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MAJOR ARTICLE

A Randomized Switch From Nevirapine-Based Antiretroviral Therapy to Single Tablet Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate in Virologically Suppressed Human Immunodeficiency Virus-1-Infected Rwandans

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Background. Many human immunodeficiency virus (HIV)-infected patients remain on nevirapine-based antiretroviral therapy (ART) despite safety and efficacy concerns. Switching to a rilpivirine-based regimen is an alternative, but there is little experience with rilpivirine in sub-Saharan Africa where induction of rilpivirine metabolism by nevirapine, HIV subtype, and dietary differences could potentially impact efficacy.

Methods. We conducted an open-label noninferiority study of virologically suppressed (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) HIV-1-infected Rwandan adults taking nevirapine plus 2 nucleos(t)ide reverse-transcriptase inhibitors. One hundred fifty participants were randomized 2:1 to switch to coformulated rilpivirine-emtricitabine-tenofovir disoproxil fumarate (referenced as the Switch Arm) or continue current therapy. The primary efficacy endpoint was HIV-1 RNA < 200 copies/mL at week 24 assessed by the US Food and Drug Administration Snapshot algorithm with a noninferiority margin of 12%.

Results. Between April and September 2014, 184 patients were screened, and 150 patients were enrolled; 99 patients switched to rilpivirine-emtricitabine-tenofovir, and 51 patients continued their nevirapine-based ART. The mean age was 42 years and 43% of participants were women. At week 24, virologic suppression (HIV-1 RNA level <200 copies/mL) was maintained in 93% and 92% in the Switch Arm versus the continuation arm, respectively. The Switch Arm was noninferior to continued nevirapine-based ART (efficacy difference 0.8%; 95% confidence interval, −7.5% to +12.0%). Both regimens were generally safe and well tolerated, although 2 deaths, neither attributed to study medications, occurred in participants in the Switch Arm.

Conclusions. A switch from nevirapine-based ART to rilpivirine-emtricitabine-tenofovir disoproxil fumarate had similar virologic efficacy to continued nevirapine-based ART after 24 weeks with few adverse events.

Keywords. antiretroviral therapy; HIV; randomized clinical trial; rilpivirine; Rwanda.

Improvements in antiretroviral therapy (ART) and cost reductions have provided for better tolerated regimens worldwide. However, there are limited data in resource-limited settings for several regimens that are considered "preferred" or "alternative" regimens for first-line therapy in North America and Europe [1, 2].

Consistent with the World Health Organization (WHO) guidelines, efavirenz (EFV), in combination with 2 nucleos(t)ide reverse-transcriptase inhibitors (NRTIs), is currently the preferred agent for initial treatment of human immunodeficiency virus (HIV) in Rwanda [3, 4]. However, many patients remain on nevirapine (NVP)-based ART if treatment was initiated before the current recommendations.

Nevirapine use can be complicated by hepatotoxicity, suboptimal antiviral efficacy, and the lack of coformulation with newer NRTIs [5, 6]. Efavirenz is generally considered an improvement over NVP due to the robust evidence supporting its efficacy and safety, but it also has limitations including increased rates of neuropsychiatric adverse effects, a potential increased risk for suicidality, drug-drug interactions with hormonal birth control, and lingering concerns regarding teratogenicity [5, 7–14]. The United Stated Department of Health and Human Services and other guideline organizations have downgraded EFV-containing ART from their lists of preferred initial treatment regimens [1]. In sub-Saharan Africa, where approximately half of patients initiating ART are women

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of child-bearing age, there remains a need to improve the safety, tolerability, and simplicity of ART.

Rilpivirine (RPV) is a once-daily nonnucleoside reverse-transcriptase inhibitor (NNRTI). It was licensed for generic manufacturing in 2011, is given at a daily dose of 25 mg, and can be coformulated with newer NRTIs [15]. Currently, RPV is coformulated as a single-tablet regimen with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). Rilpivirine/FTC/TDF is designated as a recommended regimen in European guidelines and as an alternative regimen in the United States for patients with pretreatment HIV ribonucleic acid (RNA) < 100 000 copies/mL and a CD4 count >200 cells/mm^3 and is designated a pregnancy Category B medication by the US Food and Drug Administration (FDA) [1, 2]. Rilpivirine/FTC/TDF can be a safe and effective option to maintain viral suppression for patients on either EFV- or protease inhibitor-based ART with no prior history of failure or resistance [16, 17]. Several small studies from Europe suggest that drug levels are adequate and viral suppression can be maintained when patients switch from NVP-based ART to RPV/FTC/TDF [18–20]. However, the food requirement for RPV, the induction of RPV metabolism by NVP, and polymorphisms found more frequently at codon 138 of reverse transcriptase in non-subtype B virus could all potentially impact the antiviral efficacy of RPV/FTC/TDF when used in sub-Saharan Africa [20–22].

