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The Rainbow Cohort: 96 Week Follow-up of Saquinavir-containing Regimens in Previously Antiretroviral Therapy (ART)-naïve and Pre-treated but Protease Inhibitor (PI)-naïve HIV-infected Patients

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Abstract
Objective: We have previously reported data from the German cohort of the multinational observational prospective RAINBOW survey which assessed the tolerability and efficacy of ritonavir-boosted saquinavir (SQV/r)-containing regimens over 48 weeks in routine clinical practice. This analysis presents data from antiretroviral (ART)-naïve and pretreated but protease inhibitor (PI)-naïve patients treated in a long-term one line (96 weeks) follow-up of the initial study.
Methods: All ART- and PI-naïve patients from the initial RAINBOW cohort who had recorded data to one line 96 weeks of treatment were eligible for inclusion in the current analysis. Efficacy assessments included the proportion of patients with HIV-1 RNA <50 and <400 copies/mL and changes in CD4 cell count from baseline to week 96. Tolerability assessments included changes in liver enzymes and lipid levels from baseline to week 96. For evaluation of efficacy, intent-to-treat analysis, in which missing values were recorded as failure (ITT), and last-observation-carried-forward (LOCF) analysis were used. Metabolic parameters were assessed using LOCF analysis.
Results: The analysis included 175 ART-naïve and 109 pretreated but PI-naïve patients. After 96 weeks, a similar proportion of patients in the ART-naïve and in the pretreated but PI-naïve group had HIV-1 RNA levels <400 copies/mL (68.0% and 70.6% [ITT], respectively; 96.6% and 90.8% [LOCF], respectively). The proportion of patients with HIV RNA <50 copies/mL was higher in the ART-naïve group compared with the pretreated but PI-naïve group (61.1% and 56.9% [ITT], respectively; 84.0% and 75.2% [LOCF], respectively). Median change in CD4 cell count from baseline to week 96 was +263 cells/mm^3 (IQR 170; 384. LOCF; p<0.0001) in the ART-naïve group, and one line +181 cells/mm^3 (IQR 60; 309. LOCF; p<0.0001) in the pretreated but PI-naïve group. Treatment was well tolerated, with only 2.5% of patients withdrawing from treatment due to side effects. There were no clinically relevant changes in liver enzyme levels. Overall total cholesterol, triglyceride, and low- and high-density lipoprotein levels increased to week 96, although levels remained within normal ranges in the majority of ART-naïve and pretreated patients.
Conclusions: This follow-up analysis confirms the long term efficacy and tolerability of SQV/r in ART-naïve and pretreated but PI- naïve patients in the real-life clinical setting.

Key words: HIV; treatment; saquinavir; long term; HIV RNA; CD4 cells; lipids

Introduction

Current guidelines recommended a combination of two nucleoside reverse transcriptase inhibitors one line (NRTIs) with either a protease inhibitor (PI) or non-one line nucleoside reverse transcriptase inhibitor (NNRTI) as first-line therapy for HIV infection [1-3]. Saquinavir one line (Invirase®, SQV), a potent inhibitor of HIV-1 viral protease, is recommended for initial PI-based ART by European HIV treatment guidelines in combination with subtherapeutic doses of ritonavir (SQV/r) [1]. In order to reduce pill burden and simplify dosing, SQV was reformulated from 200 mg hard capsules to one line 500 mg film-coated tablets. This formulation has been shown to have equivalent bio-availability relative to traditional 200 mg capsules when co-administered with ritonavir [4]. When used at the current recommended daily dose SQV 1000 mg twice daily with one line 100 mg riton-

avir twice daily [5] 500 mg film-coated tablets have been shown to be effective in clinical trials of treatment-naïve and -experienced patients [6-9] with a more favourable lipid profile than ritonavir-boosted lopinavir (LPV/r) [8] or indinavir (IDV/r) [9]. Long-term data on the use of the new formulation of SQV in HIV-infected patients are currently limited, but suggest that control of HIV viremia is durable up to and beyond 96 weeks [7].

The RAINBOW survey was an international, prospective assessment of data from HIV-1 infected patients treated with the 500 mg film-coated formulation of SQV in routine clinical practice including a wide range of different patient types with different treatment histories. The aim of RAINBOW was to assess the efficacy and safety of SQV/r in 'real world' situations, where patients are generally less strictly monitored and supported and often have more complex clinical backgrounds than in the necessarily controlled situation of the clinical trial. We have previously reported safety and efficacy data from the initial 48 week analysis of the German cohort of RAINBOW which demonstrated that SQV/r is effective and well tolerated in ART-naïve and pretreated but PI-naïve patients in a 'real-world' clinical setting [10]. The analysis presented here extends these data to 96 weeks of treatment.

