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A 72-week randomized study of the safety and efficacy of a d4T to AZT switch at 24 weeks compared to AZT or TDF when given with 3TC and NVP

Nittaya Phanuphak^{1,2,4}, Jintanat Ananworanich^{1,2,3,4,6}, Nipat Teeratakulpisarn², Tanate Jadwattanakul⁵, Stephen J. Kerr^{6,7}, Nitiya Chomchey^{1,2}, Piranun Hongchookiat², Pornpen Mathajittiphun⁵, Suteeraporn Pinyakorn^{1,2,6}, Patcharawee Rungrojrat^{1,2}, Pairoa Prahirunyakit^{1,2}, Mariana Gerschenson⁴, Praphan Phanuphak^{1,2,3,6}, Victor Valcour^{1,8}, Jerome H. Kim^{1,9}, and Shikumaon Cecilia^{1,4} on behalf of the SEARCH 003 Study Group

¹South East Asia Research Collaboration with Hawaii (SEARCH), Bangkok, Thailand ²Thai Red Cross AIDS Research Centre, Bangkok, Thailand ³Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand ⁴University of Hawaii, Honolulu, Hawaii, USA ⁵Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand ⁶HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand ⁷The Kirby Institute for Infections and Immunity in Society, The University of New South Wales, Sydney, NSW, Australia ⁸University of California at San Francisco, San Francisco, California, USA ⁹US Military HIV Research Program, Rockville, Maryland, USA

Abstract

Background—Due to superior long-term toxicity profile, AZT and TDF are preferred to d4T for first-line antiretroviral regimens. However, short-term d4T use could be beneficial in avoiding AZT-induced anemia.

Methods—We randomized (1:1:1) 150 treatment-naïve Thai HIV-infected adults with CD4 count <350 cells/mm³ to arm 1: 24-week GPO-VIR S30® (d4T+3TC+NVP) followed by 48-week GPO-VIR Z250® (AZT+3TC+NVP); arm 2: 72-week GPO-VIR Z250®; or arm 3: 72-week TDF+3TC+NVP. Hemoglobin (Hb), dual energy x-ray absorptiometry, neuropathic signs, estimated glomerular filtration rate (eGFR), CD4 count, plasma HIV RNA, and adherence were assessed.

Results—In ITT analysis, mean Hb decreased from baseline to week 24 in arm 2 compared to arm 1 (−0.19 vs 0.68 g/dL, $P=0.001$) and arm 3 (0.48 g/dL, $P=0.010$). Neuropathic signs were more common in arm 2 compared to arm 3 (20.4 vs 4.2%, $P=0.028$) at week 24. There were no differences in changes in peripheral fat and eGFR from baseline to weeks 24 and 72 among arms. CD4 count increased more in arm 1 than arms 2 and 3 from baseline to week 24 (168 vs 117 and 118 cells/mm³, $P=0.01$ and 0.02 , respectively) but the increase from baseline to week 72 was similar among arms.

Conclusions—A 24-week d4T lead-in therapy caused less anemia and greater initial CD4 count rise than initiating treatment with AZT. This strategy could be considered in patients with baseline anemia or low CD4 count. If confirmed in a larger study, this may guide global recommendations on antiretroviral initiation where AZT is more commonly used than TDF.

Corresponding author: Nittaya Phanuphak, MD, SEARCH, The Thai Red Cross AIDS Research Centre, 104 Rajdumri Road, Pathumwan, Bangkok, Thailand 10330: Nittaya.P@SearchThailand.org, Tel: 66 2 254 2566 Fax: 66 2 254 2567.

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Introduction

The 2010 World Health Organization (WHO) guidelines preferred first-line 3-drug antiretroviral (ARV) regimens for resource-limited settings are zidovudine (AZT) or tenofovir (TDF) plus lamivudine (3TC) or emtricitabine (FTC) as the two nucleoside reverse transcriptase inhibitors (NRTIs) backbones plus a non-NRTI (NNRTI), nevirapine (NVP) or efavirenz (EFV) [1]. This represents a change from the 2006 guidelines which included stavudine (d4T) plus 3TC as one of the preferred NRTI options [2]. D4T is an effective drug that is least expensive among the NRTIs. Its availability has allowed for rapid scale up of antiretroviral therapy (ART) in the poorest resourced settings [3]. It is now being phased out due to the risk of neuropathy and lipoatrophy with long-term use [1, 4]. Currently, more than 5 million people are receiving ART worldwide, but there are still 10 million who are in need of ART and have yet to receive it [5]. Scaling up AZT and, in particular, TDF as first-line therapy is a major cost burden for resource-poor countries. Additionally, these drugs are not without side effects [6, 7].