The aim of the current study was to compare the efficacy, safety, and tolerability of a randomized switch to the single-tablet regimen RPV/FTC/TDF versus continued therapy with NVP-based ART in virologically suppressed HIV-infected Rwandans.

METHODS

Study Design and Participants

The NEAR-Rwanda study was a 48-week, single-center, randomized, open-label study conducted at the Rwanda Military Hospital in Kigali, Rwanda, a tertiary care health center that predominantly serves the local civilian population.

We enrolled HIV-1-infected adults age ≥18 years whose most recent plasma HIV-1 RNA level within 12 months of screening was <50 copies/mL and who had a repeat HIV-1 RNA level <50 copies/mL at their screening visit. Participants were required to be on stable NVP twice daily, lamivudine (3TC), and a second NRTI for at least 12 months before screening without any history of virologic failure as defined by Rwandan national guidelines (HIV RNA > 2000 copies/mL) or without change to their antiretroviral regimen other than prior NRTI substitutions. Human immunodeficiency virus-1 RNA levels are checked yearly as part of routine monitoring of all patients in the national treatment program. Additional inclusion criteria included a desire to change ART regimen, estimated glomerular filtration rate (by the Cockcroft-Gault equation) of ≥60 mL/min, and hemoglobin level ≥8 g/dL. Exclusion criteria included active tuberculosis (due to a drug-drug interaction between RPV and rifampin) or pregnancy.

Randomization and Masking

Eligible participants were randomly assigned (2:1) to switch their regimen immediately to coformulated 25 mg RPV, 200 mg FTC, and 300 mg TDF once daily at entry (Switch Arm) or to continue their current regimen of NVP 200 mg twice daily plus 3TC 300 mg daily plus a second NRTI (Continuation Arm) using permuted block randomization. Study investigators used a web-based interface to randomize participants in real-time at study entry. The study was open-label; investigators and participants were not blinded to individual treatment allocation.

Procedures

Participants were screened, and eligible participants were required to enroll within 28 days of screening. Participants randomized to the Switch Arm started RPV/FTC/TDF within 48 hours of the study entry visit. On-study visits occurred at weeks 4, 12, and 24. The primary outcome was assessed at week 24, at which point all participants remaining on NVP-based ART had a planned switch to RPV/FTC/TDF with ongoing follow up in both arms through week 48. We assessed safety and tolerability with physical exam, adverse-event reporting, and laboratory assessments at week 4 in the Switch Arm and in all participants at weeks 12 and 24. Laboratory testing consisted of a complete blood count, comprehensive metabolic panel, fasting lipid panel, and HIV-1 RNA level (COBAS AmpliPrep/TaqMan version 2.0; Roche Diagnostics).

Participants with an HIV RNA level ≥200 copies/mL had a confirmatory measurement drawn within 2 weeks. Confirmed virologic failure was defined as a repeat HIV RNA level ≥200 copies/mL. In accordance with Rwandan National Guidelines, participants with a confirmed HIV RNA level ≥1000 copies/mL were transitioned to second-line therapy, and those with an HIV RNA level ≥2000 copies/mL had a genotype performed at the Rwandan National Reference Laboratory (ViroSeq; Abbott Laboratories, Abbott Park, IL) [4].

Adherence counseling was performed at each study visit and reinforced during monthly medication refills. Pill counts were performed at each monthly refill in participants in the Switch Arm. Participants were not provided with nutritional support or services outside the routine standard of care provided to all patients enrolled in the Rwanda National ART Program [4].