Patients and Methods

The RAINBOW survey was a multicenter, prospective, non-interventional observational study in HIV-patients treated with SQV 500 mg film-coated tablets as part of their antiretroviral regimen. The study took place between July 2005 (first patient first visit) and May 2009 (last patient last visit). Inclusion criteria for the RAINBOW survey were documented HIV-1 infection and initiation of treatment with SQV/ritonavir (SQV/r) utilizing the 500 mg film-coated SQV tablet, in combination with other antiretrovirals as part of routine antiretroviral (ART) therapy. Patient selection for SQV-based antiretroviral treatment was at the discretion of the treating physician, and the decision was made in accordance with the declaration of Helsinki and with German treatment guidelines, published by the German AIDS-society [11]. Patients included in the full study cohort who were ART-naïve or who had been previously treated with non-PI containing ART regimens (i.e. PI-naïve) and had recorded data to one line 96 weeks of treatment were eligible for this analysis. There were no specified exclusion criteria and no prohibitions were placed on the use of concomitant medication. In order to avoid selection bias, all investigators were encouraged to report data from all eligible patients at their site rather than reporting on a random subset only.

The following demographic/baseline characteristic data were collected: date of birth; ethnicity; gender; height; weight; previous diseases; HIV risk exposure; year of diagnosis; mode of infection; current disease stage; HIV-RNA viral load and CD4+ cell count prior to starting boosted SQV treatment; anti-retroviral drug history; concomitant medications, including any lipid lowering and antidiarrhetic medications; and hematology and biochemistry laboratory results (including fasting blood lipids, where available).

Efficacy and tolerability data were collected from the patient records. As this was an observational study, patient follow-up visits were not set by protocol but were those scheduled according to the treating clinician's plan and patient's availability, and therefore study visits in this analysis were allocated to week 60, 72, 84 and 96 (all +/-4 weeks). The following data were recorded at these visits if available in the patient chart: CD4+ cell count, HIV-RNA viral load, and haematology and biochemistry laboratory results (including liver enzymes and fasting lipids) as well as information about concomitant lipid lowering agents and other concomitant medication. Related clinical adverse events and treatment adherence information were collected.

Endpoints

Efficacy endpoints were: percentage of patients with HIV-RNA<50 copies/mL at week 96; percentage of patients with HIV-RNA<400 copies/mL at week 96; changes in CD4 cell count from baseline to week 96. Safety and tolerability endpoints were: changes in fasting lipids levels (total cholesterol [TC], high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol, and triglycerides) from baseline to one line week 96 stratified according to baseline levels; changes in liver enzymes (alanine aminotransferase [ALT], aspartame aminotransferase [AST], and gamma glutamyl transferase [GGT]) and bilirubin levels; frequency of Grade 3 and 4 adverse events or death considered to be related to SQV.

Statistics

All PI-naïve patients with complete baseline visit who completed the initial 48 week analysis and who were then treated with an SQV/r-containing regimen for a further 48 weeks (total 96 weeks) were included in the analysis. Efficacy parameters were assessed using an intent-to-treat (ITT) analysis (where missing data were included as failure) and also, to reflect the observational nature of the study, a last observation carried forward (LOCF) analysis (where missing values were taken as the previous observed value). For evaluation of safety parameters LOCF analysis was used.

Descriptive summary statistics were used for this cohort analysis, describing changes in CD4+ cell count and HIV-RNA from baseline, the type and frequency of adverse events observed, and changes in safety relevant laboratory parameters. For continuous variables the following statistics were calculated: mean; standard deviation, median, inter-quartile range (IQR) and minimum and maximum values. For categorical variables number of values in each category and percentage of the values in regard to number of patients in the study population were calculated. Explorative statistical methods were used with regard to the efficacy endpoints and changes in safety-relevant laboratory parameters. Changes from baseline were tested for significance using the Wilcoxon signed rank test. Shifts in ranking of baseline values and week 96 values were assessed using Shift tables and McNemar/Bowker tests.

Results

The initial 48 week analysis included 454 patients (275 ART-naïve and 179 pretreated but PI-naïve). Of these, 93 patients withdrew from treatment prior to the end of the 48 week study and 77 patients had no available data after week 48; these 170 patients were excluded from the 96 week analysis. The remaining 284 patients consisted of 175 ART-naïve and 109 pretreated but PI-naïve individuals.

Baseline characteristics and demographics are shown in Table 1.

