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Protease Inhibitors or NNRTIs as First-Line HIV-1 Treatment in West Africa (PIONA)

A Randomized Controlled Trial

Jespersen, Sanne; Hønge, Bo Langhoff; Krarup, Henrik; Medstrand, Patrik; Sørensen, Allan; Medina, Candida; da Silva Té, David; Correira, Faustino Gomes; Erikstrup, Christian; Østergaard, Lars; Wejse, Christian; Laursen, Alex Lund; Bissau HIV Cohort study group

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1 Protease Inhibitors or NNRTIs as First-Line HIV-1 Treatment in West Africa (PIONA):
2 a Randomised Controlled Trial

3
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18
19 Declaration of interests

20 We declare no competing interests.

21

22

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24

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26

27 Contributors

28 SJ and ALL conceived and designed the study. SJ, BLH, CE, LØ, CW, and ALL analysed and

1 interpreted the data. SJ, BLH, AS, CM, DdaS, and FGC carried out clinical assessments of patients.
2 HK carried out viral-load analyses. PM carried out resistance testing and interpretation. SJ drafted
3 the manuscript. SJ, BLH, HK, PM, CE, LØ, CW, and ALL critically revised the manuscript for
4 intellectual content. All authors read and approved the final manuscript.

5

6

7 **Abstract**

8 **Background:** NNRTIs are recommended as part of first-line treatment for HIV-1 in Africa.
9 However, NNRTI-based regimens are more prone to resistance development than protease
10 inhibitors (PIs) in a context in which drug interruptions are frequent. The aim of this study was to
11 compare the efficacy and tolerability of NNRTIs with PIs in HIV-1-infected patients in Guinea-
12 Bissau.

13 **Methods:** This open-label randomised, two-arm superiority trial compared the use of two NRTIs
14 plus either one NNRTI (efavirenz or nevirapine) or one PI (lopinavir/ritonavir) in treatment-naïve
15 HIV-1-infected adults in the Bissau HIV Cohort (ClinicalTrials.gov, NCT0019235). The primary
16 endpoint was HIV-1 RNA <400 copies/ml after 12 months of treatment.

17 **Results:** Between May 5, 2011 and April 26, 2013, 400 patients were included in the study. In an
18 intention-to-treat analysis, the proportions of patients with viral suppression were similar in the
19 NNRTI (65/197 (33.0%)) and PI (68/203 (33.5%)) arms ($p=0.92$). No PI resistance was detected,
20 but high-level NNRTI resistance was seen in 17/30 (56.7%) of NNRTI vs. 3/26 (11.5%) of PI-
21 treated patients, $p<0.01$. After 1 year of follow-up, 65 patients died (16.3%) and 93 were lost to
22 follow-up (23.3%). There was no difference in mortality (hazard ratio 0.84, 95% CI 0.51-1.36) or
23 frequency of clinical adverse events between treatment arms (NNRTI: 73/197 (37.1%); PI: 69/203
24 (34.0%); $p=0.52$).

25 **Conclusion:** In patients at an HIV clinic in Guinea-Bissau, treatment with PIs led to less
26 development of resistance compared with NNRTIs but was not superior in terms of viral
27 suppression, CD4 cell increment, mortality, or severe adverse events.

1 **Key words:** HIV, antiretroviral treatment, Africa, protease inhibitors, non-nucleotide reverse
2 transcriptase inhibitors, Guinea-Bissau.

3

4 **Introduction**

5 Lifelong treatment is still a new concept in parts of Africa, where healthcare systems already face
6 challenges such as insufficient numbers of healthcare providers, intermittent drug supplies, fear of
7 stigmatisation, long distance to treatment clinics, and poor medical record registration.^{1,2} All these
8 factors increase HIV patients' risk of treatment failure.