Outcomes

The primary efficacy outcome was the proportion of participants with an HIV RNA level below 200 copies/mL at week 24, assessed by the FDA Snapshot algorithm [23]. Secondary efficacy outcomes included the proportion of participants with an HIV RNA level <50 copies/mL at week 24 and the proportion of participants without treatment failure at or before week 24. We defined treatment failure as confirmed virologic failure, permanent study discontinuation, or permanent treatment discontinuation for reasons other than pregnancy, breastfeeding, or the need for antituberculosis medications or other prohibited concomitant medications. Our per-protocol analysis included

participants still on study medications and excluded participants without virologic data at 24 weeks for reasons other than adverse events. We evaluated the rates of virologic response stratified by subgroups based on sex, age, baseline CD4 T-cell count, NRTIs at entry, and prior use of other NRTIs.

The primary safety endpoint was the proportion of participants developing a grade 3 or 4 sign, symptom, or laboratory abnormality that was at least 1 grade higher than at entry (based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, National Institute of Allergy and Infectious Disease, Version 1.0, December 2004). Secondary safety outcomes included changes in weight, body mass index (BMI), and fasting lipids from entry to 24 weeks.

The primary tolerability endpoint was defined as the discontinuation of therapy secondary to an adverse effect.

Statistical Analyses

Baseline participant characteristics were compared using *t* tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. We calculated the proportion of participants with HIV RNA levels <200 copies/mL and the associated 95% confidence intervals (CIs). We calculated the difference in proportions of participants with virologic failure using a 2-sided 95% CI (Switch Arm minus Continuation Arm) with a prespecified noninferiority margin of −12%. We calculated the 2-sided 95% CI for the difference in proportions using the unconditional exact method by inverting 2 separate 1-sided exact tests [24]. Sensitivity analyses were performed excluding participants with HIV RNA level ≥50 copies/mL at study entry. Sample size was based on feasibility, assuming a response rate of 90% in both treatment arms: the sample size of 150 participants provided approximately 45% power to establish noninferiority [16, 25].

We used Fisher's exact test to compare treatment differences and adverse events between arms. Prespecified subgroup analyses were conducted using Cochran-Mantel-Haenszel and Breslow-Day statistics to examine the homogeneity of treatment effects across different strata. We compared changes in fasting lipids and BMI from baseline to week 24 using repeated measures analysis of variance models. Primary and secondary analyses for efficacy and safety were based on the principles of intention-to-treat, and all randomized participants were included in the analyses. Analysis testing was 2-sided with a type I error of 5%; thus, *P* values of <.05 were considered statistically significant with no adjustment for multiple comparisons.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Rwanda National Ethics Committee and the Stanford Institutional Review Board. All participants provided written informed consent before enrollment. The trial is registered at ClinicalTrials.gov, number NCT02104700.

RESULTS

Participants and Baseline Characteristics

Figure 1 displays participant disposition. Between April 29 and September 16, 2014, 184 individuals were screened for study enrollment with 150 randomized. Of the 34 individuals excluded from enrollment, the most common reason was a screening HIV-1 RNA level ≥50 copies/mL (n = 20).

Ninety-nine participants were randomly assigned to the Switch Arm of RPV/FTC/TDF, and 51 participants were randomly assigned to the Continuation Arm. Baseline characteristics were similar between randomized treatment arms (Table 1). Forty-three percent of participants were women; mean age was 42 years. The mean duration of ART was 6 years. At baseline, all participants were taking NVP and 3TC plus either TDF (63%), azidothymidine (AZT) (35%), or abacavir (1%). At week 24, 96 of 99 participants in the Switch Arm remained on RPV/TDF/FTC and on-study. There were 2 deaths before week 24, and 1 participant was incarcerated and removed from the study. At week 24, 49 of 51 Continuation Arm participants remained on-study with data from week 24. Of the 2 participants missing data at week 24, 1 moved before week 24 and 1 was lost to follow-up.

Efficacy

In the Switch Arm, 92.9% (95% CI, 86.0–97.1) of participants achieved the primary endpoint of an HIV RNA level <200 copies/mL at 24 weeks vs 92.2% (95% CI, 81.1–97.8) in the Continuation Arm (Table 2). The difference in the proportions (Switch minus Continuation) was 0.8% (95% CI for the difference between proportions, −7.5 to +12.0; $P = 1.0$), thus meeting the prespecified noninferiority criterion (Figure 2).

