Outcomes in Older Versus Younger Patients Over 96 Weeks in HIV-1–Infected Patients Treated with Rilpivirine or Efavirenz in ECHO and THRIVE[§]

Robert Ryan[1], Yaswant K. Dayaram[2], Deborah Schaible[2], Bruce Coate[1] and David Anderson[*,2]

[1]*Janssen Research & Development, Titusville, NJ, USA;* [2]*Janssen Scientific Affairs, LLC, Titusville, NJ, USA*

Abstract: *Objectives*: Increasing life expectancy of HIV-1–infected patients raises interest in how trial results apply to older patients. This post-hoc analysis evaluated potential differences in efficacy and safety in older (≥50 years) versus younger (<50 years) patients in the ECHO and THRIVE trials over 96 weeks.

Methods: HIV-infected, treatment-naïve adults were randomized to receive rilpivirine (RPV) or efavirenz (EFV), plus a background regimen. Virologic response rates (FDA snapshot analysis; HIV-1 RNA <50 copies/mL) were assessed at Week 96. Total-body bone mineral density was evaluated at baseline and Week 96 by dual-energy X-ray absorptiometry scans. Serum concentrations of 25-hydroxy vitamin D (ECHO trial only) were also measured at baseline, Week 24 and Week 48.

Results: 1368 patients were treated. At Week 96, virologic response rates were similar between older (77%) and younger (76%) RPV-treated patients and numerically higher in older (84%) versus younger (76%) EFV-treated patients. No clinically relevant age-related differences were observed in immunologic responses. Small differences were noted in older versus younger patients in adverse events (higher rates of depression, insomnia, and rash in older EFV-treated patients), laboratory abnormalities (increased low-density lipoprotein cholesterol and hyperglycemia in older EFV-treated patients and increased amylase in older patients across treatments), bone mineral density (larger decreases in older patients across treatments), and progression to severe vitamin D deficiency (greater in older versus younger EFV-treated patients).

Conclusion: Efficacy and safety outcomes were generally similar in older versus younger patients in the ECHO and THRIVE trials.

Keywords: Aging, ECHO, efavirenz, rilpivirine, THRIVE, treatment-naïve.

INTRODUCTION

As the life expectancy of HIV-1–infected patients increases, and HIV-1 prevalence among older individuals rises, the applicability of overall trial results to older patients with HIV-1 becomes more relevant for clinical practice [1]. It is estimated that by 2015, at least 50% of HIV-infected individuals in the United States will be ≥50 years of age [2]. Older patients differ from younger patients in response to therapy, rate of HIV disease progression and level of complications caused by comorbidities [2]. Combination antiretroviral therapy (ART) provides many benefits, but older patients are more susceptible to adverse events (AEs), use more concomitant medications, are at greater risk of drug-drug interactions, and have lower rates of immune recovery and higher mortality rates. Despite these trends, older patients have higher virologic response rates than younger patients [3-6].

*Address correspondence to this author at Janssen Scientific Affairs, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA; Tel: 609-730-2931; Fax: 609-730-6540; E-mail: DAnder20@its.jnj.com

[§]**Data previously presented at:** The 52nd.Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, CA, USA, September 9-12, 2012 and 3rd International Workshop on HIV & Aging, Baltimore, MD, USA, November 5-6, 2012.

ECHO (TMC278-C209, NCT00540449) and THRIVE (TMC278-C215, NCT00543725) were two global, randomized, double-blind, double-dummy, phase III trials in treatment-naïve, HIV-1–infected adults [7, 8]. In the Week 48 primary analyses, the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) 25 mg once daily (qd) demonstrated non-inferior efficacy compared with the NNRTI efavirenz (EFV) 600 mg qd (primary objective) in both trials [7, 8]. In the pooled 96-week analysis, RPV demonstrated sustained overall efficacy that was similar to EFV, with better tolerability [9].

We performed a post-hoc analysis to evaluate potential differences in efficacy and safety outcome by age at Week 96 in patients enrolled in ECHO and THRIVE. Treatment groups were divided into patients <50 years of age ("younger") and patients ≥50 years of age ("older").

