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A randomized factorial trial comparing four treatment regimens in treatment-naïve HIV-infected persons with AIDS and/or < 200 CD4⁺ cells/mm³ in South Africa

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Abstract

Background—Few randomized trials comparing antiretroviral therapy (ART) regimens have been conducted in resource-limited settings.

Methods—In the Republic of South Africa, antiretroviral-naïve HIV-infected individuals >14 years old, with <200 CD4⁺ cells/mm³ or prior AIDS diagnosis were randomized to: EFV or LPV/r with either ZDV+ddI or d4T+3TC in an open-label 2×2 factorial study and followed for: the primary outcome of AIDS or death; pre-specified secondary outcomes including CD4⁺ and viral load changes, treatment discontinuations and grade 4 events.

Results—1771 persons were randomized and followed for a median of 24.7 months. AIDS or death occurred among 163 participants assigned EFV and 157 LPV/r (HR=1.04; 95% CI 0.84–1.30) and among 170 assigned ZDV+ddI and 150 assigned d4T+3TC (HR=1.15; 95% CI: 0.93–1.44). HIV RNA was lower (p<0.001) and CD4⁺ count greater (p<.01) over follow-up for d4T+3TC versus ZDV+ddI. Rates of potentially life-threatening adverse events and overall treatment discontinuation were similar for d4T+3TC and ZDV+ddI; however, more participants discontinued d4T due to toxicity (12.6%) than other treatments (<5%).

Conclusion—EFV or LPV/r are effective components of first-line ART. The poorer viral and immune responses with ZDV+ddI and the greater toxicity-associated discontinuation rate with d4T+3TC suggest these treatments be used cautiously as initial therapy.

Trial Registration—clinicaltrials.gov Identifier: NCT00342355

Keywords

antiretroviral therapy; efavirenz; lopinavir/ritonavir; randomized controlled trial; treatment naïve; stavudine; didanosine; zidovudine; lamivudine

Introduction

HIV is the leading cause of death in sub-Saharan Africa with 1.7 million adult deaths in 2006 [1]. While developed nations have access to more than twenty-five antiretroviral agents for the treatment of HIV infection [2] access to potent ART is markedly constrained in large parts of Africa. In the Republic of South Africa (RSA) in 2004 when the national

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rollout of ART began [3], only seven drugs were available [4]. In 2006, only 21% of persons with AIDS in RSA were treated with ART [5].

Few randomized trials have been conducted in resource-limited settings to compare different ART regimens. The initial treatment for HIV is important in these settings since individuals present for treatment with advanced disease and the available regimens are limited.

The Phidisa II trial was designed to compare the effect of different initial ART treatments on AIDS or death among individuals with advanced HIV infection.

Methods

Study population

Eligible participants were uniformed RSA military personnel and family who were eligible to receive services from the military health system[6]. HIV infected adult patients (>14 years of age) were enrolled at one of six study sites; were antiretroviral naïve (defined as ART for <7 days) and had CD4+ T lymphocyte cell counts <200 cells/mm³ (or ≤14% for patients post-splenectomy) and/or had any history of or current AIDS-defining illness [7]. Patients with pulmonary tuberculosis had CD4+ counts <200 cells/mm³ to be eligible. Laboratory criteria for eligibility included; haemoglobin ≥9 g/dL (≥8 g/dL for women), neutrophil count >500 cells/μL, platelet count >25000/μL and serum liver transaminases <5 times upper limit of normal range. The study was approved by SANDF and NIAID institutional review boards and written informed consent was obtained from all participants.

Study design and outcome measures

PHIDISA II was a randomized, open-label comparison of four different ART regimens in a 2×2 factorial design. Eligible participants were randomly allocated in equal proportions to receive: 1) efavirenz (EFV, Stocrin[®], Merck) 600 mg daily + zidovudine (ZDV, Retrovir[®], GlaxoSmithKline) 300 mg twice daily + didanosine (ddI, Videx[®] or Videx EC[®], Bristol-Myers Squibb) 125 mg twice daily for persons <60 kg, 200 mg twice daily for persons >60 kg or 250 mg and 400 mg daily for the enteric-coated formulation (available beginning December 2005); 2) EFV + stavudine (d4T, Zerit[®], Bristol-Myers Squibb) 30 mg twice daily for persons <60 kg, 40 mg twice daily for persons >60 kg + lamivudine (3TC[®], GlaxoSmithKline) 150 mg twice daily; 3) lopinavir/ritonavir 400 mg/100 mg twice daily (LPV/r, Kaletra, Abbott) + ZDV+ddI; or 4) LPV/r+d4T+3TC (Figure 1).