The rates of virologic suppression below 50 copies/mL were similar between the treatment arms with 89.9% (95% CI, 82.2–95.1) vs 84.3% (95% CI, 71.4–93.0) of participants in the Switch and Continuation Arms, respectively, achieving this threshold (difference +5.6%; 95% CI for the difference, −5.0 to +18.7; $P = .426$).

The per-protocol analysis excluded 1 patient from the Switch Arm who was incarcerated and 2 patients from the Continuation Arm who were lost to follow up or moved before week 24. The efficacy results were similar to the intention-to-treat analysis for (1) virologic suppression <200 copies/mL: 93.9% (95% CI, 87.2–97.7) of participants in the Switch Arm vs 95.9% (95% CI, 86.0–99.5) in the Continuation Arm (difference −2.0%; 95% CI for the difference, −9.3 to +8.1; $P = .719$); and (2) virologic suppression <50 copies/mL: 90.8% (95% CI, 83.3–95.7) of participants in the Switch Arm vs 87.8% (95% CI, 75.2–95.4) in the Continuation Arm (difference 3.1%; 95% CI for the difference, −6.8 to +15.8; $P = .573$).

Treatment failure was rare. In the Switch Arm, 96.9% (95% CI, 91.4–99.4) of participants had a lack of protocol-defined treatment failure vs 96.0% (95% CI, 86.5–99.5) in the Continuation Arm (difference 0.8%; 95% CI for the difference, −5.3 to +10.4).

There were no significant differences in efficacy between arms in any of the predefined subgroups including by sex, baseline CD4 count, and prior NRTI use (Figure 3). Post hoc subgroup analyses revealed that participants in the Switch Arm on AZT at entry had a lower rate of HIV RNA level <200 copies/mL at week 24 than those on TDF at entry (33 of 37 vs 57 of 57; $P = .028$).