The adverse events associated with d4T are linked to dose and duration of use [8, 9], and certain strategies could be employed for the safe use of d4T. One option may be to reduce the d4T dose to reduce toxicity; but a randomized study to test such strategy would be needed. Another approach is to use d4T for a short lead-in time before switching to a different NRTI such as AZT, a strategy endorsed by the 2010 Thai Ministry of Public Health HIV treatment guidelines where 6-12 months of d4T may be used before switching to AZT in order to avoid gastrointestinal and hematologic side effects of AZT [10]. This has not, however, been the subject of a randomized investigation. Our primary goal in this study was to compare in a randomized fashion the toxicity profile of short-term d4T prior to switching to AZT in comparison to strategies where AZT or TDF are used solely as the backbone for first-line antiretroviral regimens.

Methods

Study setting and study population

SEARCH 003 was a 72-week randomized clinical trial comparing the safety and efficacy of three initial ARV regimens (www.clinicaltrials.gov identification NCT00669487). ART-naïve Thai HIV-infected adults were enrolled from two sites in central Thailand: the Thai Red Cross AIDS Research Centre in Bangkok and the Queen Savang Vadhana Memorial Hospital in Chonburi, Thailand. The study was approved by four Institutional Review Boards from Chulalongkorn University, Queen Savang Vadhana Memorial Hospital, University of Hawaii, and University of California San Francisco. Informed consents were obtained in Thai language from all participants.

Participants were randomized (1:1:1) to arm 1: 24-week d4T 30 mg + 3TC 150 mg + NVP 200 mg twice daily (GPO-VIR S30®) followed by 48-week AZT 250 mg + 3TC 150 mg + NVP 200 mg twice daily (GPO-VIR Z250®); arm 2: 72-week GPO-VIR Z250® twice daily and arm 3: 72-week TDF 300 mg + FTC 200 mg (Truvada®) once daily + Nevir® (NVP) 200 mg twice daily. Randomization conducted centrally using a block design stratified by baseline hemoglobin (Hb) < or = 10 g/dL. During the NVP lead-in period, AZT was given at 200 mg or 300 mg twice a day for body weight < 60 kg or >60 kg, respectively. GPO-VIR S30®, GPO-VIR Z250® and Nevir® are generic ARVs produced by the Thai Government Pharmaceutical Organization. Truvada® was provided by Gilead.

Entry criteria included documented HIV infection, age ≥ 18 years, CD4 count <350 cells/mm³, and ART-naïve status except that females with past exposure to antiretroviral drugs associated with pregnancy were allowed to enroll as long as the exposure was at least 3

months prior to entry. Subjects were excluded for abnormal laboratory values (absolute neutrophil count <750 cells/mm³, Hb <8.0 g/dL, serum alanine aminotransferase (ALT) >5 times the upper limit of normal, serum creatinine (Cr) more than 2 times the upper limit of normal), active AIDS-defining illness, other active medical illness, current use of immunomodulator therapy or any experimental therapy, pregnancy or breast-feeding, or the presence of an active malignancy.

Participants underwent a neuropathy examination during the screening process utilizing the AIDS Clinical Trials Group (ACTG)/Neurology and Neurologic AIDS Research Consortium (NARC) methodology [11]. Neuropathy examination were completed on all study participants and most were completed by one of two physicians (N.T. and T.J.). Quality assurance was performed every 6 months on all study physicians who performed neuropathy examination at both study sites to ensure consistency. Participants diagnosed to have possible peripheral neuropathy (absent or diminished ankle reflex OR either diminished vibratory, pin or temperature sensation OR contact allodynia) were excluded from the study because of the potential risk of randomization to the d4T containing arm. Hepatitis B co-infected patients were excluded to avoid randomization to the non-TDF containing arm.

Data collection

Clinical assessments including the neuropathy examination were performed at baseline, weeks 4, 8, 12, and every 3 months thereafter. We measured Hb and ALT at baseline, weeks 2, 12 and every 3 months after that. Lymphocyte CD4 counts, plasma HIV RNA, and serum Cr levels were assessed at baseline and every 3 months. We estimated the glomerular filtration rate (eGFR) using the Levey Modification of Diet in Renal Disease (MDRD) formula. Serum lactate, fasting plasma glucose, fasting lipid profiles, and full body dual energy x-ray absorptiometry (DEXA) were performed at baseline and every 6 months. Self-reported adherence using 30-day visual analog scale was assessed at weeks 4, 8, 12, and then every 3 months. Clinical and laboratory toxicities were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (December 2004). An independent Data Safety and Monitoring Board (DSMB) reviewed the overall quality of the trial and undertook two interim analyses. The first analysis occurred in accordance with the protocol when two-thirds of study participants had completed 12 weeks on the study. Stopping criteria were based on virological failure, resistance, and safety data. The DSMB recommended a second interim analysis to occur when all patients had reached 24 weeks of follow-up.