Women who were taking EFV and became pregnant on study were switched to nevirapine (Viramune[®], Boehringer-Ingelheim) 200 mg daily for 14 days, then 200 mg twice daily during pregnancy. Persons with active tuberculosis were ineligible for study until induction therapy was completed. Persons with treatment-limiting side effects to: EFV were switched to nevirapine, LPV/r were switched to EFV, ddI or d4T were switched to ZDV+3TC, ZDV were switched to d4T+3TC. Those with an AIDS-related illness after 24 weeks of therapy and persons with virologic failure (failure to achieve a plasma HIV viral load <400 RNA copies/ml by week 36 or a rebound in viral load to >20,000 copies/ml, in the absence of any intercurrent illness, after having been suppressed to <400 copies/mL) were switched to the 3 drugs they were not receiving. Resistance testing was not routinely used. For a second virologic failure or drug toxicities, other ART was used as available. All patients received prophylaxis for *Pneumocystis jiroveci* pneumonia and toxoplasmosis until CD4+ count increased, per current guidelines [8].

The protocol specified primary outcome for the study was AIDS or death; pre-specified secondary outcomes included CD4+ and viral load changes, treatment discontinuations and grade 4 events.

An Endpoint Review Committee (ERC) reviewed site reported AIDS defining illnesses, blinded to treatment assignment. Events classified as confirmed or probable by the ERC, using pre-established criteria, were considered endpoints, as were all deaths irrespective of cause.

The planned sample size of 2,800 participants provided 80% power to detect a 20% difference in the hazard for progression to AIDS or death for two primary comparisons: 1) EFV versus LPV/r; and 2) d4T+3TC versus ZDV+ddI. Follow-up was to continue until 635 primary events had accrued (estimated at 5 years) assuming 30% of people with CD4+ counts <200 cells/ μ L or symptomatic HIV disease would develop disease progression or die (the primary event) and the primary event rate in year one was twice as great as in subsequent years. We assumed that 2.5% of participants would be lost to follow-up per year.

Randomization was stratified by site using randomly mixed permuted blocks of different sizes. Assignments were obtained by calling a central toll-free number.

Data collection and follow-up of participants

Medical histories, complete physical examination, and laboratory studies, including plasma HIV RNA, CD4+ count, haematology and clinical chemistry, were obtained prior to randomization. Follow-up visits for data collection occurred monthly for 3 months and every 3 months thereafter. Interim histories were taken, selected symptoms assessed and graded on a 4-point scale (mild to potentially life-threatening)[9], adherence with study medications assessed and reinforced by pharmacists, and CD4+ counts, HIV-RNA levels, and haematology and clinical chemistry tests performed. Physicians completed a questionnaire annually assessing participants' clinical features of lipodystrophy. All changes to ART were recorded. All grade 4 events that occurred throughout follow-up were reported and coded according to the *Medical Dictionary for Regulatory Activities* (version 12.0). A final visit was conducted to confirm endpoint and vital status as of the study closing date, 31 March 2008.

Statistical analysis

The randomized treatment groups were compared by intention-to-treat; subjects were not censored for drug switches or discontinuation. Kaplan-Meier survival curves and Cox's proportional hazards models were used to compare the main effects (EFV versus LPV/r and d4T+3TC versus AZT+ddI) for progression to AIDS or death, death, grade 4 events, and HIV RNA < 400 copies/mL [10]. Follow-up was censored when participants were lost to follow-up; otherwise, on 31 March 2008.

The hazard ratio (HR) for the main effects was estimated from a Cox model stratified by site (6 strata) and with two binary indicators, one for each main effect. An interaction term was added to assess whether the two factors studied were additive. The proportional hazards assumption was tested by including an interaction term between the randomized treatment indicators and log-transformed follow-up time. Treatment comparisons were summarized with HRs and 95% confidence intervals (CIs) from the Cox models. Longitudinal regression (mixed effects) models were used to compare CD4+ counts and other laboratory measures over follow-up between groups. The percentage of participants with lipodystrophy and with targeted symptoms at 12-months were compared with chi-square tests.

Statistical analyses were performed using SAS (Version 8.2). All reported p-values are 2-sided.

Interim monitoring of safety and efficacy

An independent Data and Safety Monitoring Board (DSMB) reviewed interim analyses from Phidisa II 5 times. In June 2007, the DSMB requested a plan to increase enrolment rate; only 1,600 of 2,800 patients had been enrolled after 28 months for a planned 2 year enrollment period. Coincident with slow enrollment were reports outside of the trial detailing toxicities related to d4T. The investigators decided after considering the DSMB request, without knowledge of the treatment comparisons, to end the study early to inform use of d4T in RSA. Enrolment ceased December 31st 2007; follow-up ended March 31, 2008.

Role of the funding source

The study was supported by SANDF, NIAID, and the US Department of Defense. None of these entities nor their employees or contractors had any financial interest in the drugs used. Employees and contractors of these agencies participated in study design, data collection, data analysis, data interpretation, and writing the report. The corresponding author had access to all data and final responsibility for the decision to submit for publication.

Results

Accrual and patient characteristics

Between February 2004 and December 2007, 1771 persons were randomized: 444 participants to EFV+ZDV+ddI; 444 participants to EFV+d4T+3TC; 440 participants to LPV/r+ZDV+ddI; and 443 participants to LPV/r+d4T+3TC (Figure 1).

One participant was mistakenly randomized and did not receive study medication. All other participants received their assigned treatment following randomization. The treatment groups were well balanced at entry (Table 1). Median CD4+ count at screening was 106 cells/ μ L. Thirty-seven percent of participants had no history of tuberculosis, AIDS, or AIDS-related symptoms; 31% had a history of AIDS-related symptoms but no history of tuberculosis or other AIDS-defining illness; and 32% had a history of tuberculosis or AIDS.