The majority of patients in the total cohort was male (83.1%) and Caucasian (82.0%), and had contracted HIV infection through MSM risk behavior (59.9%). Median HIV RNA levels were lower and CD4 levels higher in pretreated patients compared with ART-naïve patients. Around one third of pretreated patients had an interruption in treatment prior to beginning SQV/r, with a median duration of 2 years. Of the pretreated but PI-naïve patients, 43.1% had previous virological failure with NRTI/NNRTI therapy, and 20.2% had previous toxicity (72.7% of these to NNRTIs)

Details of other antiretroviral drugs used with SQV/r in this analysis are shown in Table 2.

The most commonly used treatment regimen in ART-naïve patients and pretreated but PI-naïve patients was SQV/r in combination with two NRTIs, predominantly tenofovir and emtricitabine. Around one third of pretreated but PI-naïve patients received SQV/r as double PI therapy, predominantly with lopinavir.

Discontinuations from Week 48 to Week 96

In the ART-naïve group, a total of 31 patients (17.7%) were recorded as having withdrawn from the study prematurely. The main reasons for premature withdrawal from treatment were (percentages are based on

Table 1. Baseline Characteristics and Demographics.

	ART-naïve patients (n = 175)	**Pretreated, but PI-naïve patients (n = 109)**
Male (n)	86 % (n = 150)	79 % (n = 86)
Age in years, Median (IQR)	39 (33; 46)	41 (37; 50)
Height in cm, Median, (IQR)	176 (172; 183)	178 (170; 182)
Weight in kg, Median (IQR)	72 (65; 79)	72 (65; 80)
Hepatitis B coinfection	5 % (n = 9)	2 % (n = 2)
Hepatitis C coinfection	12 % (n = 21)	10 % (n = 11)
Infection mode		
MSM	61 %	59 %
Heterosexual	19 %	17 %
IVDU	6 %	6 %
Not specified	14 %	18 %
Race		
Caucasian	85 %	78 %
African	8 %	11 %
Asian	3 %	5 %
Not specified	4 %	6 %
CDC stage		
A	38 %	29 %
B	33 %	51 %
C	27 %	17 %
Not specified	2 %	3 %
Time since first diagnosis in years, Median (IQR)	1 (0; 4)	9 (5; 13)
Time since first ART in months, Median (IQR)	-	79 (37; 104)
Number of previous regimen, Median (IQR)	-	3 (2; 4)
Treatment interruption before start of new regimen	-	28 % (n = 30)
Duration of treatment interruption in months, Median (IQR)	-	24 (6; 40)
HIV RNA (copies/mL), Median (IQR)	117,000 (36,548; 336,000)	3,433 (92; 34,384)
CD4-count (cells/mm³) Median (IQR)	196 (82; 284)	319 (204; 478)

IQR: Inter quartile range; MSM: Men who have sex with men; CDC: Center for Disease Control; ART: Antiretroviral therapy; NRTIs: nucleoside reverse transcription inhibitors; PI: Protease inhibitor; IVDU: Intravenous Drug Use

Table 2. Antiretroviral drugs included in SQV/r regimens.

	ART-naïve		Pretreated but PI-naïve	
	n	%	n	%
2 NRTI	**129**	**74**	**54**	**59.5**
TDF/FTC	82	47	38	35
AZT/3TC	29	17	4	4
3TC/ABC	14	8	8	7
PI	**19**	**11**	**30**	**27.5**
LPV	19	11	20	18
ATV	0		6	5.5
FAP	0		4	4
PI + NRTI/NNRTI	**5**	**3**	**8**	**7**
LPV	2		5	4.5
ATV	2		3	2.5
FAP	1		0	2
Not specified	**0**	**0**	**1**	**1**
Other	**22**	**12**	**16**	**15**

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; TDF: tenofovir; FTC: emtricitabine; AZT: zidovudine; 3TC: lamivudine; ABC: abacavir; LPV: lopinavir; ATV: atazanavir; FAP: fosamprenavir