Data analysis

We based our study sample size on the conservative assumption that Hb levels among patients in the arms treated with d4T-based or TDF-based regimens would not change, whereas the estimated mean decrease in Hb would be -1.09 (standard deviation, SD, 1.54) g/dL after 24 weeks of AZT treatment based on data derived from the HIV-NAT 001 study [12]. A power analysis demonstrated that a sample size of 44 in each arm would provide the 90% power to detect, at the 0.05 significance level, a 1.09 g/dL change in Hb between arms. Estimating a 10% loss to follow up, we enrolled a sample size of 50 per arm.

We employed intention to treat (ITT) analyses, including all participants who were assigned to a particular treatment arm who had at least one follow-up visit according to their allocated treatment arm at baseline. Primary outcomes were changes in Hb, peripheral fat by DEXA, eGFR by MDRD, and the development of neuropathic signs or neuropathy at weeks 24 and 72. Secondary outcomes were changes in CD4 count and plasma HIV RNA from baseline to weeks 24 and 72. All hypotheses were tested using two-sided, unadjusted pairwise

comparisons of treatment difference between the switch arm and the other treatment arms at weeks 24 and 72. For the continuous laboratory or clinical parameters, we compared groups by calculating the mean difference in parameter change from baseline, the corresponding 95% confidence intervals (95% CI) and t-test derived *P*-values. The statistical significance was set at a 5% level and not adjusted for multiple endpoints. Continuous endpoints with missing data were evaluated with the last observation carried forward. In binary toxicity analyses, patients who were lost to follow-up or switched NRTI backbones due to toxicity or virological failure were imputed as failures. Treatment switch for virological failure or resistance was considered failure for binary viral load, but not toxicity endpoints if the main NRTI in the backbone was not changed. For binary endpoints, differences in proportions and corresponding 95% CI were calculated, along with chi-square-derived *P*-values. Per protocol (PP) analyses were also conducted, censoring subjects at the time of switch from their randomised treatment. Detailed PP results are presented in web appendix 1, and are also presented below when the significance levels were different to those observed in the ITT analyses.

Results

Participant characteristics

Between April 2008 and August 2009, 214 HIV-infected patients were evaluated for eligibility at the two study sites (Figure 1). Sixty-four patients were excluded with 55 not meeting inclusion criteria, 3 declining to participate, and 6 excluded for other reasons. The remaining 150 patients were randomized into one of the 3 study arms; 51 in arm 1 (GPO-VIR S switch arm), 50 in arm 2 (GPO-VIR Z arm), and 49 in arm 3 (Truvada/NVP arm). Two participants did not receive allocated study drugs; 1 in arm 2 who had asymptomatic peripheral neuropathy revealed at the baseline visit and 1 in arm 3 who did not return for the baseline visit.

Among 150 randomized participants, 55% were female and the mean (SD) age was 34 (8) years (Table 1). Clinical characteristics were comparable among treatment groups with the baseline mean (SD) CD4 count of 161 (94) cells/mm³, log₁₀ plasma HIV RNA of 4.87 (0.65) copies/mL, the Hb of 12.5 (1.6) g/dL, and an eGFR of 83.0 (15.5) mL/min/1.73m².

By week 72, at least one ARV switch due to drug toxicities occurred in 30 participants; but the majority of these did not involve NRTI – 28 for NNRTI and 6 for NRTIs. NVP-related toxicities, mostly NVP-associated rash, caused ARV changes from NVP to LPV/r in 2 cases and from NVP to EFV in 26 cases and 6 of these 26 cases subsequently needed a change from EFV to lopinavir/ritonavir (LPV/r). The NNRTI switches due to toxicities occurred in all arms – 8 in arm 1, 13 in arm 2 and 7 in arm 3. One case had d4T changed to AZT due to numbness in extremities. AZT/3TC was switched to TDF/FTC in 4 cases (three for anemia and one for lipoatrophy). In addition, one case initially had AZT/3TC switched to TDF/FTC due to hepatotoxicity and needed further switch to AZT/didanosine due to rash. AZT dose was reduced from 250 mg to 200 mg twice daily in 1 anemic case, and from 250 mg twice daily to 200 mg twice daily to 100 mg thrice daily in one patient with neutropenia.