Follow-up and Treatment Changes

Median follow-up was 24.7 months. For 87 (4.9%) participants the primary endpoint status was unknown at study closing date (range among treatments: 2.3% to 6.1%) (Figure 1).

Overall, 37% of participants discontinued or switched one or more drugs in their regimen. This percent did not differ by treatment group ($p=0.51$). The percent of follow-up time on the assigned regimen was 79.8% for EFV+ZDV+ddI, 85.4% for EFV+d4T+3TC, 80.5% for LPV/r+ZDV+ddI, and 81.8% for LPV/r+d4T+3TC. 27.3% of participants assigned to EFV+ZDV+ddI discontinued/changed all three drugs in the regimen, this percentage was 21.4% for those assigned to EFV+d4T+3TC, 23.2% to LPV/r+ZDV+ddI, and 16.5% to LPV/r+d4T+3TC ($p=0.001$). The percent of follow-up time off of all antiretroviral therapy ranged from 2.2% (LPV/r+d4T+3TC) to 3.6% (EFV+ZDV+ddI). Self-reported adherence (taking all or most of prescribed pills) ranged from 95.3% for LPV/r to 97.1% for EFV.

HIV RNA and CD4+ Cell Count Responses

For participants assigned EFV, the percent achieving an HIV RNA level < 400 copies/mL was more rapid than for those assigned LPV/r, as reflected in a HR (EFV versus LPV/r) for time to viral suppression significantly greater than 1.0 [HR=1.48 (95% CI: 1.30 to 1.67; $p<0.001$)]. After 6 months the percent with HIV RNA < 400 copies/mL was similar in the two groups (Figure 2a). The more rapid decline of HIV RNA level on EFV than LPV/r did not differ by the NRTI combination used ($p=0.79$ for interaction).

This pronounced effect on HIV RNA level in the first 6 months did not result in greater increase in CD4+ counts for EFV versus LPV/r (Figure 2c); averaged over all of follow-up, CD4+ count was approximately 18 cells lower on EFV than LPV/r ($p < 0.001$); treatment differences were greater in the later, compared to earlier, follow-up period (the p -value for the treatment by visit interaction was < 0.001). The greater increases in CD4+ count for LPV/r than EFV did not vary by the NRTI combination used ($p = 0.21$ for interaction).

For participants assigned d4T+3TC achievement of an HIV RNA level < 400 copies/mL was more rapid than for ZDV+ddI. The HR for ZDV+ddI versus d4T+3TC for time to HIV RNA < 400 copies/mL was 0.79 (95% CI: 0.70 to 0.90; $p < 0.001$). Differences between the NRTI combinations diminished with longer follow-up (Figure 2b).

CD4+ counts were similar for the first 12 months; afterwards, there were greater increases in CD4+ counts for d4T+3TC compared to ZDV+ddI (Figure 2d) (p -value for the treatment by visit interaction was < 0.001). After 12 months, the greater effects of LPV/r and d4T+3TC on CD4+ count are additive, resulting in the best CD4+ cell count response. For example, at 24 months, the CD4+ cell count increase was 274 cells/mm³ for those assigned LPV/r+d4T+3TC versus 249 cells for LPV/r+ZDV+ddI, 238 cells for EFV+d4T+3TC, and 200 cells/mm³ for those assigned EFV+ZDV+ddI ($p < 0.001$ for differences among the four groups).

Clinical Endpoints

163 participants in the EFV group (rate = 9.1/100 person-years) and 157 in the LPV/r group (8.7/100 person-years) had an AIDS event or died from any cause (primary endpoint) (Table 2). Cumulative event rates after 12, 24, and 36 months were 12.9%, 17.5%, and 21.1% for those assigned EFV and 13.2%, 17.6% and 20.3% for those assigned LPV/r (Figure 3a). The HR for AIDS or death was 1.04 (95% CI: 0.84–1.30; $p = 0.71$) ($p = 0.48$ for proportional hazards assumption). This HR (EFV versus LPV/r) was 1.23 (95% CI: 0.91–1.66) for those also assigned ZDV+ddI and 0.87 (95% CI: 0.63–1.20) for those assigned d4T+3TC ($p = 0.13$ for interaction).

170 participants in the ZDV+ddI group (9.6/100 person-years) and 150 in the d4T+3TC group (8.2/100 person-years) had an AIDS event or died from any cause. Cumulative event rates after 12, 24, and 36 months were 13.9%, 18.7%, and 22.2% for those assigned ZDV+ddI and 12.2%, 16.4% and 19.2% for those assigned d4T+3TC (Figure 3c). The HR for AIDS or death was 1.15 (95% CI: 0.93–1.44, $p = 0.20$) ($p = 0.86$ for proportional hazards assumption).

