while recent studies in HIV-negative women and men have found that the drug reaches higher concentrations in the cervico-vaginal tract and rectal mucosa than in plasma.8,9 Here, we examined whether tenofovir disoproxil/emtricitabine plus maraviroc would achieve better completion rates, adherence and tolerability than would tenofovir disoproxil/emtricitabine plus ritonavir-boosted lopinavir.
Methods

We performed an open, randomized clinical trial at a tertiary-care hospital in Barcelona. Participants were individuals who attended the emergency room (ER) between April 2012 and July 2014 due to a potential sexual exposure to HIV. Risk assessment and PEP recommendation were performed according to Spanish guidelines. Individuals who were ≥18 years old, resident in Barcelona and who agreed to participate and signed informed consent were randomized to receive tenofovir disoproxil/emtricitabine (245/200 mg) once daily plus either ritonavir-boosted lopinavir (400/100 mg) twice daily or maraviroc (300 mg) twice daily. A full 28 day prescription was given and initiated immediately (day 0). A computer-generated list of numbers was used to randomize participants. Prophylactic measures for other sexually transmitted infections (STIs) were administered. Owing to our hospital’s protocols we were not able to perform HIV testing in the ER, and therefore HIV-negative status could not be confirmed before starting PEP. After randomization, five follow-up visits were scheduled for days 1, 10, 28, 90 and 180. The primary endpoint was PEP non-completion at day 28. PEP non-completion was considered when the patient was lost to follow-up before day 28, when treatment was discontinued or switched for any reason, or if the patient died. Secondary endpoints were: being lost to follow-up at days 1, 28, 90 and 180; low adherence to PEP; number of adverse events; and rate of seroconversions. The study was approved by the hospital’s research ethics committee (approval number: HCP/2011/1106) and was registered in ClinicalTrials.gov: NCT01533272.

The day 1 visit was scheduled with an infectious diseases specialist within 72 h of starting PEP. Demographics, risk behaviour, history of STIs and previous PEP were recorded. As part of the risk assessment, we also gathered information about the sexual partner: hepatitis C virus, hepatitis B virus and HIV serostatus, ART and level of detection of viral load. This information was conferred by our patients; we had no access to any other personal information of partners or that enabled us to identify them. Laboratory monitoring and sexual risk exposure counselling were performed and repeated at days 28, 90 and 180. Treatment adherence was reinforced on days 1, 10 and 28. Adherence was measured on day 28 with the Simplified Medication Adherence Questionnaire. The degree of adherence can be calculated based on a patient’s responses and for the present study we classified <94% as low adherence, a cut-off that has also been adopted by other authors. Adverse events were assessed and graded at every scheduled visit, following WHO recommendations.

Statistical analysis

The sample size was calculated with a 1-β statistical power of 90% and a protection level versus the bilateral α Type I error of 5%, assuming a treatment discontinuation of 51% in the ritonavir-boosted lopinavir arm and 30% in the maraviroc arm, and a 30% of unevaluable patients.

An ITT analysis was performed considering PEP non-completion at day 28. Since we had no information about treatment initiation in individuals who did not attend any of the scheduled visits, we hypothesized that reasons for non-attendance could be independent of the regimen prescribed. Hence, we also performed a modified ITT analysis considering patients who attended at least on day 1. The individuals who discontinued PEP because they were found to be HIV positive on day 1 or because the sexual partner subsequently was found to be HIV negative were excluded from this analysis. Continuous variables were compared by means of the Student’s t-test or the Mann–Whitney U-test. Categorical variables were compared using either the χ² test or Fisher’s exact test. Backward logistic regression (Wald) was performed to assess the independent factors associated with PEP non-completion at day 28. Statistical analysis was conducted using SPSS.

Results

A total of 237 individuals were randomized to receive tenofovir disoproxil/emtricitabine plus either ritonavir-boosted lopinavir (n=117) or maraviroc (n=120). The study flow chart is shown in Figure 1. Participants were mostly MSM. The level of risk was appreciable (defined as any sexual exposure excluding those of low risk) in 83% of individuals (13% high and 70% moderate). Characteristics of exposed individuals are shown in Table S1 (available as Supplementary data at JAC Online). HIV infection was detected in three randomized patients at the day 1 visit and they were referred to an HIV clinic to continue follow-up.

PEP non-completion

Only 187 individuals (79%) of those who were randomized attended the first scheduled visit, there being no differences in loss to follow-up between arms (P=0.87) (Figure 1). PEP non-completion at day 28 was 38% (n=89), with significant differences between arms (ritonavir-boosted lopinavir 44% versus maraviroc 32%, P=0.05). We performed a modified ITT analysis including only those patients who attended the day 1 visit and excluding individuals who discontinued PEP because they tested HIV positive on day 1 (n=3) or because the sexual partner subsequently tested HIV negative (n=2) (n=182). Characteristics of this subgroup are shown in Table S1. PEP non-completion in this subgroup was higher in the ritonavir-boosted lopinavir arm (27% versus 13%, P=0.004), as was the proportion of patients lost to follow-up (21% versus 11%, P=0.02). Only a few patients discontinued PEP or switched treatment due to adverse events (Figure 1). The Simplified Medication Adherence Questionnaire was administered on day 28 and showed that the proportion of patients with low adherence to PEP was similar between arms (ritonavir-boosted lopinavir 52% versus maraviroc 47%, P=0.56). There were no seroconversions during this study.