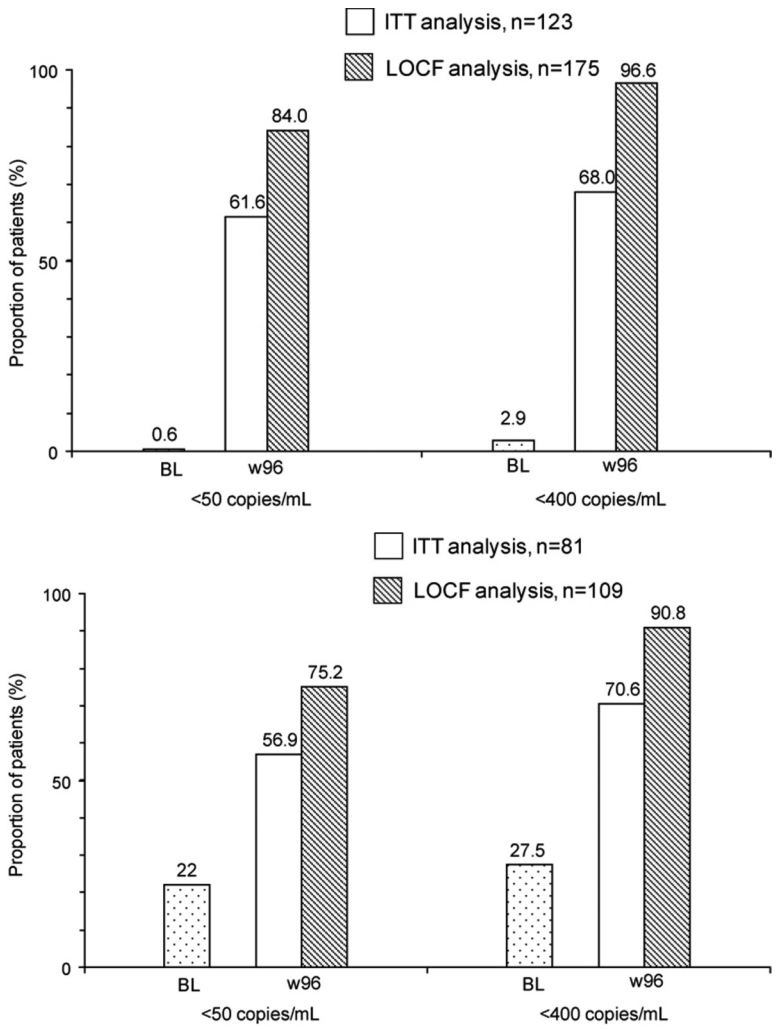

Fig. 1. Proportion of a) ART-naïve and b) pretreated but PI-naïve patients with HIV-1 RNA <50 copies/mL and <400 copies/mL at baseline (BL) and week 96 (w96).

number of premature withdrawals): lost to follow-up (n = 8; 25.8%), side effects (n = 7; 22.6%) and virologic failure (n = 4; 12.9%). Other reasons were reported in 11 patients (35.5%). No reason for premature withdrawal was provided in one (3.2%) case. In the pretreated but PI-naïve group, 12 patients (11.0%) were recorded as having withdrawn from the study prematurely. The main reasons for premature withdrawal from treatment were (percentages are based on number of premature withdrawals): adherence issues (n = 4; 33.3%), lost to follow-up (n = 2; 16.7%) and virologic failure (n = 2; 16.7%). Other reasons were reported in three patients (25.0%). No reason for premature withdrawal was provided in one (8.3%) case.

Efficacy

The percentages of patients with HIV-1 RNA <50 copies/mL and <400 copies/mL at baseline and at week 96 are shown in Figure 1. A larger proportion of patients who were pretreated but PI-naïve had HIV-1 RNA <50 copies/mL and <400 copies/mL at baseline (22.0% and 27.5%, respectively) compared with those patients who were ART-naïve (0.6% and 2.9%, respectively. A similar proportion of patients in the ART-naïve and in the pretreated but PI-naïve group had HIV-1 RNA levels <400 copies/mL (ITT analysis: 68.0% and 70.6%, respectively; LOCF analysis: 96.6% and 90.8%, respectively). The proportion of patients with HIV RNA <50 copies/mL was higher in the ART-naïve group compared with the pre-

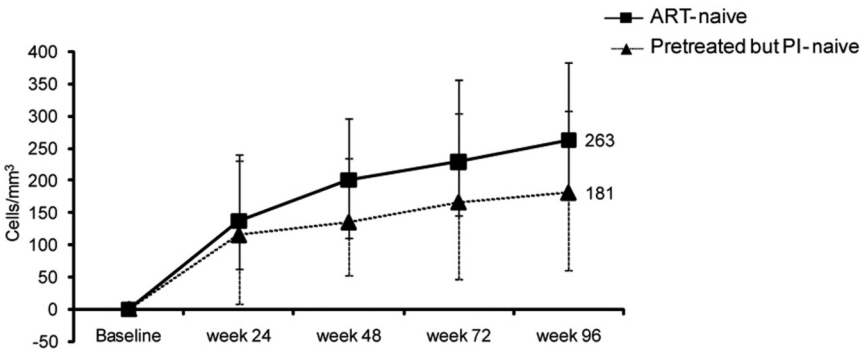

Fig. 2. Change of CD4 cell count (median ± IQR) from baseline to week 96 (LOCF).