9 Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are recommended as part of first-line
10 treatment for HIV-1 in Africa.³ NNRTIs have a longer elimination half-life than other antiretroviral
11 treatments (ARTs), which make NNRTI-based regimens more prone to resistance development in a
12 context of frequent drug interruptions. This problem is even more pronounced in Black Africans,
13 who more frequently harbour a polymorphism in cytochrome P450 2B6 associated with slower
14 plasma clearance of efavirenz (EFV).⁴

15 Large randomised trials comparing NNRTIs with protease inhibitors (PIs) have been conducted in
16 Europe and the United States of America,⁵⁻¹⁰ but these results are not generalisable to an African
17 setting due to differences in genetics, sex distribution, and adherence.^{4,11} Most studies comparing
18 NNRTIs with PIs in adults that have been conducted in Africa have indicated equivalent efficacy;
19 however, most of these studies only included women and treatment procedures were supported
20 economically and practically to a larger extent than is common in the vast majority of centers in
21 Sub-Saharan Africa. Thus, these trials probably do not reflect the typical reality of HIV treatment
22 on the African continent.¹²⁻¹⁵

23 The aim of this study was to compare the efficacy and tolerability of an NNRTI-based regimen with
24 those of a PI-based regimen in HIV-1-infected patients in Guinea-Bissau. We hypothesised that PIs
25 are a better choice as first-line treatment than NNRTIs in Guinea-Bissau.

26

27

1 **Methods**

2 *Study design*

3 This trial, named “PI or NNRTI as first-line HIV treatment in a West African population with low
4 adherence – the PIONA trial,” was an open-label, randomised, two-arm superiority trial in which
5 treatment-naïve patients infected with HIV-1 were randomised to a regimen including either an
6 NNRTI or a PI (ClinicalTrials.gov, NCT0019235). This study was approved by the National Ethics
7 Committee of Guinea-Bissau (Parecer NCP/No.11/2010). The Danish National Committee on
8 Biomedical Research Ethics gave its consultative approval (Case No. 1001028). An independent
9 Data and Safety Monitoring Board reviewed interim analyses from the PIONA trial every six
10 months.

11

12 *Participants*

13 Participants in the PIONA trial were included from the HIV clinic at Hospital National Simão
14 Mendes in Bissau, the capital of Guinea-Bissau. This clinic is the base of the Bissau HIV Cohort.¹⁶
15 We included all ART-naïve, HIV-1-infected adults ≥ 18 years of age seen at the clinic during the
16 study period and who fulfilled the criteria to commence ART according to WHO guidelines (CD4
17 cell count ≤ 350 cells/ μ l and/or clinical signs of immune suppression (WHO clinical stage 3 or 4)
18 irrespective of CD4 cell count)¹⁷. Exclusion criteria were tuberculosis treatment with rifampicin at
19 the time of enrolment, co-infection with HIV-2, liver enzyme elevation >5 times the upper normal
20 limit, cerebral disturbances that complicated the ability to give informed consent, or treatment with
21 nevirapine (NVP) to prevent mother-to-child transmission of HIV within the past year. Prior to
22 enrolment, all patients voluntarily provided signed and dated informed consent, or a fingerprint if
23 illiterate.

24

25

1 *Randomisation*

2 Computer-generated block randomisation (blocks of 10) was performed with a ratio of 1:1 to
3 NNRTI-based or PI-based ART after stratification by sex and CD4 cell count (≤ 200 or >200
4 cells/ μl). Sealed-window envelopes contained information about subsequent treatment.

5

6 *Procedures*

7 All patients received two NRTIs according to local guidelines. Patients in the NNRTI treatment arm
8 further received one NNRTI (EFV 600 mg once daily or NVP 200 mg once daily for the first 2
9 weeks and 200 mg twice daily subsequently). EFV was given to all males as well as females beyond
10 childbearing age. Pregnant patients and female patients with childbearing potential were treated
11 with NVP when CD4 cell count was ≤ 350 cells/ mm^3 . The PI treatment arm consisted of two NRTIs
12 and one PI (ritonavir-boosted lopinavir (LPV/r) 400/100 mg twice daily). Patients were switched to
13 second-line treatment based on clinical and/or immunological criteria. Immunological treatment
14 failure was defined as (1) a fall in CD4 counts to baseline (or below) or (2) CD4 levels persistently
15 <100 cells/ μl ¹⁷. In patients undergoing rifampicin-containing tuberculosis treatment, NVP and
16 LPV/r were replaced by EFV and patients in the LPV/r arm were withdrawn from the study.

17 Patients who developed grade 3 adverse effects interrupted ART and resumed all medications when
18 the adverse effect resolved to \leq grade 2 or the offending drug was substituted without interrupting
19 all ART. Patients experiencing grade 4 adverse effects were switched to another regimen.