The majority (171) of the 320 primary events were death (53%), most occurring in the first 6 months of follow-up. There were 106 deaths among those assigned EFV (5.6/100 person-years) and 102 among those assigned LPV/r (5.4/100 person-years) (Table 2). Thirty-seven of the 208 deaths followed a confirmed or probable AIDS event. The HR (EFV versus LPV/r) for death from any cause was 1.05 (95% CI: 0.80–1.37) (Figure 3b). The HR for death was similar for those assigned ZDV+ddI and d4T+3TC ($p = 0.23$ for interaction).

There were 111 deaths in the ZDV+ddI groups and 97 in the d4T+3TC groups. The HR for death from any cause was 1.15 (95% CI: 0.88–1.51) (Table 2, Figure 3d).

HRs for AIDS were 1.18 (95% CI: 0.85–1.62) for EFV versus LPV/r and 1.29 (95% CI: 0.94–1.79) for ZDV+ddI versus d4T+3TC (Table 2). The most common AIDS events were tuberculosis (113 participants); cryptococcal disease (15); *Candida* esophagitis (8), Kaposi sarcoma (7), and *Mycobacterium avium* complex (2).

Adverse Events and Reasons for Treatment Discontinuation

Grade 4 event rates were similar for different treatment groups. The HR for grade 4 events for EFV versus LPV/r groups was 1.07 (95% CI: 0.84–1.36); for ZDV+ddI versus d4T+3TC it was 1.16 (95% CI: 0.91–1.48) (Table 2)[11]. Of grade 4 adverse events, only blood and lymphatic disorders differed significantly between treatment groups (21 participants on ZDV+ddI, 7 on d4T+3TC; $p=.01$). Most of these events were anemia. Grade 4 lactic acidosis occurred among 6 persons taking d4T+3TC and 2 persons taking ZDV+ddI. Grade 4 pancreatitis occurred in 3 participants assigned d4T+3TC and 8 persons assigned ZDV+ddI.

D4T was discontinued for toxicity ($n=112$, 12.6% of participants) more frequently than other drugs; discontinuation rates ranged from 2.6% for 3TC to 4.3% for LPV/r. Thirty-nine (35%) stopped d4T for peripheral neuropathy, 30 (27%) for lipodystrophy, 25 (22%) for hyperlactatemia, 5 (5%) for lactic acidosis, 5 (5%) for lipoatrophy, and 8 (7%) for other reasons.

Compared to ZDV and ddI, d4T and 3TC had lower rates of discontinuation due to virologic failure – 2.5% for 3TC and 2.6% for those assigned d4T versus 6.1% for both ddI and ZDV.

At 12 months, based on the physician's assessment of lipodystrophy, significantly higher rates of fat wasting in the face, arms, buttocks, and legs were found in the d4T+3TC group versus the ZDV+ddI group (Appendix Table 1). There were no significant differences between EFV and LPV/r groups in any lipodystrophy measure at 12-months.

Selected symptoms were assessed at each follow-up visit; the percent with grade 1 or higher conditions through 12-months is summarized in Appendix Table 2. Compared to EFV, the LPV/r group had higher rates of nausea (23% versus 16%), diarrhea (25% versus 12%) and vomiting (11% versus 7%) ($p<.01$ for each) through 12-months; ZDV+ddI had higher rates of nausea (22% versus 17%) constipation (11% versus 7%) and fatigue (24% versus 19%) ($p<0.05$ for each), and lower rates of peripheral neuropathy compared to the 3TC+d4T group (17% versus 26%) ($p<0.001$).

Weight and Laboratory Changes

In all groups, weight increased following randomization and continued throughout follow-up. Overall, weight increases were similar for the EFV versus LPV/r groups (average difference = 0.16 kg; $p=0.62$); the average weight increase was 0.60 kg greater for those assigned d4T+3TC versus those assigned ZDV+ddI ($p=0.06$).

SGPT (average difference = 0.24 log IU/L), SGOT (0.13 log IU/L), albumin (0.70 g/L), hemoglobin (0.19 g/dL), and hematocrit (0.51%) were significantly greater and creatinine ($-4.1 \mu\text{mol/L}$) was significantly lower for those assigned EFV compared to LPV/r during follow-up ($p=0.003$ for hematocrit and $p<0.001$ for other laboratory measures). These measures also differed between the NRTI groups: SGPT (0.10 log IU/L), albumin (0.43 g/L), hemoglobin (0.35 g/dL), and hematocrit (0.96%) were significantly greater and platelet count ($-9.0 \times 10^9/\text{L}$) was lower for those assigned d4T+3TC compared to ZDV+ddI ($p=0.01$ for albumin and $p<0.001$ for other laboratory measures).

Discussion

The Phidisa II trial was initiated to provide randomized evidence on the relative risks and benefits of available antiretroviral drugs in the RSA in 2006. A factorial design was employed to assess combined and separate effects of a protease inhibitor (LPV/r) and a NNRTI (EFV) and two NRTI combinations (d4T+3TC and ZDV+ddI). Consequent to

stopping the trial early, the number of primary events reported and adjudicated (320) was about one-half of that planned and confidence intervals are wide for the clinical outcome comparisons. EFV had a more rapid effect in suppressing HIV RNA level than LPV/r and LPV/r had a small, but significantly greater, effect on raising CD4+ counts. The clinical relevance of this difference is uncertain. The HR for the primary endpoint was 1.04, but, due to the smaller than planned number of endpoints, we cannot rule out the possibility of a 30% higher rate of AIDS or death and a 37% higher death rate on EFV compared to LPV/r.