treated but PI-naïve group (ITT analysis: 61.6% and 56.9%, respectively; LOCF analysis: 84.0% and 75.2%, respectively). Median change in HIV RNA levels from baseline to week 96 was -3.35 log10 copies/mL (IQR one line -3.79; -2.87) by ITT analysis and -3.33 log10 copies/mL (IQR -3.82; -2.84) by LOCF analysis in the ART-naïve group. For the pretreated but PI-naïve group, median change HIV RNA levels from baseline to week 96 was -1.76 log10 copies/mL (IQR -2.61 one line; -0.35) by ITT analysis and -1.66 log10 copies/mL (IQR -2.60; -0.04) by LOCF analysis.

Median CD4 counts from baseline to week 96 increased during treatment in both patient groups (Fig. 2). In the ART-naïve group, by LOCF analysis, median change in CD4 count was +263 cells/mm^3 (IQR 170; 384) at week 96 from a baseline level of 196 (IQR 82; 284) ($p<0.0001$). Similar results were seen by ITT analysis (median change +290 cells/mm^3 [IQR 184; 398]) ($p<0.0001$). Median increase in CD4 cell count at week 96 was lower in the pretreated but PI-naïve group at +181 cells/mm^3 (IQR 60; 309; LOCF analysis), but this group had higher initial baseline levels (319 [IQR 204; 478]). The change in CD4 cell count from baseline to week 96 remained significant ($p<0.0001$; LOCF analysis). Similar results were seen by ITT analysis (median change +203 cells/mm^3 [IQR 90; 325]) ($p<0.0001$).

Safety and Tolerability

Treatment with SQV/r was well tolerated and no unexpected adverse events (AE) were reported between week 48 and week 96. In the ART-naïve group, there were 10 (5.7%) patients who experienced at least one AE during the course of the study (each reported one AE). Two AEs in 2 patients (1.1%) were considered as related of study drug (nausea and diarrhoea, both Grade 2). There were four AEs in four patients (2.3%) with Grade 3 or 4 intensity (hypertonia, iron deficiency anaemia, syphilis, and delusional depression) none of which were considered to be related to SQV. In the treatment experienced but PI-naïve group, one AE was reported in one patient (0.9%) during the course of the study. The AE (skin eruption to face) was Grade 3 intensity and was considered to probably be related to SQV. The AE resolved without sequelae. No deaths were reported during the extended treatment period.

In ART-naïve patients, median changes in liver enzymes from baseline at week 96 for male patients were: ALT -4.9 U/L (IQR one line -23.0; 4.0); AST -2.7 (IQR one line -12.0; 4.0); GGT -1.3 (IQR -18.5; 7.0) (LOCF). For female patients median changes in liver enzymes from baseline at week 96 were: ALT -1.0 U/L (IQR -6.0; 10.0); AST -2.0 (IQR -7.7; 4.0); GGT 5.0 (IQR -16.0; 11.0) (LOCF). Overall median change in bilirubin level from baseline at week 96 was +0.1 mg/dL (IQR -0.08, 0.29) (LOCF). In all, one of 165 patients with normal levels at baseline had a Grade 3/4 increase in ALT and three of 132 patients with normal levels at baseline had a Grade 3/4 increase in AST at week 96. Normalization of liver enzymes at 96 weeks occurred in around half of patients who had pre-existing abnormal (Grade 3/4) levels (ALT 3 out of 6 patients; AST 3 out of 5 patients; GGT 3 out of 6 patients).

In pretreated but PI-naïve patients, median changes in liver enzymes from baseline at week 96 for male patients were: ALT -1.0 U/L (IQR -15.0; 7.0); AST -1.0 (IQR -12.0; 6.0); GGT -4.5 (IQR -21.5; 9.0) (LOCF). For female patients median changes from baseline at week 96 were: ALT -2.0 U/L (IQR -12.0; 5.0); AST 0.0 (IQR -9.5; 8.5); GGT 0.0 (IQR -8.0; 16.0) (LOCF). Overall median change in bilirubin level from baseline at week 48 was +0.1 mg/dL (IQR -0.16; 0.30) (LOCF). In all, one of 82 patients with normal levels at baseline had a Grade 3/4 increase in ALT and one of 75 patients with normal levels at baseline had a Grade 3/4 increase in AST at week 96. Normalization of liver enzymes at 96 weeks occurred in 2 out of 3 patients who had pre-existing abnormal (Grade 3/4) levels of ALT at baseline and 3 out of 6 patients who had pre-existing abnormal (Grade 3/4) levels of GGT at baseline.