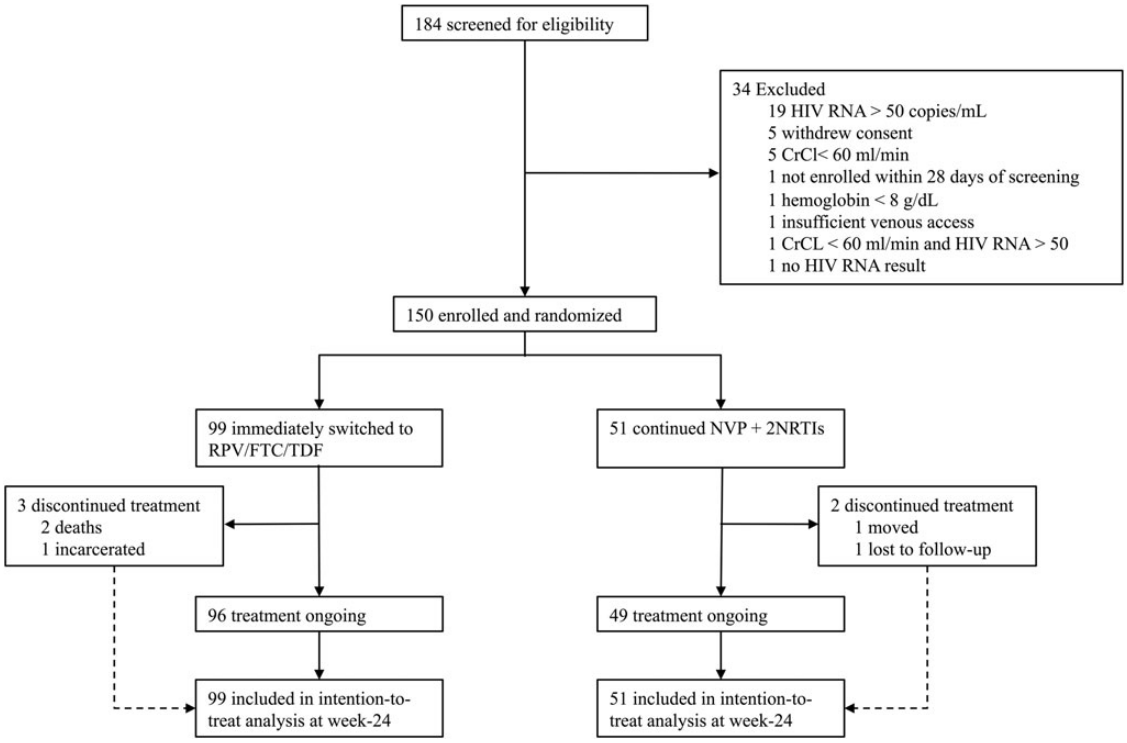

Figure 1. Study screening, enrollment, and follow-up through week 24. Abbreviations: CrCl, creatinine clearance; FTC, emtricitabine; HIV, human immunodeficiency virus; NRTIs, nucleos(t)ide reverse-transcriptase inhibitors; NVP, nevirapine; RNA, ribonucleic acid; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

Sensitivity analyses excluding participants with an HIV RNA level ≥50 copies/mL at entry did not change our results substantively. All 10 participants with an HIV RNA level ≥50 copies/mL at entry achieved an HIV RNA level ≤50 copies/mL at week 24.

Genotypic Resistance Testing

One participant in the Switch Arm had confirmed virologic failure at week 24. Human immunodeficiency virus-1 genotypic testing showed infection with HIV-1 subtype A virus with the reverse-transcriptase mutations M41L, K65R, Y181V, M184V, and H221Y, conferring high-level resistance to all components of the participant's antiretroviral regimen. No prior genotype was available for comparison.

Safety and Tolerability

Four participants in the Switch Arm reported 8 total serious adverse events, but none were attributed to study medication. Two participants died during the study. One individual with hepatitis B coinfection and cirrhosis died from bleeding esophageal varices after an episode of spontaneous bacterial peritonitis at study week 16. One participant suffered 3 serious adverse events with worsening back pain leading to diagnosis of tuberculous vertebral osteomyelitis. The individual was switched to EFV/3TC/TDF and later died on treatment for tuberculosis. One individual was hospitalized for gastroenteritis requiring intravenous fluid, and another had unilateral vision loss of undetermined cause. There were no serious adverse events reported in the Continuation Arm.

The rates of newly reported symptoms during the study were similar between arms, and headache and self-limited respiratory complaints were the most common complaints (see Supplementary Table 1). Laboratory adverse events of at least 1 grade higher than baseline were recorded in 71% of study participants: 70% in the Switch Arm vs 75% in the Continuation Arm ($P = .54$). There were no grade 3 or 4 elevations in liver transaminases or bilirubin. The most commonly reported laboratory abnormality was low bicarbonate. There was a higher proportion of participants with hypophosphatemia of any grade in the Continuation Arm vs the Switch Arm (24% vs 5%; $P = .02$).

Compared with baseline, small reductions were seen in mean fasting total cholesterol and high-density lipoprotein (HDL) cholesterol at week 24 in the Switch Arm (see Supplementary Material). There was a trend toward a reduction in total cholesterol and HDL cholesterol in the Switch Arm vs the Continuation Arm ($P = .07$ and $P = .02$, respectively). No significant differences were detected in other fasting lipid measurements at week 24.

DISCUSSION

We found that a switch to coformulated RPV/FTC/TDF in HIV-infected, virologically suppressed Rwandan adults was similar to continuing NVP-based ART for maintaining virologic suppression. These findings were consistent across all tested virologic thresholds, intention-to-treat and per-protocol analyses, and met prespecified criteria for noninferiority.