MATERIALS AND METHODS

Study Design

The ECHO and THRIVE trials have been described previously [7, 8]. Both were conducted in accordance with the Declaration of Helsinki. The primary objective was to demonstrate non-inferiority (12% margin) of RPV to EFV in confirmed response (HIV-1 RNA <50 copies/mL, intent-to-treat time-to-loss-of-virologic-response [ITT-TLOVR] algo-

1873-4251/13 $58.00+.00

rithm) at week 48. Secondary objectives included efficacy and safety/tolerability over 96 weeks. Main inclusion criteria were HIV-1 RNA ≥5000 copies/mL, no NNRTI resistance-associated mutations (RAMs; from a list of 39 NNRTI RAMs) and phenotypic sensitivity to the nucleoside/nucleotide reverse transcriptase inhibitors (determined using virco®TYPE) [10]. HIV-infected, treatment-naïve adults aged ≥18 years were randomized to receive RPV 25 mg qd or EFV 600 mg qd (1:1), plus either tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) in ECHO or TDF/FTC, zidovudine/lamivudine (3TC) or abacavir/3TC in THRIVE.

Study Assessments

In a pooled week 96 analysis of ECHO and THRIVE, efficacy and safety outcomes were evaluated for each age group within each treatment arm; post-hoc age subgroup cutoffs were <50 years ("younger") and ≥50 years ("older") at baseline. The age cutoff of 50 was selected both for its common use in HIV studies and because cutoffs at higher ages resulted in n's that were too small to make meaningful comparisons. Total body bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DEXA) scans at baseline and week 96. Serum concentration measurements of 25-hydroxy vitamin D at baseline, Week 24 and week 48 (collected only in the ECHO trial to Week 48) were also assessed. Variables were summarized using descriptive statistics. Statistical analyses were performed in a pooled week 96 post-hoc analysis for response rates (ITT-TLOVR, HIV-1 RNA <50 copies/mL) and rates of AEs (grade ≥2 at least possibly related, grade ≥3 all causality, and serious AEs [SAEs]) using the Mantel-Haenszel chi-square test. Change in CD4+ cell count from baseline to week 96 was assessed using nonparametric statistics (Wilcoxon rank sum test).

RESULTS

A total of 1368 patients were treated (1242 younger; 126 older). Demographics and baseline disease characteristics were generally similar between age and treatment groups (Table **1**). Most patients were male (76% younger; 70% older) and white (60% younger; 64% older). Hepatitis C virus (HCV) co-infection was noted in 8% of younger

Table 1. Patient Baseline Demographics and Disease Characteristics

	Treatment Arm, Age Group, Years				Both Treatment Arms, Age Group, Years	
	RPV		EFV			
	<50 N=617	≥50 N=69	<50 N=625	≥50 N=57	<50 N=1242	≥50 N=126
Median age, years (range)	35 (18, 49)	54 (50, 78)	34 (19, 49)	54 (50, 69)	35 (18, 49)	54 (50, 78)
Sex, n (%)						
Female	148 (24)	20 (29)	145 (23)	18 (32)	293 (24)	38 (30)
Male	469 (76)	49 (71)	480 (77)	39 (68)	949 (76)	88 (70)
Race, n (%)						
White	375 (61)	45 (65)	375 (60)	35 (61)	750 (60)	80 (64)
Black or African American	145 (24)	20 (29)	140 (22)	16 (28)	285 (23)	36 (29)
Asian	74 (12)	4 (6)	94 (15)	3 (5)	168 (14)	7 (6)
Other[a]	7 (1)	0	4 (1)	3 (5)	11 (1)	3 (2)
Smoker	227 (37)	19 (28)	210 (34)	13 (23)	437 (35)	32 (25)
HCV,[b] n (%)	44 (7)	9 (13)	50 (8)	5 (9)	94 (8)	14 (11)
Clinical stage of HIV, n (%)						
A	442 (72)	43 (62)	436 (70)	38 (67)	878 (71)	81 (64)
B	146 (24)	20 (29)	154 (25)	15 (26)	300 (24)	35 (28)
C	29 (5)	6 (9)	35 (6)	4 (7)	64 (5)	10 (8)
Median (range) duration of HIV disease at screening, years	1 (0, 23)	2 (0, 24)	1 (0, 25)	1 (0, 28)	1 (0, 25)	2 (0, 28)
N(t)RTI use, n (%)	617 (100)	69 (100)	625 (100)	57 (100)	1242 (100)	126 (100)
Abacavir sulfate with lamivudine	38 (6.2)	6 (8.7)	34 (5.4)	2 (3.5)	72 (6)	8 (6)
Emtricitabine and tenofovir disoproxil fumarate	493 (79.9)	59 (85.5)	498 (79.7)	49 (86.0)	991 (80)	108 (86)
Zidovudine with lamivudine	101 (16.4)	6 (8.7)	98 (15.7)	6 (10.5)	199 (16)	12 (10)
Median (range) CD4+ cell count at baseline, cells/mm^3	253[c] (1, 888)	220 (5, 879)	261 (1, 919)	257 (2, 1137)	258[d] (1, 919)	233 (2, 1137)
Mean (SD) HIV-1 RNA at baseline, $\log_{10}$ copies/mL	4.9 (0.62)	5.0 (0.64)	4.9 (0.63)	5.1 (0.56)	4.9 (0.63)	5.1 (0.61)