20 Study visits occurred at 2 (if NVP was initiated), 4, 8, and 12 weeks after treatment initiation and
21 every 1-3 months thereafter. Patients were asked about pre-specified adverse events. Adverse events
22 were graded by severity. Adherence was assessed according to the number of days the patient was
23 late for their visit. Patients were followed until 12 months after treatment initiation. When patients
24 were late for their final blood samples, we allowed viral-load measurements and CD4 cell counts
25 obtained up to 18 months after treatment initiation to be included in analyses. Patients were
26 considered lost to follow-up if they had not visited the clinic for 6 months. Information on death and

1 transfer was collected through conversation with the patient, telephone calls with contact persons,
2 or from hospital wards.

3 HIV screening was conducted with the rapid Determine HIV-1/2 assay (Abbott Laboratories,
4 Abbott Park, IL, USA). Confirmation and discrimination were performed with the SD Bioline HIV
5 1/2 3.0 rapid test (Standard Diagnostics Inc., Kyonggi-do, South Korea) or the First Response HIV
6 Card 1-2.0 (PMC Medical, Mumbai, India). HIV type was confirmed via ImmunoComb HIV 1 & 2
7 BiSpot (Organics, Yavne, Israel) from stored plasma samples in Aarhus, Denmark. Venous blood
8 samples were collected for biochemical analyses (alanine aminotransferase levels, creatinine,
9 haemoglobin levels, white blood cell count, and platelets) when the patients initially came to the
10 clinic and after 1, 3, 6, and 12 months of ART.

11 CD4 cell counts were measured by flow cytometry using Partec CyFlow® SL_3 cytometer (Partec,
12 Munster, Germany) before ART initiation and after 3, 6, and 12 months of treatment. HIV-1 viral
13 load was measured from stored plasma samples (shipped to the Department of Clinical
14 Biochemistry, Aalborg University Hospital, Denmark) with the Abbott m2000 system (Abbott
15 Realtime HIV 1, version 9.00; Abbott Molecular Inc., Abbott Park, IL, USA) before ART initiation
16 and after 6 and 12 months of treatment. The lower level of detection was 75 copies/mL.

17 Samples from patients experiencing virologic failure were tested for HIV-1 resistance. In addition,
18 pre-therapy samples were tested for resistance from all patients with resistance after 12 months of
19 treatment. Genotypic resistance testing of protease and partial reverse-transcriptase (amino acids 6-
20 99 and 1-252, respectively) was performed using an in-house method as described.¹⁸ Drug
21 resistance mutations were examined according to the calibrated population resistance tool version
22 8.5 (<https://hivdb.stanford.edu/hivdb/by-mutations/>). Quality control was performed using the
23 online Quality Control program of the Los Alamos HIV sequence database (hiv.lanl.gov).
24 Nucleotide sequences reported in this study have been deposited in the Genbank repository
25 (Accession Numbers: MH476364-MH476446).

26

27

1 *Outcomes*

2 The primary outcome for the study was viral load suppression <400 copies/ml after 12 months of
3 ART. Secondary key effect measures were viral load suppression <75 copies/ml after 12 months of
4 ART, CD4 cell count increment of at least 100 cells/ μ l compared with baseline, adverse events,
5 adherence, development of resistance and mortality.

6
7 *Statistical analyses*

8 We hypothesised that virologic failure occurred more frequently in the NNRTI group, with
9 estimated failure rates of 12% for PI and 25% for NNRTI¹⁹⁻²¹. We therefore calculated the
10 necessary sample size to be 154 patients in each arm with a power of 80%; we needed to include
11 386 patients to account for an estimated 20% LTFU. We used the chi-squared test to compare the
12 proportions of patients who achieved viral suppression after 12 months of treatment. In a post-hoc
13 analysis, we compared the proportions of patients who achieved a composite endpoint of virologic
14 failure or death after 12 months of treatment; we also assessed endpoints after six months of
15 treatment. Mortality was assessed with Cox proportional hazard models. A post-hoc sensitivity
16 analysis classified patients lost to follow-up as dead.

17 The primary analyses were intention-to-treat analyses that included all randomised patients
18 irrespective of changes in ART. In a modified intention-to-treat analysis, we excluded patients who
19 were mistakenly included because they were randomised before information on eligibility was
20 obtained. An on-treatment analysis of viral suppression included only patients who completed the
21 study on the initial randomised regimen and had complete outcome assessments.