Grade 4 event rates were similar for EFV and LPV/r and discontinuation rates did not differ.

ZDV+ddI was not as effective as d4T+3TC in suppressing HIV RNA level or in raising CD4+ count, but the clinical significance of this difference is uncertain. There was an excess risk of AIDS or death, and of death alone for ZDV+ddI compared to d4T+3TC of 15% but the confidence around this estimate was wide with non-significant differences. Grade 4 event rates did not differ between the NRTI combinations, but more participants discontinued d4T due to toxicity than other NRTIs. This was offset by a lower rate of treatment discontinuation attributed to virologic failure.

The greater early effect of EFV compared to LPV/r on suppression of HIV RNA levels has been reported in another randomized trial (N=503) [12], but not in an observational trial (N=1550) [13]. In our study, the differential effect on HIV RNA disappeared after 6 months. The superiority of d4T+3TC compared to ZDV+ddI for HIV RNA and CD4+ count was also observed in a Botswana study [14]. A specific ARV-associated mutational pattern was identified peculiar to the HIV-1C subtype found in sub-Saharan Africa when treated with the ZDV+ddI that may lead to early virological failure [15]. Effects of EFV versus LPV/r and ZDV+ddI versus d4T+3TC on HIV RNA and CD4+ count changes appear to be additive. Taken together, a greater drop in HIV RNA is evident for those assigned a d4T+3TC-containing regimen in the first 24 months, with the greatest effect in the first 6 months for those also taking EFV. CD4+ increases after the first year are greater for participants taking d4T+3TC and LPV/r. The group with poorest CD4+ response (EFV+ZDV+ddI) also had the highest rate of AIDS or death (10.6/100 person-years).

More than one-half of the deaths on study, 108 of 208 (51.9%), occurred within the first 6 months of beginning antiretroviral therapy. For all clinical outcomes, there were no differences between groups in the first 6 months, consistent with other studies initiating antiretroviral therapy in similar settings [16–21]. The marked decrease in the mortality rate over time for all regimens suggests that these regimens are potent and introducing ART into an ARV-naïve population with advanced disease is the most critical issue in subsequent successful control of HIV infection. The marked decrease in deaths after six months on therapy argues strongly for initiating ART earlier than the CD4+ count <200 cells/mm³ criterion for entry onto this study [22–24].

Preceding the early termination of our study, there were reports of hyperlactataemia, lipodystrophy, and pancreatitis related to d4T from other African cohorts [25–29]. The frequency of severe cases in our cohort was small. Though recent data and guidelines recommend limiting d4T use due to toxicity [11,30,31], d4T use in this trial was well tolerated by many participants for up to 36 months. A reasonable approach would be to consider the use of d4T when no other options exist and closely monitor its use.

A major limitation of the study was our inability to precisely characterize the treatment differences with respect the primary endpoint of AIDS or death. The open-label study design could have impacted assessments of symptoms and other subjective conditions. A strength of our study is the excellent follow-up and adherence to the assigned regimens and the well-characterized virologic and immunologic responses to the regimens studied.

In summary, our findings show that either EFV or LPV/r can be supported as components of first line ART. Regimens containing ZDV + ddI should be monitored for slower virologic response and more modest immunologic enhancement and d4T+3TC monitored for higher rates of toxicities in this setting. The results of this study indicate that randomized trials can be successfully conducted in this setting to obtain evidence to support policy development for ART roll-out programs and the provision of care to people with advanced HIV disease in Southern Africa.

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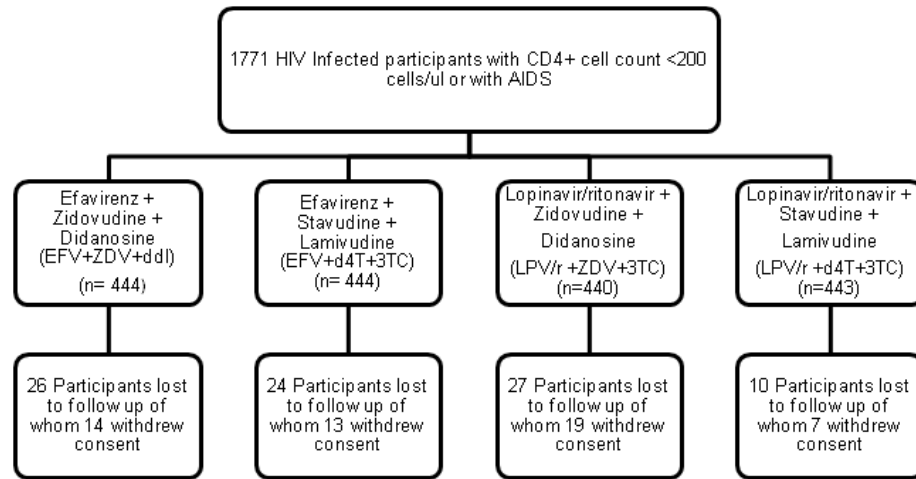
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All participants have been included in the analysis. Follow up for participants for whom vital status was not known (lost-to-follow) on the closing date (31 March 2008) were censored on the date they were last seen. One participant, who was pregnant, was randomized by mistake and never received study treatment. Only baseline data was included for that participant.