RPV, rilpivirine; EFV, efavirenz; HCV, hepatitis C virus; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; SD, standard deviation.
[a]Includes "not allowed to ask"; [b]HCV antibody positive or reactive; [c]N=616; [d]N=1241.

patients and 11% of older patients. Mean baseline viral load was 5.1$\log_{10}$ copies/mL in older patients and 4.9 $\log_{10}$ copies/mL in younger patients, and median CD4+ cell count was 233 cells/mm^3 in older patients and 258 cells/mm^3 in younger patients.

Disposition was generally similar between younger and older patients for both the RPV and EFV treatment arms (Table **2**). In the EFV treatment arm, 88% of older patients completed treatment through week 96, compared with 79% of younger patients. In the RPV treatment arm, the same proportion (81%) of older and younger patients completed week 96. Overall, a higher number of younger patients discontinued due to "other" reasons (9% younger; 2% older); "other" reasons included patient lost to follow-up, withdrew consent, noncompliant, ineligible to continue trial, and sponsor's decision.

Week 96 virologic response rates (FDA snapshot analysis; HIV-1 RNA <50 copies/mL) were similar in older (77%) and younger (76%) patients treated with RPV (Table **2**). Numerically higher response rates were observed in older (84%) patients compared with younger (76%) patients in the EFV arm, mainly explained by a higher attrition rate due to "other reasons" rather than efficacy or safety/tolerability reasons in the younger group. Week 96 virologic response rates determined by TLOVR (HIV-1 RNA <50 copies/mL) were 75% in older patients and 78% in younger patients treated with RPV and 82% in older patients and 77% in younger patients treated with EFV (Table **2**). When evaluating the EFV and RPV arms combined, no statistically significant difference in week 96 virologic response rates was noted in older (79%) versus younger (78%) patients (p=0.775). Median changes in CD4+ cell counts at Week 96 (observed case, no imputation) were similar between older and younger patients for RPV (older, 237 versus younger, 263 cells/mm^3) and for EFV (older, 278 versus younger, 251 cells/mm^3; Table **2**). Almost all of the 1098 older and younger patients with both baseline and week 96 values available saw an increase in CD4+ cell count at Week 96. Among patients in the RPV arm with <200 cells/mm^3 at baseline, 85% of older patients and 92% of younger patients experienced an increase in CD4+ cell counts to ≥200 cells/mm^3 at week 96; in the EFV arm improvements were 100% and 91%, respectively. Among patients in the RPV arm with 200-349 cells/mm^3 at baseline, 90% of older patients and 94% of younger patients experienced an increase in CD4+ cell counts to ≥350 cells/mm^3 at week 96; in the EFV arm improvements were 91% and 96%, respectively. When evaluating the EFV and RPV arms combined, no statistically significant difference in week 96 CD4+ cell count change from baseline was noted in older versus younger patients (p=0.303).