22 Median changes in CD4 cell counts from baseline to 1 year of ART were compared with the
23 Wilcoxon rank sum test. The proportions of patients with CD4 cell count increments of at least 100
24 cells/ μ l since baseline and frequencies of adverse events were compared between treatment arms
25 with the chi-squared test. Adherence was assessed by calculating the median number of days each
26 patient was late for their appointment. Comparisons between treatment groups were made with the
27 Wilcoxon rank sum test.

1 All statistical analyses were carried out using Stata IC 13.1 (StataCorp, College Station, TX, USA).

2

3 *Role of the funding source*

4 AbbVie Pharmaceuticals donated LPV/r (Aluvia) for the trial. AbbVie had no role in study design,
5 data collection, or data analysis, but was permitted to review the manuscript and suggest changes.

6 Final decisions on content were exclusively made by the authors.

7

8 **Results**

9 Between May 5, 2011 and April 26, 2013, 400 patients were enrolled in the study (Figure 1). HIV-
10 1-infected patients not included in the study were more likely to have higher baseline CD4 cell
11 counts and body mass index and were more likely to not start ART at HIV diagnosis
12 (Supplementary Table 1, <http://links.lww.com/QAI/B199>). After randomisation, confirmation of
13 HIV type led to the exclusion of 3 patients with HIV-2 and 12 patients with HIV-1/2 dual infection
14 who were initially incorrectly diagnosed with HIV-1. Five patients did not fulfil the inclusion
15 criteria for other reasons (Figure 1). Results from 380 patients were included in the modified
16 intention-to-treat analyses. Sixty-five patients died within the first 12 months of treatment. After
17 completion of 12 months of initial randomised treatment, final viral-load measurements were
18 obtained for 87 NNRTI-treated patients (44.2%) and 84 PI-treated patients (41.4%; $p=0.57$). These
19 patients were included in the on-treatment analyses.

20 Treatment was halted prematurely for 8/197 NNRTI-treated patients (4.1%) and for 12/203 PI-
21 treated patients (5.9%; $p=0.40$). The main reasons for stopping or switching treatment were start of
22 tuberculosis treatment (5 patients), HIV-2 or HIV-1/2 dual infection (4 patients), grade 3 or 4
23 adverse events (4 patients), consent withdrawn/patient wished to withdraw (3 patients), and
24 immunological treatment failure (2 patients, both in the NNRTI-arm). Another 31 patients fulfilled
25 the criteria for immunological treatment failure by the end of the study.

26 Characteristics of the patients are presented in Table 1.

1 There were no significant differences in the proportions of patients achieving viral suppression after
2 6 or 12 months between treatment arms (Table 2). No differences in viral suppression were detected
3 between NRTI-backbones. Thirty-one of 197 NNRTI-treated patients (15.7%) and 26/203 PI-
4 treated patients (12.8%; $p=0.40$) displayed virologic failure with viral load >400 copies/ml after 12
5 months of treatment. In the on-treatment analysis, 29/87 NNRTI-treated patients (33.3%) and 23/84
6 PI-treated patients (27.4%) exhibited virologic failure ($p=0.40$).

7 Among 57 patients with virologic failure, samples were available for resistance testing in 56
8 patients. The most common HIV-1 subtype was circulating recombinant form 02_AG (CRF02_AG)
9 found in 52/56 (92.9%). Genotypes from time of virologic failure revealed that 22/30 (73.3%) in the
10 NNRTI-arm and 7/26 (26.9%) in the PI-arm had any NRTI or NNRTI mutation, $p<0.01$. No cases
11 of major PI mutations were detected, while NNRTI resistance was common among patients
12 receiving NNRTI (Table 3). The most common NNRTI mutations were K103N (Supplementary
13 Table 3, <http://links.lww.com/QAI/B199>). Among the 25 patients with NNRTI resistance, pre-
14 therapy sequencing was successfully performed in 22 showing pre-therapy NNRTI resistance in six
15 patients (27.2%), including two patients in the PI-arm.