Table 1. Baseline Characteristics

Characteristic[a]	Switch Arm (n = 99)	Continuation Arm (n = 51)	*P* Value
Female sex	43 (43%)	22 (43%)	.97
Mean age, years	42.5 (7.8)	43 (7.3)	.67
Marital Status[b]			.38
Single	14 (14%)	7 (14%)	
Married	53 (54%)	36 (71%)	
Other	32 (32%)	8 (16%)	
Highest Education[c]			.20
Primary or lower	44 (44%)	28 (55%)	
Vocational	45 (45%)	14 (27%)	
Secondary or higher	8 (8%)	8 (16%)	
Employment, n (%)			.55
Fulltime	60 (61%)	29 (57%)	
Parttime	16 (16%)	7 (14%)	
Unemployed or retired	23 (23%)	14 (27%)	
Medical History, n (%)			
Tuberculosis	10 (10%)	5 (10%)	.95
Malaria	32 (32%)	16 (31%)	.90
WHO HIV Stage (highest), n (%)			.30
Stage 1	78 (79%)	36 (71%)	
Stage 2	12 (12%)	5 (10%)	
Stage 3	8 (8%)	9 (17%)	
Stage 4	1 (1%)	1 (2%)	
Mode of HIV acquisition, n (%)			.43
Heterosexual	88 (89%)	43 (84%)	
Homosexual	1 (1%)	0	
IV drug use	0	1 (2%)	
Unknown	10 (10%)	7 (14%)	
Years since HIV diagnosis, mean (SD)	9.1 (4)	9.1 (4)	.92
Years on ART, mean (SD)	5.9 (2.5)	6.2 (2.3)	.42
NRTIs at randomization			.23
Lamivudine	99 (100%)	51 (100%)	
Tenofovir DF	58 (59%)	37 (73%)	
Zidovudine	39 (39%)	14 (27%)	
Abacavir	2 (2%)	0	
Prior NRTI use			
Stavudine	25 (25%)	15 (29%)	.69
Zidovudine	5 (5%)	6 (12%)	.19
CD4 nadir, cells/mm^3	215 (96)	202 (103)	.47
CD4 at entry, cells/mm^3	479 (192)	457 (212)	.54
HIV RNA > 50 c/mL at entry	4 (4%)	6 (12%)	.16
BMI	23.3 (3.9)	24.1 (4.8)	.27
Hemoglobin, g/dL	15.2 (1.9)	15.1 (2.0)	.75
eGFR, mL/min[d]	102 (24)	100 (26)	.66

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DF, disoproxil fumarate; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IV, intravenous; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; RNA, ribonucleic acid; SD, standard deviation; WHO, World Health Organization.

[a] Number and percent or mean and SD.

[b] Other included separated, widowed, divorced, and unknown.

[c] Two percent of participants in each group declined to answer.

[d] Calculated using Cockcroft-Gault formula: (140-age) × (weight in kg) × (0.85 if female)/(72× creatinine mg/dL).

Table 2. Virologic Efficacy[a]

Virologic Outcomes at Week 24	Switch Arm (n = 99)	Continuation Arm (n = 51)
HIV RNA < 200 copies/mL, % (95% CI)	93% (86%–97%)	92% (81%–98%)
HIV RNA < 50 copies/mL, % (95% CI)	90% (82%–95%)	84% (71%–93%)
No virologic data		
Discontinued: death or AE, n (%)	2 (2%)	0 (0%)
Discontinued: other reason, n (%)	1 (1%)	2 (4%)
On study but missing data, n (%)	0 (0%)	0 (0%)

Abbreviations: AE, adverse event; CI, confidence interval; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

[a] Snapshot analysis at week 24.

This is the first randomized study specifically evaluating the efficacy and safety of switching from NVP to RPV. It is the first randomized trial of RPV/FTC/TDF to include a substantial proportion of women and sub-Saharan Africans, 2 groups frequently underrepresented in clinical research but who stand to benefit from safe, well tolerated alternatives. The 4 key phase 3 and 3b studies of RPV included only 17% women and few African participants [16, 26–27]. We enrolled similar proportions of women and men, consistent with demographics of those infected with HIV in Rwanda and elsewhere in sub-Saharan Africa, and we detected no difference in safety or efficacy based on gender [16, 25, 26, 28]. Despite the lack of frequent virologic monitoring in participants before enrollment, consistent with clinical practice in much of sub-Saharan Africa, we saw low rates of virologic failure, similar to the rates reported in recent switch studies conducted in resource-rich countries.

The induction of RPV metabolism by NVP does not appear to contribute to suboptimal antiviral activity in persons with HIV-1 RNA < 50 copies/mL who switch ART. Two single-arm studies assessed RPV plasma concentrations in 32 and 50 participants after switching from a NVP-based regimen and showed adequate drug levels 1 week after the switch [18, 20]. Similar to our findings, over 90% of patients in each of these studies remained virologically suppressed on RPV 24 weeks after the switch. Plasma drug levels were not measured as part of the current study but were sufficient to maintain virologic suppression.