Rates of grade ≥2 treatment-related AEs, grade ≥3 AEs regardless of relationship and SAEs were numerically higher in older versus younger patients for both treatment arms, except for grade ≥2 treatment-related AEs, for which rates were higher in younger RPV-treated patients compared with older RPV-treated patients (Table **3**). However, the most frequent (≥5% of patients) grade ≥2 treatment-related AEs had similar rates between younger and older patients in the RPV treatment arm (Table **3**). Higher rates of depression (7%, n=4), insomnia (7%, n=4), and rash (9%, n=5) were observed in older EFV-treated patients compared with younger EFV-treated patients (1% [n=8], 2% [n=13], and 5% [n=31], respectively; Table **3**). However, because of the small number of patients in this subgroup, these data should be interpreted with caution. When evaluating the EFV and RPV arms combined, no statistically significant difference in rates of grade ≥2 treatment-related AEs from baseline was noted in older (25%) versus younger (25%) patients (p=0.914); no statistically significant difference in rates of SAEs (13% older, 10% younger; p=0.162) or grade ≥3 AEs

Table 2. Patient Disposition and Week 96 Virologic Response Rates

	Treatment Arm, Age Group, Years				Both Treatment Arms, Age Group, Years	
	RPV		EFV			
	<50 N=617	≥50 N=69	<50 N=625	≥50 N=57	<50 N=1242	≥50 N=126
Disposition, n (%)						
Completed Week 96	498 (81)	56 (81)	495 (79)	50 (88)	993 (80)	106 (84)
Discontinuation due to adverse events	24 (4)	4 (6)	53 (9)	6 (11)	77 (6)	10 (8)
Discontinuation due to virologic failure	46 (8)	7 (10)	19 (3)	0 (0)	65 (5)	7 (6)
Discontinuation due to other reasons[a]	49 (8)	2 (3)	58 (11)	1 (2)	107 (9)	3 (2)
Efficacy Parameters						
HIV-1 RNA <50 copies/mL, FDA snapshot analysis, n (%)	471 (76)	53 (77)	474 (76)	48 (84)	945 (76)	101 (80)
HIV-1 RNA <50 copies/mL, TLOVR, n (%)	480 (78)	52 (75)	482 (77)	47 (82)	962 (77)	99 (79)
Median (range) change in CD4+ cell count from baseline, cells/mm^3	263[b] (–108, 763)	237[c] (37, 815)	251[d] (–126, 1216)	278[e] (–328, 763)	257[f] (–126,1216)	246[g] (–328, 815)

RPV, rilpivirine; EFV, efavirenz; FDA, Food and Drug Administration; TLOVR, time to loss of virologic response.

[a]Other reasons included lost to follow-up, withdrew consent, noncompliant, ineligible to continue trial, and sponsor's decision; [b]N=497; [c]N=58;[d]N=494; [e]N=49; [f]N=991;[g]N=107.

Table 3. Adverse Events, Serious Adverse Events and Grade ≥3 Laboratory Abnormalities

n (%)	Treatment Arm, Age Group, Years				Both Treatment Arms, Age Group, Years	
	RPV		EFV			
	<50 N=617[a]	≥50 N=69	<50 N=625[b]	≥50 N=57[c]	<50 N=1242[d]	≥50 N=126[e]
Grade ≥2 treatment-related[f] AEs	107 (17)	9 (13)	204 (33)	22 (39)	311 (25)	31 (25)
Grade ≥3 AEs regardless of relationship	104 (17)	16 (23)	125 (20)	14 (25)	229 (18)	30 (24)
SAEs	55 (9)	10 (15)	64 (10)	7 (12)	119 (10)	17 (13)
Grade ≥2 Treatment-Related[f] AEs Occurring in ≥5% of Patients						
Nervous system disorders	22 (4)	1 (1)	64 (10)	5 (9)	86 (7)	6 (5)
Dizziness	4 (1)	0 (0)	42 (7)	2 (4)	46 (4)	2 (2)
Psychiatric disorders	39 (6)	2 (3)	57 (9)	8 (14)	96 (8)	10 (8)
Depression	10 (2)	1 (1)	8 (1)	4 (7)	18 (2)	5 (4)
Insomnia	12 (2)	1 (1)	13 (2)	4 (7)	25 (2)	5 (4)
Skin and subcutaneous tissue disorders	10 (2)	1 (1)	51 (8)	9 (16)	61 (5)	10 (8)
Rash	3 (1)	1 (1)	31 (5)	5 (9)	34 (3)	6 (5)
Grade ≥3 Metabolic Laboratory Abnormalities Regardless of Relationship, Occurring in Any Patient						
Lipids (fasted)						
Total cholesterol	1 (0.2)	0 (0)	19 (3)	3 (5)	20 (2)	3 (2)
Triglycerides	3 (1)	1 (1)	22 (4)	1 (2)	25 (2)	2 (2)
LDL-C	10 (2)	1 (1)	30 (5)	10 (18)	40 (3)	11 (9)
Glucose (fasted)						
Glucose increased	2 (0.3)	1 (1)	2 (0.3)	2 (4)	4 (3)	3 (2)
Grade ≥3 Non-Metabolic Laboratory Abnormalities Regardless of Relationship, Occurring in Any Patient						
Amylase	22 (4)	8 (12)	30 (5)	7 (13)	52 (4)	15 (12)
Lipase	4 (1)	2 (3)	8 (1)	2 (4)	12 (1)	4 (3)
Phosphorous	7 (1)	0 (0)	7 (1)	2 (4)	14 (1)	2 (2)
AST	13 (2)	2 (3)	23 (4)	1 (2)	36 (3)	3 (2)
ALT	9 (2)	1 (1)	25 (4)	2 (4)	34 (3)	3 (2)
White blood cell count decreased	7 (1)	1 (1)	5 (1)	0 (0)	12 (1)	1 (1)