16 CD4 cell counts after at least 12 months of treatment were available for 96/197 NNRTI-treated
17 patients and 93/203 PI-treated patients. Although numerically higher in the PI-arm, there were no
18 significant differences in the increase in absolute CD4 cell count (NNRTI: 167 cells/ μ l, IQR 37-293
19 cells/ μ l; PI: 202 cells/ μ l, IQR 87-351 cells/ μ l; $p=0.25$) and no between-treatment difference in the
20 proportion of patients with a CD4 cell-count increment of at least 100 cells/ μ l (NNRTI: 59/96,
21 61.5%; PI: 67/93, 72.0%; $p=0.12$).

22 After 1 year of follow-up, 35 deaths (17.8%) occurred in the NNRTI-arm and 30 deaths (14.8%)
23 occurred in the PI-arm ($p=0.42$). Ninety-three patients (23.3%) were lost to follow-up and 23
24 patients (5.6%) withdrew. There was no difference in mortality between arms (hazard ratio (HR)
25 0.84, 95% CI: 0.51-1.36) but patients with baseline CD4 cell count below 200 cells/ μ l had higher
26 mortality than those with higher CD4 cell counts (HR 5.30, 95% CI: 2.42-11.60). In a sensitivity
27 analysis in which patients lost to follow-up were classified as dead, there was no between-treatment
28 difference in mortality (LTFU). (HR 0.98, 95% CI: 0.72-1.33). When death and virologic failure

1 were treated as a composite endpoint, no difference in outcome was detected between treatment
2 arms (HR 0.89, 95% CI 0.60-1.32; Supplementary Table 2, <http://links.lww.com/QAI/B199>).

3 The frequencies of clinical adverse events were similar in the two treatment arms (NNRTI: 73/197
4 (37.1%); PI: 69/203 (34.0%); $p=0.52$). More patients receiving NNRTI experienced a grade 1 or 2
5 elevation of alanine aminotransferase (ALT) (NNRTI: 47/197 (23.9%); PI: 22/203 (10.8%);
6 $p<0.01$) or grade 1 or 2 anaemia compared with patients treated with PI (NNRTI: 98/197 (49.8%);
7 PI: 80/203 (39.4%); $p=0.04$) (Table 4). No difference in ALT were seen according to choice of
8 NNRTI (EFV: 26/117 (22.2%); NVP: 21/80 (26.3%); $p=0.52$)

9 There was a non-significant trend toward lower adherence among patients in the PI-arm than among
10 patients in the NNRTI-arm (median number of days late per visit, 30 days (IQR 12-45 days) vs. 23
11 days (IQR 10-41 days), respectively; $p=0.07$). Patients with resistance mutations had lower
12 adherence than patients without (median number of days late per visit, 39 days (IQR 30-48 days) vs.
13 24 days (IQR 10-42 days), respectively; $p=0.01$).

14

15 **Discussion**

16 In this randomised study comparing PIs with NNRTIs conducted among HIV-1-infected patients in
17 Guinea-Bissau, the risk of developing resistance was lower for patients receiving PIs. However, a
18 PI-based treatment regimen was not superior to an NNRTI-based treatment regimen after 12 months
19 of follow-up in terms of virologic suppression, increases in CD4 cell count, or mortality. Both
20 regimens were well tolerated. There was a trend towards lower adherence for patients receiving PIs,
21 when compared with NNRTI.

22 The strength of this trial is that it reflects real life in many African HIV clinics; few data are
23 reported from these clinics, and few larger, randomised, controlled, treatment trials have been
24 carried out among adult HIV-infected patients of both sexes in Africa. However, the real-life
25 approach of this trial also led to several limitations. Data on adherence were insufficient, and only
26 half of the patients not registered as deceased had a viral-load measurement available after 1 year of
27 treatment, due to high rate of early mortality in patients with advanced disease as well as LTFU.

1 More patients than predicted died or were lost to follow-up, probably reflecting poor health-care
2 seeking behaviour as well as high levels of resistance. Virologic treatment failure should be
3 confirmed by a second measurement after assessing adherence, but due to the retrospective
4 measurements of viral load employed here; this confirmation was not possible and could have
5 overestimated the true prevalence of treatment failure. The comparison of PI with NNRTI is a
6 mixed comparison of NVP and EFV. However, previous studies have shown that NVP and EFV
7 have similar benefits in initial treatment of HIV infection when combined with two NRTIs²².