Figure 1.
Randomization and follow-up of subjects on study
Phidisa II study design.

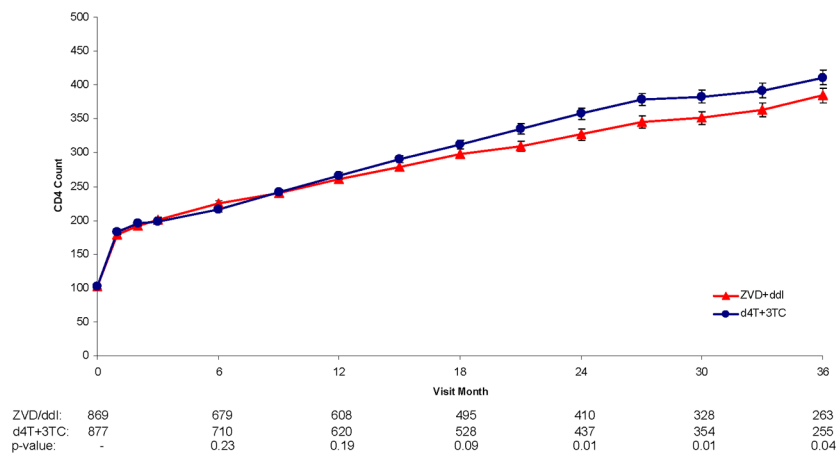
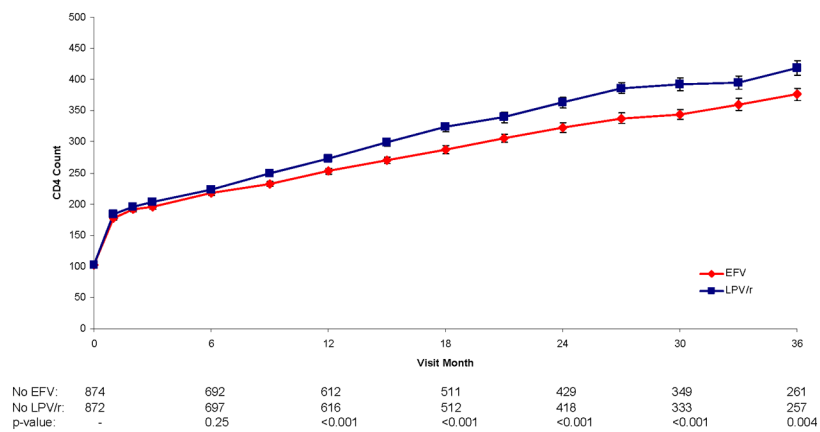
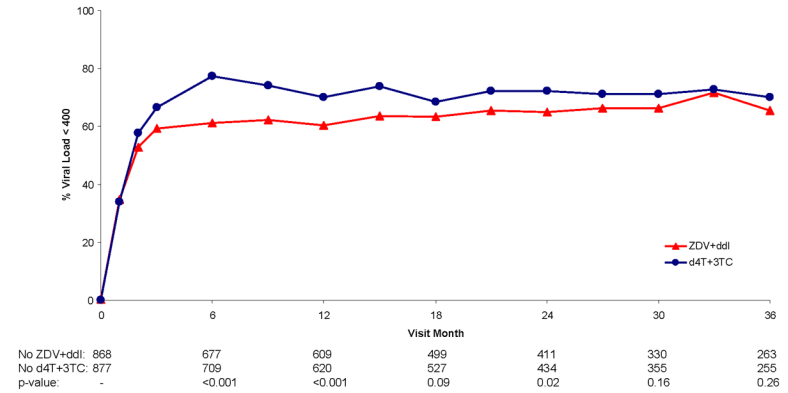
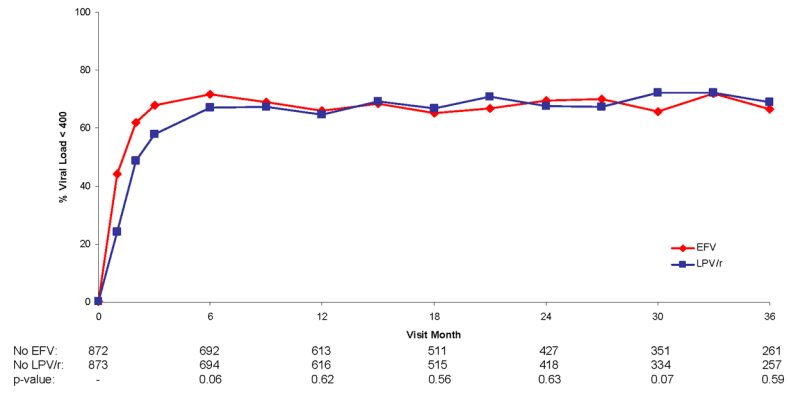


Figure 2.