ART-related toxicities

Hemoglobin—After 24 weeks of treatment, there was a significant difference between the mean change in Hb between patients treated with AZT (-0.19 g/dL) compared to those on d4T (0.68 g/dL, *P*=0.001) or TDF (0.48 g/dL, *P*=0.010) (Table 2, Figure 2A). The mean absolute Hb at week 24 was 13.1 g/dL in arm 1, 12.2 g/dL in arm 2, and 13.2 g/dL in arm 3. Arm 1 patients had a sharp decline in Hb at week 36 after switching from d4T to AZT at week 24 (mean change from baseline of -0.15 g/dL). By week 72, there was a significant

increase in mean Hb from baseline in arm 3 (0.90 g/dL) compared to arm 1 (0.17 g/dL, $=0.006$). Both arms 1 and 2 patients on AZT had lower Hb than patients treated with TDF in arm 3 (Figure 2A). The mean absolute Hb at week 72 was 12.6 g/dL in arm 1, 12.8 g/dL in arm 2, and 13.7 g/dL in arm 3, $P=0.009$. Throughout the study, there were no differences between proportion of patients with Hb <10 g/dL across arms.

Peripheral fat by DEXA—Across treatment arms, patients had similar increases in peripheral fat by week 24 (mean changes of 65 g in arm 1, 97 g in arm 2, and 68 g in arm 3) (Table 2, Figure 2B). However, by week 72, there was a trend towards a decrease in peripheral fat in patients who switched from d4T to AZT in arm 1 (mean change of -301 g) compared to those who were on TDF in arm 3 (281 g, $=0.086$), but not for those on AZT in arm 2 (143 g, $P=0.187$). Clinical lipodystrophy was reported in only one patient in arm 2 at week 48, at which time, the patient had AZT replaced by TDF. The mean changes in lean body mass were similar across arms.

eGFR by MDRD—At week 24, the mean changes in eGFR did not differ among arms at -0.8 in arm 1 compared to -1.37 in arm 2 and -3.1 mL/min/1.73m² in arm 3, $P>0.05$ (Table 2, Figure 2C). The eGFR values varied over time across arms, and by week 72, there was a non-significant decline in eGFR from baseline in arm 3 (mean change of -8.7 mL/min/1.73m²) compared to arm 2 (-3.7, $P=0.143$) and arm 1 (-2.80, $P=0.071$). In PP analysis, mean eGFR change from baseline to week 72 was significantly greater in arm 3 (-10.6 mL/min/1.73m²) compared to arm 1 (-2.3, $P=0.04$) but not to arm 2 (-3.8, $P=0.12$). Urinalysis was normal throughout the study except for grade 2 proteinuria in 2 patients (an arm 1 patient at week 48 and an arm 3 patient at baseline, weeks 12 and 24) and glucosuria in an arm 2 patient at baseline and week 72.

Neuropathic signs and neuropathy by detailed neuropathy examination—At week 24, the proportions of patients with neuropathic signs, defined as diminished sensation by any modality detected *bilaterally* in the lower extremities or absent or diminished ankle reflexes relative to knees, was higher in arm 2 (AZT) compared to arm 3 (TDF) (20.4% vs 4.2%, $P=0.028$) but was not statistically different from arm 1 (9.8%, $P=0.168$) (Table 2, Figure 2D). This significant difference between arm 2 and arm 3 at week 24 did not persist to week 72; however, there was a trend for arm 2 to have higher proportion of patients with neuropathic signs than arm 1 (24.5% vs 9.8%, $P=0.064$). In PP analysis, the proportion of patients with neuropathic signs in arm 2 (13.3%) at week 24 was not higher than those in arm 1 (4.3%, $P=0.15$) and arm 3 (2.3%, $P=0.11$). At week 72, however, a significantly higher proportion of patients in arm 2 had neuropathic signs than in arm 1 (14.3% vs 0.0%, $P=0.01$). There were no differences by study arm in the proportion of patients who developed peripheral neuropathy, defined as reduced vibration sensation in both great toes or absent or diminished ankle reflexes bilaterally relative to knees. The rates were 7.8%, 10.2%, and 2.1% at week 24 and 9.8%, 16.3%, and 8.3% at week 72 for study arms 1, 2, and 3, respectively.

Other adverse events—The mean total cholesterol rise after 24 weeks of treatment was significantly less in arm 3 compared to arm 1 (17.3 vs 36.8 mg/dL, $P=0.01$) but not less than that in arm 2 (25.1 mg/dL, $P=0.3$). This trend remained present at week 72 with the mean total cholesterol rise being less in arm 3 than in arm 1 (16.4 vs 38.4 mg/dL, $P=0.005$), and in arm 2 (32.1 g/dL, $P=0.043$). The mean high density lipoprotein (HDL) cholesterol level in arm 1 increased significantly more at week 24 than that seen in arm 2 (14.7 vs 8.9 mg/dL, $P=0.021$) and in arm 3 (7.2 mg/dL, $P=0.003$). We also observed an increase in the mean HDL cholesterol level at week 72 in arm 1 compared to that in arm 3 (mean change of 19.4 vs 12.2 mg/dL, $P=0.022$). Among arms, there were no differences in changes of low density