8 The number of randomised trials in Sub-Saharan Africa remains low, even though the majority of
9 people living with HIV are treated in this low-resource setting.²³ The OCTANE trials^{12,24} were
10 some of the first and largest randomised controlled trials to compare PIs with NNRTIs in Africa,
11 but only included females. The OCTANE Trial 1 indicated that NVP was inferior to LPV/r as an
12 initial ART among women with prior single-dose NVP exposure,²⁴ in accordance with later findings
13 from the Democratic Republic of Congo.²⁵ The OCTANE Trial 2, which included only women with
14 no prior NVP exposure, revealed that the two treatment regimens had equivalent virologic efficacy,
15 with 17% of NVP and 20% of LPV/r treated subjects experiencing virologic failure or death,²⁶ rates
16 that were lower than those detected in our study. The South African Phidisa II trial also determined
17 that EFV and LPV/r were equally effective, without differences in grade 4 adverse events,¹⁴ while a
18 study among pregnant Ugandan women reported equally high proportions of virologic suppression
19 (91% of EFV vs. 88% of LPV/R treated individuals) through one year postpartum, but more
20 gastrointestinal adverse events occurred in the LPV/r arm.¹³ In a randomised four-arm treatment
21 trial in Senegal, dual therapy with tenofovir and LPV/r was less efficient compared with two NRTIs
22 plus one NNRTI or with triple NRTI treatment,¹⁵ while unboosted atazanavir in combination with
23 lamivudine and didanosine showed good efficacy and safety in naïve HIV-1-infected patients in
24 Senegal.²⁷ Most of these large randomised trials were supported economically and practically to a
25 larger extent than is common in the vast majority of centers in Sub-Saharan Africa and may not be
26 representative for the situation in most HIV clinics in this area. Overall, in the current investigation,
27 the rates of viral suppression were only 33% in the intention-to-treat population and 69% in the on-
28 treatment population. These rates are lower than those reported in a review of 89 studies from Sub-
29 Saharan Africa in which 78% viral suppression was achieved after six months of ART.²⁸ The lower
30 proportion of virologic suppression in our study may be explained by poor adherence; patients were

1 often late for their appointments, suggesting periods without treatment. As in many similar clinics
2 in Sub-Saharan Africa, conditions in Bissau are bad regarding the structure of the healthcare
3 system, economy, mobility of the population, adherence, drug supply, and political stability, all of
4 which lead to greater risk of treatment failure. Other important reasons for low level of viral
5 suppression were high rates of LTFU as well as lack of final viral load measurements in all patients.

6 A recent comprehensive metaanalysis found no difference in clinical or viro-immunological
7 outcomes between NNRTIs and PIs but did not address resistance development.¹⁰ Genotype
8 analysis in our study of samples from patients failing treatment revealed NNRTI or NRTI resistance
9 mutations in nearly three of four patients in the NNRTI-arm, which is even higher than that reported
10 in other studies,^{12,29} and reflect poor adherence. The high proportion of pre-therapy resistance can
11 be due to transmitted resistance or previous ART exposure. However, since pre-therapy resistance
12 testing was only done in those patients developing treatment failure it is not a true marker of
13 baseline resistance in Guinea-Bissau. Major PI mutations were not detected similar to findings from
14 other studies thus PIs can be used again despite treatment failure.^{29,30}

15 Here, the frequency of mild adverse events was low compared with other studies.¹³ We expected
16 neurocognitive adverse events to be more common among patients treated with an NNRTI because
17 a higher serum concentration of EFV, which is often seen in black Africans, is known to be
18 associated with adverse events.⁴ The true prevalence of adverse events may have been
19 underestimated since patients in Guinea-Bissau are unfamiliar with the concept of describing
20 adverse events despite being well monitored for this. Furthermore, low adherence may have given
21 the patients fewer adverse events due to lower serum concentrations. In addition, due to limited
22 laboratory capacity in Guinea-Bissau it was not possible to monitor lipids. This may reflect reality
23 in many African HIV clinics.

24 Patients in the PI-arm of our study were often late for their appointments at the clinic. LPV/r was
25 prescribed as two tablets twice daily. If patients misunderstood this regimen, tablets would remain
26 when the patients planned to come for their next visit and they would most likely postpone their
27 visit until they ran out of tablets.