RPV, rilpivirine; EFV, efavirenz; AE, adverse event; SAE, serious adverse event; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

The number of observations for each parameter does not always equal the total number of patients in each subgroup due to unavailable test results for a small number of patients: [a]N=616 for metabolic laboratory abnormalities; [b]N=613 for total cholesterol and triglycerides, N=611 for LDL-derived, N=612 for glucose, N=617 for phosphorous and AST, N=623 for white blood cell count; [c]N=56 for metabolic laboratory abnormalities; [d]N=1241 for metabolic laboratory abnormalities, N=1230 for total cholesterol and triglycerides, N=1228 for LDL-derived, N=1229 for glucose, N=1234 for phosphorous and AST, N=1240 for white blood cell count; [e]N=125 for metabolic laboratory abnormalities; [f]Deemed at least possibly related by investigator.

regardless of relationship was observed (24% older, 18% younger; p=0.143).

No clinically relevant differences in grade ≥3 metabolic laboratory abnormalities occurred between age groups, except abnormal low-density lipoprotein cholesterol (LDL-C) levels in 18% (n=10) of older compared with 5% (n=30) of younger EFV-treated patients (Table **3**) and hyperglycemia, observed in 4% (n=2) of older compared with 0.3% (n=2) of younger EFV-treated patients. Thirteen patients (1%) entered the trials on lipid-lowering medication; 28 patients initiated lipid-lowering agents during treatment (23 in EFV arm), and no differences were observed in younger (2%) versus older (2%) patients overall with regard to initiation of lipid therapy. Grade ≥3 amylase levels were observed in older (12%) compared with younger patients overall (4%; Table **3**). Reported non-metabolic laboratory abnormalities (grade ≥3) were similar between age and treatment groups, including levels of evaluated hepatic transaminases, electrolytes and hematologic parameters (Table **3**). It should be noted that the number of patients who experienced grade ≥3 metabolic or non-metabolic laboratory abnormalities was low overall, so comparisons between groups should be made with caution.

Estimated glomerular filtration rate (eGFR), based on serum creatinine, decreased from baseline to Week 96 regardless of age or treatment group; the magnitude of

change was similar between age categories within the two treatment groups. The median change from baseline at Week 96 for the RPV treatment arm was –13.6 mL/min/1.73 m^2 in younger and –11.0 mL/min/1.73 m^2 in older patients, and for the EFV treatment arm, –3.9 mL/min/1.73 m^2 in younger and –9.2 mL/min/1.73 m^2 in older patients. The majority of eGFR changes in patients taking RPV occurred during the first 2 weeks of exposure and remained fairly stable thereafter. Bone mineral density, as measured by DEXA, decreased from baseline to week 96 regardless of age or treatment group. Larger median decreases were observed in older (–0.035 g/cm^2, RPV arm; –0.049 g/cm^2, EFV arm) compared with younger patients (–0.014 g/cm^2, RPV arm; –0.014 g/cm^2, EFV arm).

Median 25-hydroxy vitamin D changes from baseline were greater in older (–3.2 ng/mL; n=29) versus younger (–1.6 ng/mL; n=261) patients in the EFV arm. Levels remained relatively unchanged for both older (0.8 ng/mL; n=31) and younger (–0.8 ng/mL; n=261) patients in the RPV arm. Risk of progression from insufficient (50-74 nmol/L) or deficient (25-49 nmol/L) to severely deficient (<25 nmol/L) 25-hydroxy vitamin D levels from baseline to Week 48 occurred in 0% (n=0) of older and 2% (n=4) of younger RPV-treated patients. Among EFV-treated patients, risk of progression was 13% (n=2) for older and 8% (n=13) for younger patients.