Both treatment arms had low rates of clinical and laboratory adverse events. Compared with the Continuation Arm, the Switch Arm saw modestly greater reductions in both total cholesterol and HDL cholesterol from baseline to week 24 without a change in the ratio of total cholesterol to HDL cholesterol.

Only 1 participant in our study had confirmed virologic failure; the genotype at the time of failure showed resistance to RPV as well as to FTC and TDF. In phase 3 clinical trials in treatment-naive subjects, those who failed RPV-based ART had a greater risk of developing resistance than those failing EFV [26–28]. However, given the presence of M41L, which would be an unusual mutation to select de novo on RPV/FTC/TDF, we suspect that this participant may have had archived resistance before the switch, despite being virologically suppressed, as has been reported elsewhere [29, 30]. Rilpivirine absorption is partially dependent on

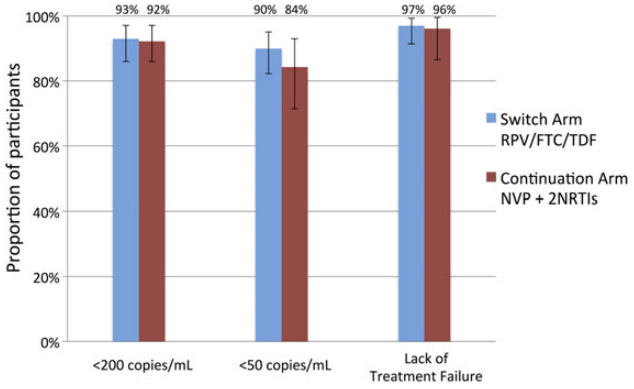

Figure 2. Primary outcome: virologic suppression and lack of treatment failure at week 24 for intention to treat analysis. Graphs show the proportion of participants with virologic suppression, error bars indicate the 95% confidence intervals. Abbreviations: FTC, emtricitabine; NRTIs, nucleos(t)ide reverse-transcriptase inhibitors; NVP, nevirapine; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

food and an acidic gastric environment. Fluctuations in absorption may be a factor that leads to selection of RPV resistance. To ensure the generalizability of our study, participants were not provided with supplemental nutrition. We collected food diaries and counseled participants regarding nutritional requirements. It is worth noting that no screened patient was excluded from study participation based on an inability to meet the suggested nutritional requirements.

We did find that participants in the Switch Arm who were on AZT at baseline had a statistically significantly higher rate of HIV RNA levels ≥200 copies/mL at week 24. These participants switched all 3 drugs in their ART regimen at study entry, whereas participants on TDF at baseline switched 2 medications (NVP and 3TC). All 4 participants with an HIV RNA ≥ 200 copies/mL at week 24 had a repeat HIV RNA level <200 copies/mL and therefore did not meet study criteria for confirmed virologic failure.

There are limitations to our study that deserve highlighting. The study was relatively small, and our efficacy estimates reflect this with broad CIs. The findings are consistent with other studies of RPV/FTC/TDF and supported by pharmacologic data from patients switching from NVP to RPV [16–18, 20]. Ongoing study follow up until week 48 will later help inform the durability of our findings. The study size also limits our ability to potentially detect safety signals but are consistent with adverse event rates in larger studies of this regimen [26, 28]. The study was not blinded, and we cannot exclude that knowledge of the randomization allocation influenced either investigators or participants. Participants may have been more or less likely to report clinical adverse events based on their knowledge of their treatment. Our analyses did not correct for multiple comparisons; therefore, marginally significant associations should be interpreted cautiously.