1 Patients starting rifampicin-containing treatment for tuberculosis were excluded from the PI-arm of
2 the current trial due to drug interactions, while patients on tuberculosis treatment were allowed to
3 continue in the study if they were randomised to NNRTIs. This difference could potentially have
4 led to an overestimated risk of death in the NNRTI-arm. Overall, few patients were switched from
5 the randomised treatment in the current trial, yet we speculate that treatment failure was overlooked.

6 If lack of viral-load measurements in this study is a marker of poor healthcare-seeking behaviour,
7 then perhaps these patients are less likely to be virologically suppressed. This issue is expected to
8 be more problematic for an NNRTI-based regimen than for a more robust PI-based regimen, which
9 may overestimate the proportion of NNRTI-treated patients who were virologically suppressed. The
10 many reasons for this lack of measurements reflect challenges faced regularly in daily clinical life
11 in low-resource settings, such as patients not showing up as planned, unstable supplies of reagents,
12 and breakdowns of CD4 equipment. A multifaceted effort is suggested to be required to improve
13 adherence and LTFU in Guinea-Bissau, targeting both the individual, the health care system and the
14 social environment. However, considering the country's weak health care system, such a
15 comprehensive effort is not realistic, leaving peer support and ART groups preceded by education
16 of local staff as the best proposal for a solitary intervention^{31,32}.

17
18 We previously described problems with rapid HIV discriminatory tests.³³ In the current study, 15
19 patients turned out to be HIV-2 or HIV-1/2-dually infected and had to be withdrawn from the trial.
20 Treatment with PIs or integrase inhibitors with a high genetic barrier could be used in a setting with
21 high HIV-2 prevalence to enable a common first-line treatment. Such a simplified treatment
22 regimen for all patients will be of high value in a setting where logistical difficulties constantly
23 threaten regular drug availability and where some patients become dually infected while undergoing
24 treatment that is only effective against HIV-1.

25 **Conclusions**

26 Among HIV-1-infected patients in Guinea-Bissau, first-line treatment with PIs led to less
27 development of resistance compared with NNRTIs but was not superior in terms of viral
28 suppression, CD4 cell increment, mortality, or severe adverse events. A PI-based treatment may
29 still be important in a setting in which treatment interruptions are frequent and access to second-line

1 treatment is limited. It is possible that accumulated viral resistance against NNRTI will translate
2 into poorer outcomes during life-long treatment. Promoting adherence and decreasing LTFU must
3 be a top priority in Bissau.
4

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5

6 Figure 1: Screening, randomization and follow-up of study patients

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Table 1: Baseline characteristics

	NNRTI n=197	PI n=203
Female sex (%)	123 (62)	127 (63)
Age in years, median (IQR)	35 (30-42)	36 (30-41)
CD4 cell count in cells/ μ l, median (IQR)	139 (68-260)	153 (71-242)
CD4 cell percentage of total lymphocyte count	6.3 (3.7-11.9)	7.1 (3.7-11.6)
HIV-1 RNA in log ₁₀ copies/ml, median (IQR)	5.0 (4.4-5.5)	5.1 (4.3-5.7)
Body mass index in kg/m ² , median (IQR)	19.5 (17.4-22.2)	20.2 (17.7-22.7)
Education (%)		
None	59 (30)	56 (28)
1-4 years	17 (9)	21 (10)
5-11 years	115 (58)	121 (60)
School but level unknown	5 (3)	3 (1)
Missing	1 (1)	2 (1)
Marital status (%)		
Married	97 (49)	112 (55)
Divorced	9 (5)	13 (6)
Widowed	33 (17)	16 (8)
Single	55 (28)	62 (31)
Missing	3 (2)	0 (0)
NRTI backbone (%)		
Zidovudine+lamivudine	109 (55)	114 (56)
Tenofovir+emtricitabine	41 (21)	38 (19)
Abacavir+lamivudine	31 (16)	30 (15)
Tenofovir+lamivudine	15 (8)	19 (9)
Stavudine+lamivudine	1 (1)	2 (1)
NNRTI (%)		
Efavirenz	117 (59)	-
Nevirapine	80 (41)	-
Marital status (%)		
Married	97 (49)	112 (55)
Divorced	9 (5)	13 (6)
Widowed	33 (17)	16 (8)
Single	55 (28)	62 (31)
Missing	3 (2)	0 (0)

NRTI: Nucleoside/nucleotide reverse transcriptase inhibitor. NNRTI: Non-nucleoside reverse transcriptase inhibitor.