lipoprotein (LDL) cholesterol, triglyceride, or glucose, and of the frequency of grade 2, 3 and 4 lipid and glucose abnormalities. The white blood cell decreased more at weeks 24 and 72 in arm 2 (-0.90 and $-0.67 \times 10^3/\text{mm}^3$) compared to that in arm 1 (0.78 and $0.14 \times 10^3/\text{mm}^3$, $P<0.001$) and in arm 3 (0.56 and $0.68 \times 10^3/\text{mm}^3$, $P<0.001$) (data not shown). The absolute neutrophil counts decreased more at week 24 in arm 2 ($-0.55 \times 10^3/\text{mm}^3$) compared to that in arm 1 ($0.63 \times 10^3/\text{mm}^3$, $P<0.001$) and in arm 3 ($0.41 \times 10^3/\text{mm}^3$, $P=0.001$) and at week 72 in arm 2 ($-0.29 \times 10^3/\text{mm}^3$) compared to that in arm 3 ($0.53 \times 10^3/\text{mm}^3$, $P=0.004$) (data not shown).

Immunological and virological responses—At week 24, the absolute CD4 count increased more in arm 1 (mean change of 168 cells/ mm^3) than in arm 2 (117 cells/ mm^3 , $P=0.01$), and in arm 3 (118 cells/ mm^3 , $P=0.01$) but the overall change by week 72 did not differ across arms (207 cells/ mm^3 in arm 1, 167 cells/ mm^3 in arm 2, and 198 cells/ mm^3 in arm 3, $P>0.05$) (Figure 3A). In PP analysis, in addition to higher CD4 count change in arm 1 compared to arm 2 ($P=0.01$) and arm 3 ($P=0.03$) by week 24, CD4 count change from baseline was also significantly higher in arm 1 vs arm 2 at week 72 ($P=0.03$). From baseline to week 24 and week 72, mean absolute CD4 count increased from 154 to 322 and 361 cells/ mm^3 in arm 1, from 174 to 290 and 340 cells/ mm^3 in arm 2, and from 157 to 274 and 355 cells/ mm^3 in arm 3.

The proportion of patients with plasma HIV RNA <50 copies/mL was similar among arms at weeks 24 and 72 (Figure 3B). At week 24, these were 86.3% in arm 1, 81.6% in arm 2, and 79.2% in arm 3 ($P>0.05$). At week 72, 84.3% of patients in arm 1 vs 91.8% in arm 2 vs 83.3% in arm 3 had plasma HIV-RNA <50 copies/mL ($P>0.05$).

The proportion of participants who reported $<95\%$ adherence was similar among arms at all study visits (4.1%, 2.1%, and 0.0% in arms 1, 2, and 3, respectively at week 72).

Discussion

In this 72-week randomized comparison of hematologic, metabolic, renal, and neurologic toxicities of the three most commonly used first-line ARV regimens worldwide, we demonstrated that short-term d4T use for 24 weeks before switching to AZT did not result in greater toxicities compared to the other two regimens. In contrast, after 24 weeks of treatment, d4T-treated patients had a significantly higher Hb level than that seen in the AZT arm, and had a larger CD4 count increase than that observed in both the AZT and TDF arms. These changes could be pertinent in settings where patients start ART with low CD4 counts, since the magnitude of CD4 count rise following treatment is associated with improved clinical outcomes in patients with low nadir CD4 counts [13]. Our findings may have important implications for treatment programs in resource-limited settings where patients generally start treatment late and anemia is frequent. The benefit of this treatment strategy may even be greater for HIV-infected patients in malarious areas with high burden of anemia. As expected, we noted lower Hb levels in patients treated with AZT. More neuropathic signs were identified in patients treated with AZT compared to those on TDF; but, unexpectedly, the frequency of neuropathic signs was not greater for the d4T arm compared to the other arms. Virologic suppression did not differ among arms.

Our data concur with a meta-analysis of 6 prospective, randomized, comparative studies identifying a greater negative impact on hematologic parameters with AZT-based relative to d4T-based ARV regimens [14]. The use of d4T is being phased out globally because of long-term risks of peripheral neuropathy and lipoatrophy. In our study, we did not observe an increased risk of d4T-related neuropathic signs or neuropathy. In fact, in both ITT and PP analyses a higher proportion of subjects in the AZT arm had abnormal neurologic

examinations compared to either the d4T or TDF arms. This suggests that there is a low risk for neuropathy with short-term use of d4T in patients carefully screened to not have neuropathic signs or symptoms before initiation of the medication. Our ongoing study to quantify epidermal nerve fiber density before and after ART in this cohort may shed some light on why neuropathic signs were more common with AZT than with d4T.