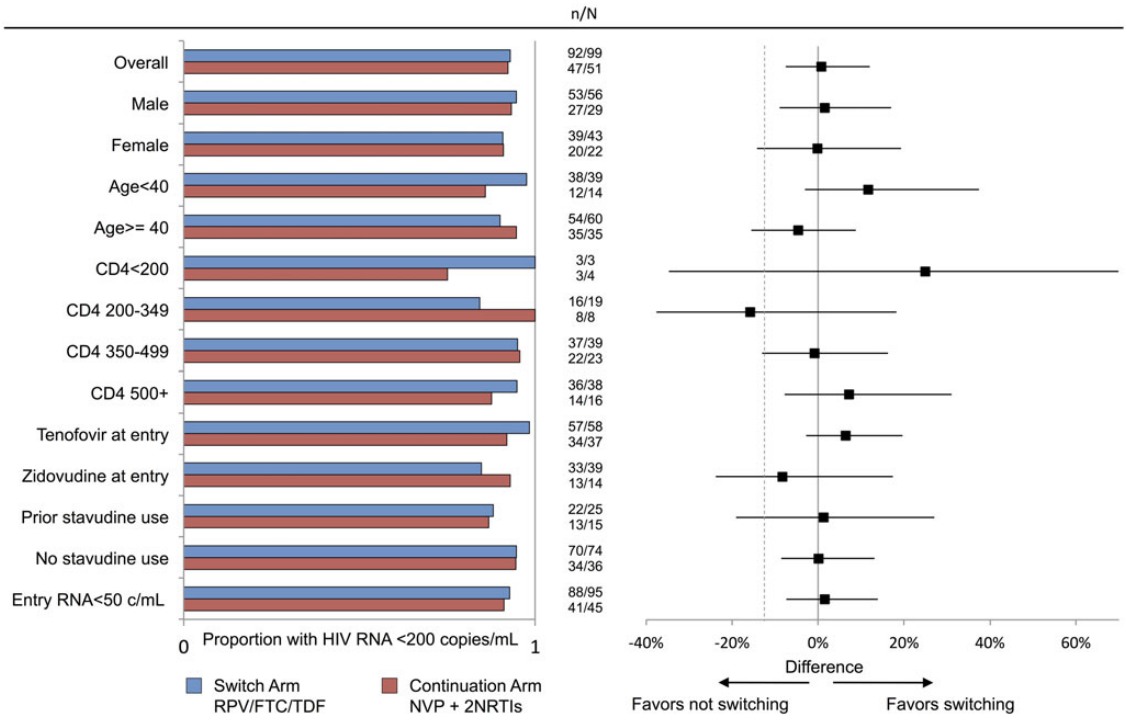

Figure 3. Virologic suppression stratified by subgroup. The left side bar graph shows the proportion of participants with virologic suppression. The right side shows the point estimate for the difference between treatment groups, with horizontal bars indicating the 95% confidence interval. The dotted vertical line indicated the noninferiority margin of −12%. CD4 subgroups are based on CD4 at the time of study entry. Abbreviations: FTC, emtricitabine; HIV, human immunodeficiency virus; NRTIs, nucleos(t)ide reverse-transcriptase inhibitors; NVP, nevirapine; RNA, ribonucleic acid; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

After 24 weeks of therapy, we found RPV/FTC/TDF to be a safe and effective antiretroviral combination compared with continued NVP plus 2 NRTIs. Currently, RPV is seldom used in sub-Saharan Africa; it is not included on the WHO list of essential medicines and is only available as a part of a few national antiretroviral programs [31]. Despite licensing agreements that helped establish the rationale for this study, generically manufactured RPV is not yet available [15]. The integration of RPV into treatment guidelines in sub-Saharan Africa has been limited by concerns related to drug-drug interactions with rifampin and inferior virologic efficacy in individuals with high viral loads [27]. Our data suggest that the dietary requirements for optimal absorption of RPV do not impair RPV's efficacy in resource-limited settings.

CONCLUSIONS

Since the study's inception, guideline agencies in the United States and Europe currently recommend integrase-strand transfer inhibitors (INSTIs), and not NNRTIs, as the third agent. The WHO guidelines still favor NNRTIs both for cost consideration and due to a relative lack of data for INSTI-based first-line therapy in low-income countries. Although the majority of individuals will tolerate one of the options currently available in sub-Saharan Africa, additional options are needed for those not tolerating or those failing their ART. Availability of RPV could provide for greater flexibility in ART management in the appropriately selected patient and may provide future options for novel treatment strategies or long-acting therapies [32]. Our study supports RPV/FTC/TDF as a well tolerated, once-daily treatment option in individuals suppressed on NVP-based ART.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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Author contributions. S. E. C. had full access to study data, performed the analyses, interpreted the results, drafted the manuscript, and had final responsibility for the decision to submit for publication.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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