DISCUSSION

Several challenges exist for the aging HIV-1–infected population, including age-related physiologic changes in renal and hepatic function and attenuated immune competence, independent of suppression of HIV replication. Comorbid conditions requiring drug treatments that may complicate ART also need to be considered [11]. Many HIV clinical trials that examine the effect of novel antiretrovirals (ARVs) exclude or underrepresent older patients, as well as those with comorbid conditions, and many do not compare outcomes in older versus younger patients [12, 13].

This post-hoc analysis of the pooled ECHO and THRIVE trials showed that when treatment arms were combined, older (aged ≥50 years) patients generally responded to treatment as well as younger (aged <50 years) patients, both immunologically and virologically. There were slightly increased response rates among older versus younger patients treated with EFV. No evaluation of differences by NRTI backbone could be made as 80% of patients were receiving TDF.

Older age is associated with reduced hepatic and renal function, potentially affecting the ability to metabolize drugs [14]. This may result in elevated serum concentrations of ARVs, and associated drug toxicity. Comorbidities requiring drug treatment also complicate ART; drug-drug interactions potentially alter tolerability or efficacy [2]. Similarly, older patients are more likely to change therapy due to AEs [15]. In this study, rates of depression, insomnia and rash were slightly higher in older versus younger EFV-treated patients. Generally, older patients did not experience higher levels of neuropsychiatric, hepatic or renal treatment-related AEs compared with younger patients. Rates of grade ≥3 metabolic laboratory abnormalities were similar in older and younger patients in both RPV and EFV treatment arms, except for LDL-C and glucose, which were greater in older EFV-treated patients. The need to introduce lipid-lowering therapy was not greater in older versus younger patients; generally, few patients started such therapy, regardless of age. Because of the smaller number of patients aged ≥50 and the even smaller number of patients who experienced AEs in our study, comparisons between age and treatment group should be interpreted with caution.

Decreases in eGFR from baseline to Week 96 were modest and did not differ considerably between age groups. eGFR changes during the first 2 weeks of RPV treatment were likely related to inhibition of tubular secretion of creatinine. Increases in eGFR, estimated using cystatin C (indicator of renal filtration), following treatment with RPV (THRIVE trial) suggest that RPV was not associated with decreases in glomerular function [7].

In this analysis, BMD decreased from baseline in both age groups with the largest median decrease found in older patients. Cigarette use (self-reported), known to worsen BMD, was infrequent. Decreased BMD is a feature of osteoporosis, which is common in the older HIV-infected population. HIV disease-related chronic immune activation and treatment with ARV regimens reduce BMD, therefore increasing the risk of osteoporosis and subsequent risk of fractures [16-19].

Vitamin D insufficiency and deficiency are common among HIV-infected individuals, and EFV treatment is associated with reduction in 25-hydroxy vitamin D levels [20]. Vitamin D analysis at Week 48 (ECHO trial) demonstrated that older RPV-treated patients showed no increased risk of lower 25-hydroxy vitamin D levels or progression to severe deficiency compared with younger RPV-treated patients. Older EFV-treated patients had greater decreases in 25-hydroxy vitamin D levels than younger EFV-treated patients and greater risk of progression to severe vitamin D deficiency.

Older HIV-1–infected patients face additional challenges compared with younger patients. Thus, patient age needs to be considered when choosing an optimal treatment plan. This substudy is informative in that similar data on age-related HIV drug treatment outcomes are not well represented in published literature. Limitations of this analysis are the small number of older compared with younger patients and its post-hoc nature; an age-matched HIV-negative group for comparison was not included in ECHO/THRIVE; therefore, an evaluation of whether changes observed between younger and older patients were simply age-related is not possible.

In this analysis, safety outcomes were similar between older and younger patients. Although rates of grade ≥3 AEs and SAEs were higher in older patients, discontinuations due to AEs were low and similar between older and younger patients. Changes in eGFR and rates of laboratory abnormalities were similar between age groups with few exceptions. Higher rates of LDL-C and glucose elevations in older patients were driven by higher rates of these abnormalities in older EFV-treated patients, and amylase elevations were noted in older patients in both treatment arms. Furthermore, differences in bone metabolism markers

between older and younger patients warrant further investigation.