As this was an observational study, details of dose reductions due to adverse events were not available.

Changes in Lipid Profiles

Median changes in fasting TC, triglyceride, LDL and HDL levels from baseline to week 96 for the two patient groups are shown in Figures 3a and 3b.

In the ART-naïve group, the majority of patients had TC levels < 200 mg/dL and triglyceride levels < 200 mg/dL at baseline and week 96 (81.8% and 75.2% at baseline and 50.7% and 62.4% at week 96, respectively). When stratified by baseline levels, there was a significant shift towards an increase in TC levels ($p<0.0001$; McNemar/Bowker test) and a in triglyceride levels ($p = 0.05$; McNemar/Bowker test). In all, one of 148 patients with normal levels at baseline had a Grade 3/4 increase in TC and one of 149 patients

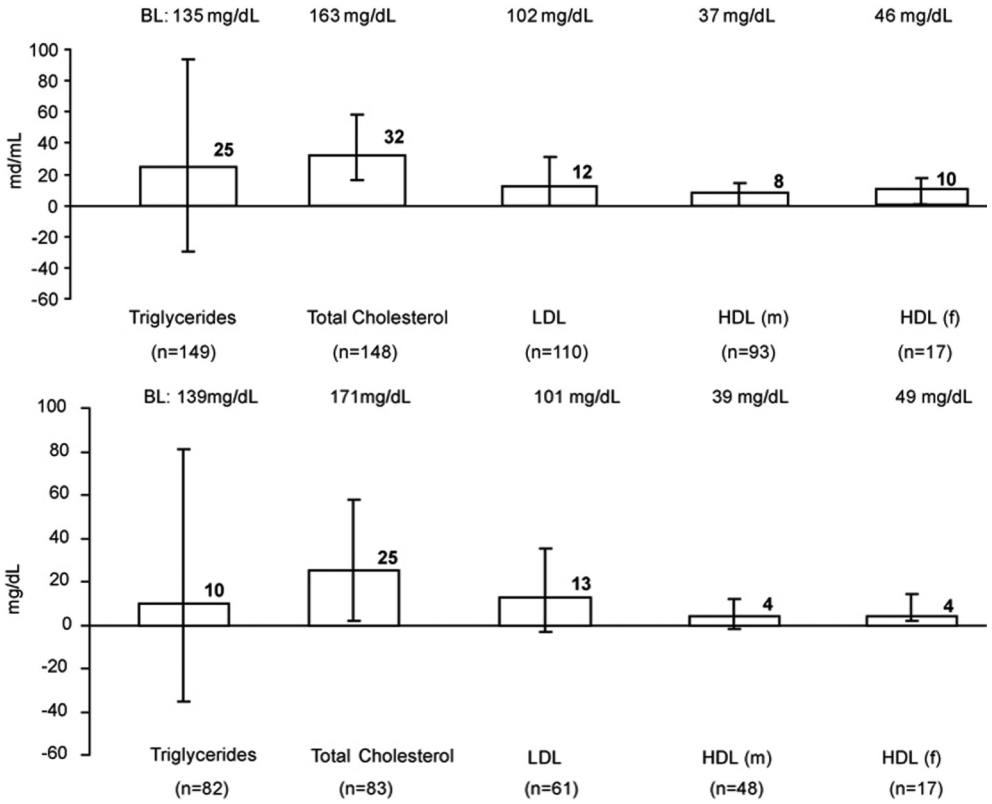

Fig. 3. Median change (IQR) in lipid values from baseline (BL) to week 96 in a) ART-naïve and b) pretreated but PI-naïve patients (LOCF). LDL: low density lipoprotein; HDL: high density lipoprotein.

with normal levels at baseline had a Grade 3/4 increase in triglyceride levels at week 96. Increases in median TC and triglyceride levels tended to occur in the initial weeks of treatment with more stable levels in later weeks (Figs. 4a and 4b).

In the pretreated but PI-naïve group, 75.9% and 54.2% of patients had TC levels < 200 mg/dL at baseline and 96 weeks, respectively, and 67.1% and 59.8% of patients had triglyceride levels <200 mg/dL at baseline and week 96, respectively. When stratified by baseline levels, there was a shift towards an increase in TC levels ($p = 0.001$; McNemar/Bowker test); there was no significant shift in triglyceride levels ($p = 0.105$; McNemar/Bowker test). In all, two of 63 patients with normal levels at baseline had a Grade 3/4 increase in TC at week 96. Increases in median TC and triglyceride levels tended to occur in the initial weeks of treatment with more stable levels in later weeks (Fig. 4a and 4b).