Table 2: Proportion of patients with virologic suppression

	NNRTI n/N (%)	PI n/N (%)	P-value
Intention-to-treat analyses			
HIV-1 RNA <400 copies/ml			
After 12 months of ART	65/197 (33.0)	68/203 (33.5)	0.92
After 6-12 months of ART	68/197 (34.5)	60/203 (29.6)	0.29
HIV-1 RNA <75 copies/ml			
After 12 months of ART	58/197 (29.4)	52/203 (25.6)	0.39
After 6-12 months of ART	54/197 (27.4)	44/203 (21.7)	0.19
Modified intention-to-treat analyses			
HIV-1 RNA <400 copies/ml			
After 12 months of ART	61/187 (32.6)	66/193 (34.2)	0.75
After 6-12 months of ART	62/187 (33.2)	56/193 (29.0)	0.38
HIV-1 RNA <75 copies/ml			
After 12 months of ART	54/187 (28.9)	50/193 (25.9)	0.52
After 6-12 months of ART	48/187 (25.7)	40/193 (20.7)	0.25
On-treatment analyses			
HIV-1 RNA <400 copies/ml			
After 12 months of ART	58/87 (66.7)	61/84 (72.6)	0.40
After 6-12 months of ART	47/87 (54.0)	45/84 (53.6)	0.96
HIV-1 RNA <75 copies/ml			
After 12 months of ART	51/87 (58.6)	45/84 (53.6)	0.51
After 6-12 months of ART	34/87 (39.1)	32/84 (38.1)	0.90

n: Number of patients with virologic suppression; *N*: Total number of patients in the analysis group.

Table 3: Summary of drug resistance mutations

	NNRTI n/N (%)	PI n/N (%)	P-value
High-level NNRTI resistance at time of virologic failure	17/30 (56.7)	3*/26 (11.5)	<0.01
Low-level NNRTI resistance at time of virologic failure	4/30 (13.3)	1*/26 (3.9)	0.21
NRTI resistance at time of virologic failure	8/30 (26.7)	5/26 (19.2)	0.51
Major PI resistance at time of virologic failure	0/30 (0)	0/26 (0)	-
Any resistance at time of virologic failure	22/30 (73.3)	7/26 (26.9)	<0.01
Baseline resistance**	4/30 (13.3%)	2/26 (7.7%)	0.50

**All females. Two with pre-therapy resistance. ** Baseline resistance testing was only performed in patients where any mutations were detected at time of virologic failure.*

Table 4: Adverse events

	NNRTI n=197	PI n=203	P-value
Any grade 1 or 2 sign or symptom, n (%)	63 (32.0)	63 (31.0)	0.84
Diarrhoea	19 (9.6)	15 (7.4)	0.42
Nausea/vomiting	16 (8.1)	21 (10.3)	0.44
Impaired cognition or memory	4 (2.0)	2 (1.0)	0.39
Insomnia	13 (6.6)	10 (4.9)	0.47
Any grade 3 or 4 sign or symptom, n (%)	13 (6.6)	9 (4.4)	0.34
Diarrhoea	4 (2.0)	2 (1.0)	0.39
Nausea/vomiting	4 (2.0)	3 (1.5)	0.67
Impaired cognition or memory	0 (0)	1 (0.5)	0.32
Insomnia	1 (0.5)	0 (0)	0.31
Any grade 1 or 2 laboratory abnormality, n (%)	116 (58.8)	98 (48.3)	0.03
Anaemia	98 (49.8)	80 (39.4)	0.04
ALT elevation >1.25-5 times the upper normal limit	47 (23.9)	22 (10.8)	<0.01
Any grade 3 or 4 laboratory abnormality, n (%)	25 (12.7)	18 (8.9)	0.22
Anaemia	22 (11.2)	13 (6.4)	0.09
ALT elevation >5 times the upper normal limit	3 (1.5)	1 (0.5)	0.30
Hospitalisation, n (%)	22 (11.2)	18 (8.9)	0.44

ALT: Alanine aminotransferase.

Figure 1: Screening, randomization and follow-up of study patients