In summary, older and younger patients had similar efficacy outcomes in both RPV and EFV treatment arms, with some small differences noted in safety/tolerability. On the basis of these data, there were no clinically relevant differences in outcomes between older and younger patients in the phase III ECHO and THRIVE trials.

CONFLICT OF INTEREST

RR, YKD, DS and DA are employees of Janssen and stockholders of Johnson & Johnson. BC was a full-time contract employee for Janssen at the time this study was conducted. The ECHO and THRIVE studies were sponsored by Janssen.

ACKNOWLEDGEMENTS

We thank the patients and their families for their participation and support during the studies. The authors also acknowledge the ECHO and THRIVE study teams, study center staff and principal investigators. Editorial assistance was provided by Jennifer Granit, PhD, Medicus International New York. Funding for the study and for editorial support was provided by Janssen.

PATIENT CONSENT

Patients provided written informed consent to participate in the clinical trials described herein.

HUMAN/ANIMAL RIGHTS

Declared none.

REFERENCES

[1] Centers for Disease Control and Prevention. HIV/AIDS among persons aged 50 and older: CDC HIV/AIDS facts. February 12, 2008. Available from: http://www.cdc.gov/hiv/topics/over50/index.htm. Accessed March 4, 2013.

[2] Kirk JB, Goetz MB. Human immunodeficiency virus in an aging population, a complication of success. J Am Geriatr Soc 2009; 57: 2129-38.

[3] Fourie J, Flamm J, Rodriguez-French A*, et al.* Effect of baseline characteristics on the efficacy and safety of once-daily darunavir/ritonavir in HIV-1-infected, treatment-naive ARTEMIS patients at week 96. HIV Clin Trials 2011; 12: 313-22.

[4] Blanco JR, Caro AM, Perez-Cachafeiro S*, et al.* HIV infection and aging. AIDS Rev 2010; 12: 218-30.

[5] Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study Group, Sabin CA, Smith CJ*, et al.* Response to combination antiretroviral therapy: variation by age. AIDS 2008; 22: 1463-73.

[6] Mussini C, Manzardo C, Johnson M*, et al.* Patients presenting with AIDS in the HAART era: a collaborative cohort analysis. AIDS 2008; 22: 2461-9.

[7] Cohen CJ, Andrade-Villanueva J, Clotet B*, et al.* Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229-37.

[8] Molina JM, Cahn P, Grinsztejn B*, et al.* Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378: 238-46.

[9] Cohen CJ, Molina JM, Cassetti I*, et al.* Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomised trials. AIDS 2013; 27: 939-50.

[10] Tambuyzer L, Azijn H, Rimsky LT*, et al.* Compilation and prevalence of mutations associated with resistance to non-nucleoside reverse transcriptase inhibitors. Antivir Ther 2009; 14: 103-9.

[11] Zhao H, Goetz MB. Complications of HIV infection in an ageing population: challenges in managing older patients on long-term combination antiretroviral therapy. J Antimicrob Chemother 2011; 66: 1210-4.

[12] Manfredi R. HIV disease and advanced age: an increasing therapeutic challenge. Drugs Aging 2002; 19: 647-69.

[13] Rhee MS, Greenblatt DJ. Pharmacologic consideration for the use of antiretroviral agents in the elderly. J Clin Pharmacol 2008; 48: 1212-25.

[14] Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 1997; 61: 331-9.

[15] Lodwick RK, Smith CJ, Youle M*, et al.* Stability of antiretroviral regimens in patients with viral suppression. AIDS 2008; 22: 1039-46.

[16] Brown TT, McComsey GA, King MS*, et al.* Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr 2009; 51: 554-61.

[17] Duvivier C, Kolta S, Assoumou L*, et al.* Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS 2009; 23: 817-24.

[18] Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab 2008; 93: 3499-504.

[19] Walker Harris V, Brown TT. Bone loss in the HIV-infected patient: evidence, clinical implications, and treatment strategies. J Infect Dis 2012; 205 Suppl 3: S391-8.

[20] Brown TT, McComsey GA. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. Antivir Ther 2010; 15: 425-9.

Received: December 2, 2013 **Revised: January 14, 2014** **Accepted: January 25, 2014**