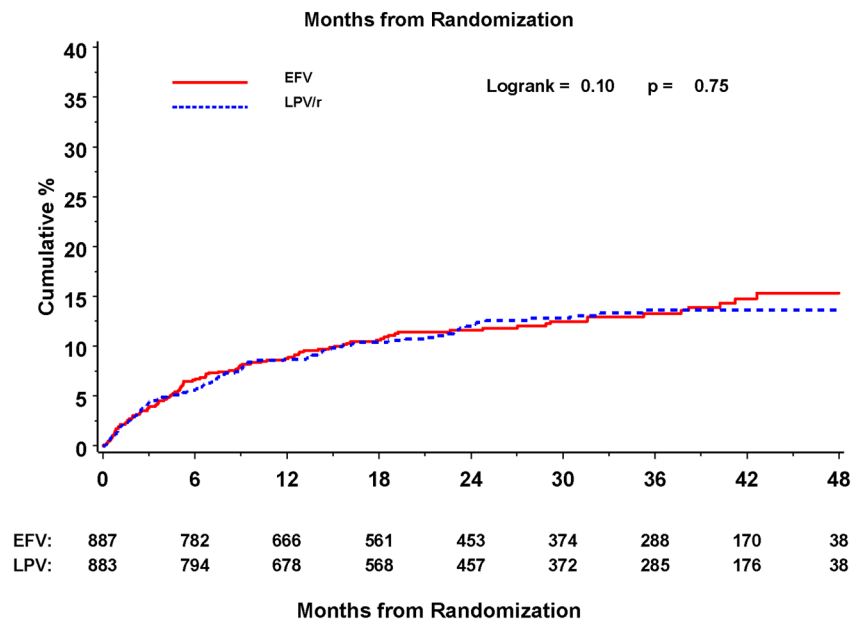
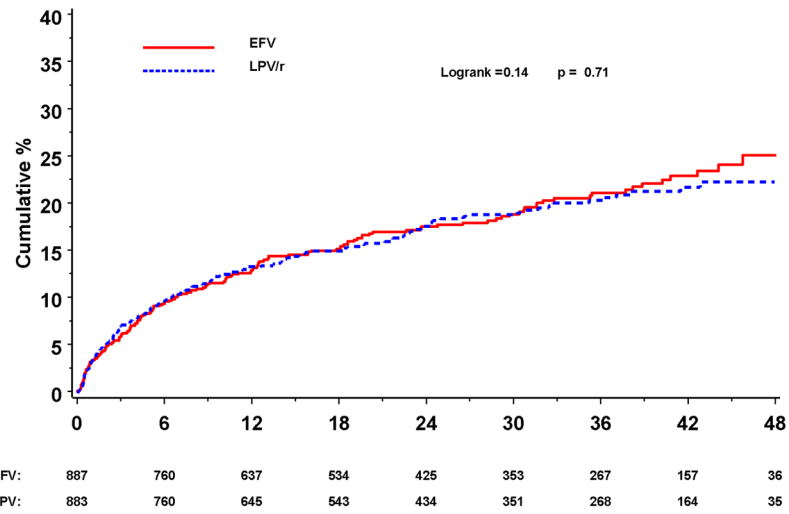
Cumulative percent of subjects with HIV viral loads <400 copies/mL for EFV vs. LPV/r (2a) and for ZDV + ddI vs. d4T + 3TC (2b). CD4+ lymphocyte cell counts/mm³ for EFV vs. LPV/r (2c) and for ZDV + ddI vs. d4T + 3TC (2d) The numbers below the x-axis represent the numbers of subjects in each group at each time point.

Figure 2a. Percent Viral Load < 400 Over Follow-up for Efavirenz vs. Lopinavir/Ritonavir

Figure 2b. Percent Viral Load < 400 Over Follow-up for Zidovudine + Didanosine vs. Stavudine + Lamivudine

Figure 2c. CD4 Count Over Follow-up for Efavirenz vs. Lopinavir/Ritonavir

Figure 2d. CD4 Count Over Follow-up for Zidovudine + Didanosine vs. Stavudine + Lamivudine