After 24 weeks of treatment, clinical lipoatrophy was not seen in patients on d4T and the peripheral fat mass was similar across arms. However, treatment with 24 weeks of d4T is likely too short a duration to cause significant changes in fat. In the GS-903 and GS-934 studies, clinical lipodystrophy and peripheral fat mass loss were observed in patients treated with three years of d4T compared to those on TDF or AZT [15, 16]. Unexpectedly, we identified trends toward lower peripheral fat mass at week 72 in the d4T lead-in arm when compared to the AZT and TDF arms despite transition off d4T at 24 weeks. The peripheral fat mass loss in the d4T switched arm was small with differences in fat mass loss among arms being around 500g or less, which is not likely to be clinically relevant. The GS-903 study reported a 2.9 Kg difference in peripheral fat mass between d4T and TDF arms at three years. The lack of standardized DEXA criteria to diagnose lipodystrophy further limits our ability to identify the clinical impact of such findings [17].

Similar to other reports, the increase in total cholesterol was less with TDF than observed with AZT or d4T [15, 16]. In contrast to the GS-903 study [15], we saw a more favorable HDL cholesterol profile with d4T than TDF. The HDL cholesterol increase was also higher with d4T than with AZT in our study. Other studies have not identified differences in the HDL cholesterol profile when participants on d4T were compared to those on AZT [18, 19]. These findings need to be confirmed by larger studies.

AZT- and TDF-based first-line regimens are currently recommended in resource-limited settings including Thailand [1, 10]. We found TDF to be a safe and well tolerated drug. Some studies have reported an unexpectedly high early virologic failure rate of 25-43% with TDF plus 3TC or FTC plus NVP regimen [20, 21], especially in patients with high baseline plasma HIV RNA, but these findings were not found by others [22, 23]. Our study was not powered to compare virologic efficacy between treatment arms. Nevertheless, treatment failures were uncommon in all arms. We saw a small but non-significant decline in eGFR with TDF that is consistent with previous reports [15, 16]. Acute renal failure after TDF, particularly in patients with advanced HIV disease has been reported [6]. It is possible that in such patients, short-term d4T could be used as the initial NRTI before switching to TDF to lessen such risk. Thus, with the expanded use of TDF in developing countries, regular and long-term monitoring of renal function is necessary.

Our study was designed and powered to test short-term outcomes associated with a d4T lead-in strategy so our ability to comment on less common toxicities, such as lactic acidosis, and hepatic steatosis, or those that occur after long-term ART is limited due to a small sample size and short duration of follow up. In addition, our patients who were mostly well, lacked neuropathic signs and had nadir CD4 counts close to 200 cells/mm³ may not represent the majority of patients in developing countries who because of advanced disease may be at greater risk for ARV-related toxicities. Nevertheless, we included equal proportions of female and male participants, which more closely reflects the patient population needing treatment in developing countries, and the prospective, systematic and detailed evaluation of ARV-related toxicities in subjects randomly assigned to one of three commonly used NRTIs strengthens the validity of our findings.

In summary, we demonstrated that initiating ART with d4T for 6 months before switching to AZT was safe among subjects without neuropathic signs, and resulted in greater initial CD4

count and Hb rise when compared to initiating treatment with AZT. TDF was also safe, and resulted in higher Hb and lower neuropathic signs than observed with AZT; however, its higher cost may limit its scale up in resource-limited settings. Our results provide important information which, if confirmed in a larger study, will be useful for the refinement and further development of existing global recommendations for initiating ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Diagram SEARCH 003 patient disposition

GPO-VIR S30® is a fixed-dose combination that contains stavudine (d4T) 30 mg, lamivudine (3TC) 150 mg, and nevirapine (NVP) 200 mg. GPO-VIR Z250® is a fixed-dose combination that contains zidovudine (AZT) 250 mg, 3TC 150 mg and NVP 200 mg. Truvada® is a fixed-dose combination that contains tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg. Arm 1 received GPO-VIR S30® twice daily for 24 weeks followed by GPO-VIR Z250® twice daily for 48 weeks. Arm 2 received GPO-VIR Z250® twice daily for 72 weeks, and arm 3 received Truvada® once daily and NVP 200 mg twice daily for 72 weeks. AE, adverse event; ARV, antiretroviral; LPV/r, lopinavir/ritonavir; LTFU, lost to follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Figure 2. Comparison of toxicity primary endpoints between treatment arms by intention to treat analysis