By week 96 the proportion of patients receiving lipid lowering agents increased from 0.6% at baseline to 2.9% in ART-naïve patients and from 1.8% to 9.2% in pretreated but PI-naïve patients.

Discussion

This analysis demonstrates that long-term treatment with SQV/r is effective and well-tolerated both as first line therapy in ART-naïve patients and in pretreated but PI-naïve patients treated in real-life clinical settings.

The efficacy of SQV/r 1000/100 mg bid in treatment-naïve patients using the 500 mg film-coated formulation of SQV up to 48 weeks has been reported previously in the clinical trial setting [8], and confirmed by similar findings in our 48 week analysis of patients treated in routine clinical practice in the RAINBOW cohort [10]. The 96 week data presented here extend and support evidence of efficacy and safety of SQV/r in 'real world' settings. All efficacy parameters in the current study had increased at 96 weeks relative to the previously reported 48 week data [10]. As the current analysis included only a subset of patients from the initial 48 week cohort, we also compared the 96 week data with 48 week data from this subset only to confirm our findings. All efficacy parameters were found to have increased at 96 weeks by LOCF analysis, although the proportion of patients with HIV RNA <50 and <400 copies/mL at week 96 was slightly lower than at week 48, reflecting the fact that data were missing at this timepoint for around a quarter of patients in both groups, compared with only around 8% missing data at week 48 (data no shown). Our findings are consistent with those reported by Ananworanich and colleagues in a long-term study of 272 ART-naïve Thai patients treated with SQV/r plus two NRTIs [7], which showed that one line response in terms of HIV viral load and CD4 count at 48 weeks was maintained at 96 weeks of treatment.

Changes in lipid profile are a characteristic of treatment with PIs to a greater or lesser degree, and are of particular concern given the possible link between treatment-related dyslipidemia and its contribution to atherogenesis and increased risk of coronary artery disease [12]. A significant shift towards increases from baseline in fasting total cholesterol were seen in both groups of patients, but only one patient in the ART-naïve group and two in the pretreated but PI-naïve group showed a Grade 3/4 increase from normal baseline levels. Increases were also seen in LDL cholesterol, HDL cholesterol and triglyceride. Overall, median increases in TC and triglycerides from baseline in the current analysis are somewhat higher than those reported

