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

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Declaration of interests

We declare no competing interests.

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Contributors

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

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

Abstract

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

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

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

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

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

Introduction

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

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

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

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

Methods

Study design

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

Participants

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

Randomisation

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

Procedures

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

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

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

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

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

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

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

Outcomes

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

Statistical analyses

We hypothesised that virologic failure occurred more frequently in the NNRTI group, with estimated failure rates of 12% for PI and 25% for NNRTI [19-21]. We therefore calculated the necessary sample size to be 154 patients in each arm with a power of 80%; we needed to include 386 patients to account for an estimated 20% LTFU. We used the chi-squared test to compare the proportions of patients who achieved viral suppression after 12 months of treatment. In a post-hoc analysis, we compared the proportions of patients who achieved a composite endpoint of virologic failure or death after 12 months of treatment; we also assessed endpoints after six months of treatment. Mortality was assessed with Cox proportional hazard models. A post-hoc sensitivity analysis classified patients lost to follow-up as dead.

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

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

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

Role of the funding source

AbbVie Pharmaceuticals donated LPV/r (Aluvia) for the trial. AbbVie had no role in study design, data collection, or data analysis, but was permitted to review the manuscript and suggest changes. Final decisions on content were exclusively made by the authors.

Results

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

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

Characteristics of the patients are presented in Table 1.

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

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

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

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

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

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

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

Discussion

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

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

More patients than predicted died or were lost to follow-up, probably reflecting poor health-care seeking behaviour as well as high levels of resistance. Virologic treatment failure should be confirmed by a second measurement after assessing adherence, but due to the retrospective measurements of viral load employed here; this confirmation was not possible and could have overestimated the true prevalence of treatment failure. The comparison of PI with NNRTI is a mixed comparison of NVP and EFV. However, previous studies have shown that NVP and EFV have similar benefits in initial treatment of HIV infection when combined with two NRTIs [22].

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

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

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

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

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

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

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

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

Conclusions

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

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

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

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/µl, 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