Figure 2A. Mean hemoglobin change from baseline

Figure 2B. Mean peripheral fat change from baseline assessed by dual energy x-ray absorptiometry

Figure 2C. Mean estimated glomerular filtration rate change from baseline assessed by modification of diet in renal disease formula

Figure 2D. Proportions of patients with neuropathic signs assessed by detailed neuropathy examination

GPO-VIR S is a fixed dose combination that contains stavudine (d4T) 30 mg, lamivudine (3TC) 150 mg, and nevirapine (NVP) 200 mg. GPO-VIR Z is a fixed dose combination that contains zidovudine (AZT) 250 mg, 3TC 150 mg, and NVP 200 mg. Truvada is a fixed dose combination that contains tenofovir 300 mg and emtricitabine 200 mg.

All arms received standard doses of antiretrovirals. Arm 1 received GPO-VIR S twice daily for 24 weeks followed by GPO-VIR Z twice daily for 48 weeks. Arm 2 received GPO-VIR Z twice daily for 72 weeks, and arm 3 received Truvada once daily and NVP 200mg twice daily for 72 weeks.

Table 1
Baseline characteristics of SEARCH 003 participants, by study arm

Parameter	Arm 1 GPO-VIR S/ GPO-VIR Z (n = 51)	Arm 2 GPO-VIR Z (n = 49)	Arm 3 Truvada/ NVP (n = 48)	All arms(n = 148)
Site, n (%)				
Bangkok	29 (57)	29 (59)	29 (60)	87 (59)
Chonburi	22 (43)	20 (41)	19 (40)	61 (41)
CDC classification, n (%)				
A	25(49)	26 (53)	27 (56)	78 (53)
B	23 (45)	21 (43)	21 (44)	65 (44)
C	3 (6)	2 (4)		5 (3)
Female, n (%)	28 (55)	28 (57)	25 (52)	81 (55)
Mean (SD) age, years	35 (7)	34 (8)	35 (9)	34 (8)
Mean (SD) weight, kg	56.7 (12.0)	58.2 (11.2)	58.9 (9.6)	57.9 (10.9)
Mean (SD) CD4 count, cells/mm ³	154 (91)	174 (97)	157 (94)	161 (94)
Mean (SD) plasma HIV RNA, log ₁₀ copies/mL	4.8 (0.67)	4.9 (0.63)	4.9 (0.68)	4.9 (0.65)
Mean (SD)hemoglobin (g/dL)	12.4 (1.7)	12.4 (1.6)	12.8 (1.6)	12.5 (1.6)
Hemoglobin <10g/dL, n(%)	3 (6)	3 (6)	2 (4)	8 (5)
Mean (SD) peripheral fat by DEXA scan, g	7380 (3792)	7460 (3229)	7850 (2586)	7559 (3237)
Mean (SD) eGFR by MDRD, mL/min/1.73m ²	82.5 (12.8)	83.3 (15.5)	83.0 (18.3)	83.0 (15.5)
Mean (SD) fasting lipids and glucose ^a				
Total cholesterol, mg/dL	164.3 (33.1)	168.2 (34.5)	177.8 (34.8)	170.0 (34.4)
HDL cholesterol, mg/dL	38.9 (11.0)	40.5 (12.6)	41.4 (10.3)	40.2 (11.3)
LDL cholesterol, mg/dL	96.1 (24.8)	98.2 (26.7)	107.3 (25.6)	100.4 (26.0)
Triglycerides, mg/dL	112.9 (80.4)	111.4 (55.7)	108.0 (37.4)	110.8 (60.5)
Glucose, mg/dL	82.1 (8.0)	82.7 (11.6)	83.5 (8.6)	82.8 (9.4)

^aIncluded one patient in arm 3 who did not fast.

SD, standard deviation; IQR, interquartile range; DEXA, dual energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HDL, high density lipoprotein; LDL, low density lipoprotein

GPO-VIR S is a fixed dose combination that contains stavudine (d4T) 30 mg, lamivudine (3TC) 150 mg, and nevirapine (NVP) 200 mg. GPO-VIR Z is a fixed dose combination that contains zidovudine (AZT) 250 mg, 3TC 150 mg, and NVP 200 mg. Truvada is a fixed dose combination that contains tenofovir 300 mg and emtricitabine 200 mg.

All arms received standard doses of antiretrovirals. Arm 1 received GPO-VIR S twice daily for 24 weeks followed by GPO-VIR Z twice daily for 48 weeks. Arm 2 received GPO-VIR Z twice daily for 72 weeks, and arm 3 received Truvada once daily and NVP 200mg twice daily for 72 weeks.