Factors associated with PEP non-completion

The factors associated with PEP non-completion were analysed (Table 1). The logistic regression model showed that being in the ritonavir-boosted lopinavir arm (P=0.015), non-Caucasian ethnicity (P<0.0001), a low risk of exposure (P<0.0001) and previous PEP (P=0.005) were independent factors associated with PEP non-completion.

Adverse events

There were 353 adverse events in 111 individuals (Table S2). No grade III or IV adverse events related to medication were reported. All adverse events resolved. Regarding laboratory abnormalities at day 28, no significant differences between groups were observed and all were resolved at day 90.

Discussion

In this study, we found that rates of PEP non-completion and adverse events were significantly higher in patients allocated to ritonavir-boosted lopinavir, as compared with maraviroc. Additionally, non-Caucasian individuals with a low risk of exposure and those who had had previous PEP had a significant and independent higher risk of PEP non-completion.

The present study was conducted concurrently with another one of similar characteristics and using the same methods, which compared ritonavir-boosted lopinavir with raltegravir, both with tenofovir disoproxil/emtricitabine as the backbone,
and we found that rates of loss to follow-up, poor adherence and adverse events were significantly higher in patients allocated to the ritonavir-boosted lopinavir arm.

In line with previous reports,16,17 21% of the individuals who were initially randomized in our study did not attend any of the follow-up visits; furthermore, drop-out rates increased over time, such that only one-third of participants completed all 6 months of follow-up. This is an important limitation to our study, since adverse events, laboratory changes or seroconversions could not be assessed in this group and might represent a

Table 1. Factors associated with PEP non-completion at day 28 due to any cause or to adverse events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PEP discontinuations due to any cause in the entire cohort (n=237), OR (95% CI)</th>
<th>PEP discontinuations due to any cause in patients who attended the day 1 visit (n=182), OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of analysisa</td>
<td>univariate</td>
<td>multivariate</td>
</tr>
<tr>
<td>Randomization arm: ritonavir-boosted lopinavir</td>
<td>1.3 (1.0–1.7), P = 0.05</td>
<td>2.6 (1.2–5.4), P = 0.015</td>
</tr>
<tr>
<td>Race: non-Caucasian</td>
<td>2.1 (1.6–2.8), P &lt; 0.0001</td>
<td>5.6 (2.5–12.3), P &lt; 0.0001</td>
</tr>
<tr>
<td>Risk assessment: low</td>
<td>1.2 (1.1–1.4), P = 0.009</td>
<td>5.3 (2.1–12.9), P &lt; 0.0001</td>
</tr>
<tr>
<td>Previous PEP: yes</td>
<td>1.4 (1.1–1.7), P &lt; 0.0001</td>
<td>3.3 (1.5–7.7), P = 0.005</td>
</tr>
<tr>
<td>Presence of adverse events due to PEPb: no</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold formatting represents significant P values.

aIndividuals attending the day 1 visit with an HIV-positive test at baseline or with an HIV-negative partner were excluded from analysis.

bNot measured in patients not attending the day 1 visit.

and we found that rates of loss to follow-up, poor adherence and adverse events were significantly higher in patients allocated to the ritonavir-boosted lopinavir arm.

In line with previous reports,16,17 21% of the individuals who were initially randomized in our study did not attend any of the follow-up visits; furthermore, drop-out rates increased over time, such that only one-third of participants completed all 6 months of follow-up. This is an important limitation to our study, since adverse events, laboratory changes or seroconversions could not be assessed in this group and might represent a
threat for efficacy and generate safety issues, as well as limiting any conclusions that can be drawn from the results. We consider that in addition to tolerability of the PEP regimen, the possible reasons for drop-out include pill-burden, difficulties accessing the health system and a non-anonymous environment, a reduced perception of risk, easier access to non-clinical community organizations and rapid HIV/STI tests.

Adherence was also compromised to a similar extent as in previous reports. In the present study both antiretrovirals were prescribed twice daily and missing doses were frequently reported, which suggests that a single tablet three-drug regimen could improve outcomes.

Contrary to what we expected, the presence of adverse events related to PEP was not associated with non-completion. A possible explanation for this could be that although adverse events were frequently described by participants, most were mild, well tolerated and easily resolved.

Other limitations to our study are that we only included sexual exposures and only 8% of our study population were women. Different outcomes may therefore have been observed with parenteral risk and with a sample that was more balanced by gender.

In summary, we observed an improvement in PEP completion and toxicity with a maraviroc-containing regimen, suggesting that maraviroc is a well-tolerated candidate for prophylactic use.

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ViV Healthcare reviewed a preliminary version of this manuscript for factual accuracy. The authors are solely responsible for final content and interpretation.

Author contributions

Supplementary data
Tables S1 and S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)

References