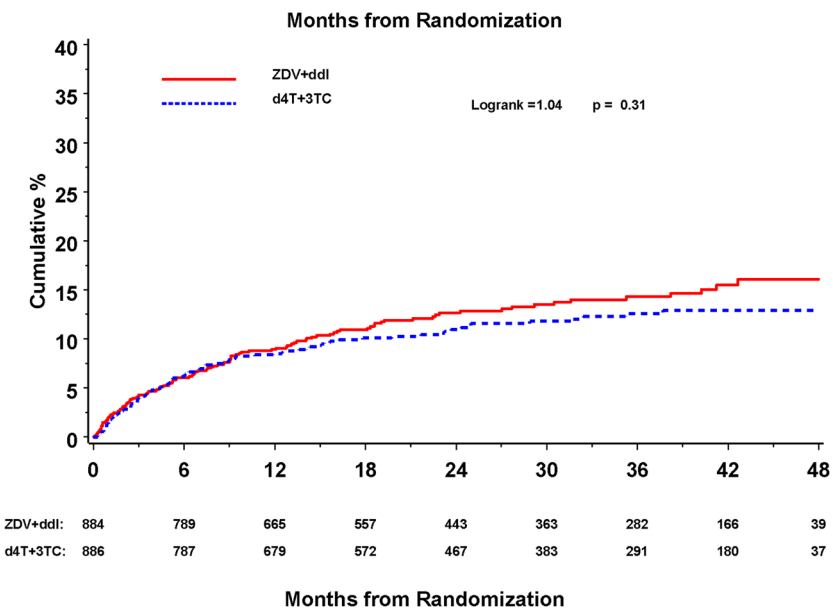
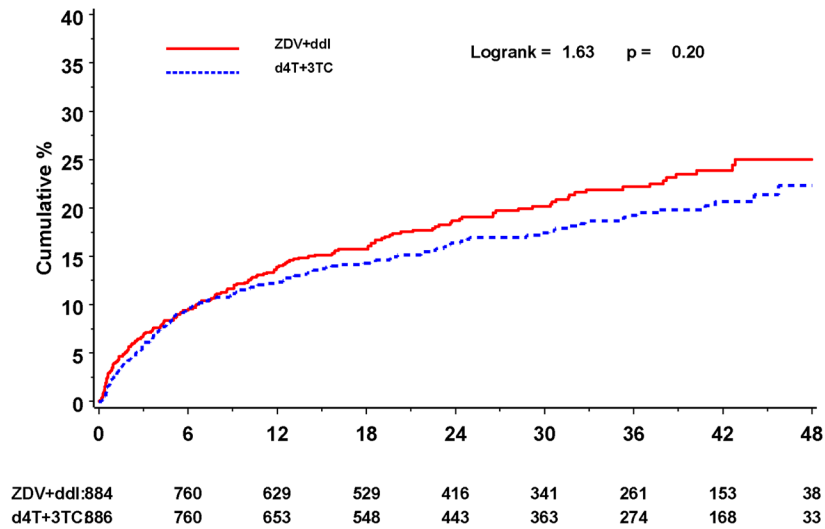


Figure 3.

Kaplan-Meier curves for death or progression of disease for EFV vs. LPV/r (3a), death for EFV vs. LPV/r (3b), death or progression of disease for ZDV + ddI vs. d4T + 3TC (3c), and death for ZDV + ddI vs. d4T + 3TC (3d).

Figure 3a. KM Curve for Death or Progression of Disease for Efavirenz Versus Lopinavir/Ritonavir

Figure 3b. KM Curve for Death for Efavirenz Versus Lopinavir/Ritonavir

Figure 3c. KM Curve for Death or Progression of Disease for Zidovudine + Didanosine Versus Stavudine +Lamivudine

Figure 3d. KM Curve for Death for Zidovudine + Didanosine Versus Stavudine +Lamivudine

Table 1

Baseline Characteristics of the Participants by Treatment Group

	EFV+ZDV+ddI	EFV+d4T+3TC	LPV/r+ZDV+ddI	LPV/r+d4T+3TC
No.	444	444	440	443
Average age (years) (SD)	35.3 (5.4)	35.5 (5.5)	35.3 (5.5)	35.6 (5.5)
Female sex (%)	32.9	30.6	32.5	32.1
Median CD4+ cell count (cells/mm ³) (25 th , 75 th percentiles)	107 (48, 156)	102 (38, 155)	104 (43, 151)	112 (51, 154)
Median plasma HIV-RNA level (copies/mL) (25 th , 75 th percentiles)	131,000 (50200, 228000)	136,100 (54200, 302000)	157,000 (49200, 325000)	152,000 (57400, 307000)
Mean Haemoglobin (g/dl) (SD)	12.7 (2.0)	12.6 (2.0)	12.6 (1.9)	12.5 (2.1)
Mean Body Mass Index (BMI) (kg/m ²) (SD)	23.9 (4.9)	23.6 (4.8)	23.6 (4.7)	23.7 (4.6)

Table 2

Summary of Primary and Major Secondary Endpoints

Endpoint	PI/NRTI Comparison No. of Patients with Endpoint (Rate per 100 person years)		NRTI Comparison No. of Patients with Endpoint (Rate per 100 person years)		HR (95% CI)	P-value	HR (95% CI)	P-value
	EFV (N=888)	LPV/r (N=883)	ZDV+ddI (N=884)	d4T+3T C (N=887)				
AIDS or death	163 (9.1)	157 (8.7)	170 (9.6)	150 (8.2)	1.04 (0.84-1.30)	0.71	1.15 (0.93-1.44)	0.20
Death	106 (5.6)	102 (5.4)	111 (5.9)	97 (5.1)	1.05 (0.80-1.37)	0.75	1.15 (0.88-1.51)	0.31
AIDS	80 (4.4)	69 (3.7)	83 (4.6)	66 (3.5)	1.18 (0.85-1.62)	0.32	1.29 (0.94-1.79)	0.12
Grade 4 event	137 (7.9)	129 (7.2)	142 (8.1)	124 (7.0)	1.07 (0.84-1.36)	0.57	1.16 (0.91-1.48)	0.23