Table 2
Changes in hemoglobin, peripheral fat, neuropathic signs, peripheral neuropathy, renal function, CD4 count, and plasma HIV RNA, from baseline to week 24 and week 72, by study arm (intention to treat analysis)

ITT analysis Parameters	Arm1	Arm 2	Arm 3	Arm 2 vs Arm 1		Arm 3 vs Arm 1		Arm 3 vs Arm 2	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean change difference (95%CI)	P	Mean change difference (95%CI)	P	Mean change difference (95%CI)	P
Hemoglobin (g/dL)									
Week 0	12.4 (1.7)	12.4 (1.6)	12.8 (1.6)						
Week 24	13.1 (1.7)	12.2 (1.9)	13.2 (1.8)	-0.86 (-1.36, -0.37)	0.001	-0.20 (-0.70, 0.30)	0.436	0.67 (0.16, 1.17)	0.01
Week 72	12.6 (1.9)	12.8 (1.8)	13.7 (1.7)	0.22 (-0.30, 0.73)	0.408	0.73 (0.21, 1.25)	0.006	0.51 (-0.02, 1.04)	0.057
Peripheral fat (g)									
Week 0	7380 (3792)	7460 (3229)	7850 (2586)						
Week 24	7446 (3620)	7557 (3286)	7918 (2750)	31 (-378, 441)	0.88	3 (-409, 414)	0.99	-29 (-444, 387)	0.89
Week 72	7080 (3355)	7603 (3204)	8132 (3086)	444 (-217, 1105)	0.187	582 (-83, 1246)	0.086	138 (-533, 809)	0.685
Neuropathic signs, n (%)									
Week 0	1 (2)	0 (0)	1 (2.1)						
Week 24	5 (9.8)	10 (20.4)	2 (4.2)	0.11 (-0.03, 0.25)	0.168	-0.06 (-0.16, 0.04)	0.438	-0.16 (-0.29, -0.04)	0.028
Week 72	5 (9.8)	12 (24.5)	6 (12.5)	0.15 (0, 0.29)	0.064	0.03 (-0.10, 0.15)	0.755	-0.12 (-0.27, 0.03)	0.191
Peripheral neuropathy, n (%)									
Week 0	0 (0)	0 (0)	0 (0)						
Week 24	4 (7.8)	5 (10.2)	1 (2.1)	0.02 (-0.09, 0.14)	0.738	-0.06 (-0.14, 0.03)	0.363	-0.08 (-0.18, 0.01)	0.204
Week 72	5 (9.8)	8 (16.3)	4 (8.3)	0.07 (-0.07, 0.20)	0.384	-0.01 (-0.13, 0.10)	1	-0.08 (-0.21, 0.05)	0.356
eGFR (mL/min/1.73m²)									
Week 0	82.5 (12.8)	83.3 (15.5)	83.0 (18.3)						
Week 24	81.7 (13.1)	82.0 (11.5)	79.9 (15.2)	-0.57 (-7.22, 6.08)	0.866	-2.26 (-8.95, 4.42)	0.504	-1.69 (-8.44, 5.06)	0.621
Week 72	79.8 (13.5)	79.6 (15)	74.3 (15.0)	-1.10 (-7.63, 5.43)	0.74	-6.04 (-12.61, 0.53)	0.071	-4.94 (-11.57, 1.69)	0.143
CD4 count (cells/mm³)									
Week 0	154 (91)	174 (97)	157 (94)						
Week 24	322 (162)	290 (142)	274 (133)	-50.8 (-90.7, -10.9)	0.01	-49.9 (-90.1, -9.8)	0.02	0.9 (-39.7, 41.4)	0.97

ITT analysis Parameters			Arm 1		Arm 2 vs Arm 1		Arm 3 vs Arm 1		Arm 3 vs Arm 2	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean change difference (95%CI)	P	Mean change difference (95%CI)	P	Mean change difference (95%CI)	P
Week 72	361 (146)	340 (149)	355 (138)		-40.0 (-82.0, 2.1)	0.06	-8.7 (-50.9, 33.6)	0.68	31.3 (-11.4, 74.0)	0.15
Plasma HIV RNA <50 copies/mL, n(%)										
Week 0	0 (0)	0 (0)	0 (0)							
Week 24	44 (86.3)	40 (81.6)	38 (79.2)		-0.05 (-0.19, 0.10)	0.53	-0.07 (-0.22, 0.08)	0.35	-0.02 (-0.18, 0.13)	0.76
Week 72	43 (84.3)	45 (91.8)	40 (83.3)		0.08 (-0.05, 0.2)	0.25	-0.01 (-0.15, 0.14)	0.89	-0.09 (-0.22, 0.05)	0.2

ITT, intention to treat; SD, standard deviation; CI, confidence interval; eGFR, estimated glomerular filtration rate