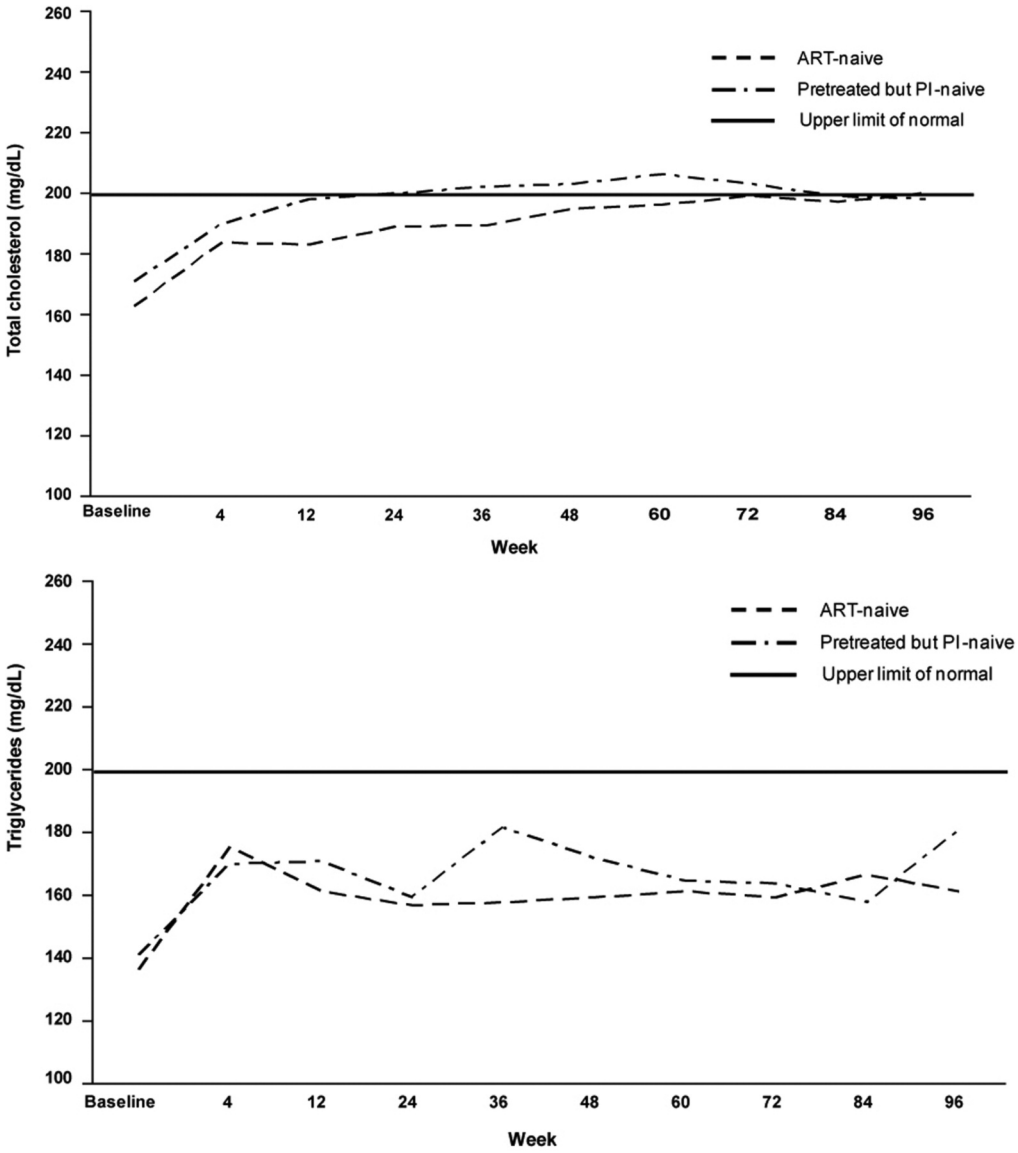

Fig. 4. Median a) total cholesterol and b) triglyceride levels over time on treatment (LOCF).

after 48 weeks of treatment in both our previous analysis and the GEMINI study [8, 10], which might suggest a general increase in lipid levels with time on treatment. However, when changes were examined only in the cohort of patients treated for the full 96 weeks in the current analysis, increases were largely seen in the early stages of treatment and lipid levels remained relatively stable in later weeks. The TC, triglyceride and LDL one line levels at 96 weeks are somewhat higher in the current study than those reported in a long-term study of 272 ART-naïve Thai patients treated with SQV/r plus two NRTIs [7]. This may reflect the difference in race between the study populations which has been shown to affect SQV pharmacokinetics [13, 14], differences in body mass index in Thai compared with Caucasian patients, and differences in the combinations of antiretrovirals used, which makes direct comparison between the studies difficult. Overall, the incidence of Grade 3/4 changes in lipid level following 96 weeks treatment was low in the current analysis of the RAINBOW COHORT, and at least 50% of patients remained within the normal range.

Treatment with SQV/r was well tolerated up to one line 96 weeks, with only seven patients in the total cohort (2.5%) withdrawing from treatment due to side effect issues, confirming the low incidence reported at 48 weeks [8, 10]. The incidence and nature of AEs were similar in both ART-naïve and pretreated but PI-naïve patients, and were similar to those previously reported (most commonly gastrointestinal and diarrhea). With regard to laboratory values, there was no evidence of relevant changes in liver enzymes or bilirubin in either patient group, with the exception of two patients who showed a Grade 3/4 rise from within normal limits at baseline in ALT (one patient from each group) and four patients with normal levels at baseline who had a Grade 3/4 increase in AST (three in the ART-naïve and one in the pretreated but ART-naïve group).

The main strengths of the current analysis of patients from the RAINBOW survey lies in the fact that it consists of an unselected cohort of HIV-infected patients treated under routine, 'real-life' conditions in contrast to the highly selective and controlled randomised trial situation. The data derived from such cohorts may more closely reflect clinical practice than results obtained from the optimized setting of clinical studies. However the study has limitations associated with observational analyses. It is not possible to rule

out selection bias, although all RAINBOW investigators were encouraged to report data from all eligible patients at their site rather than reporting on a random subset only. Another potential bias of observational studies where clinic visits are not mandatory is the potential for missing data, and efficacy data at 96 weeks were missing for a proportion of patients in our cohort. We have therefore presented these data using both ITT (missing = failure) and LOCF analyses to allow an assessment of the overall efficacy, with each method having particular merits and drawbacks in this situation. Finally, a comparison group was not available to act as a study control.

In conclusion, 96 week data from the RAINBOW cohort extends shorter term data which confirm the efficacy and tolerability of SQV/r seen in clinical trials and in the 'real-world' setting in both ART-naïve and pretreated but PI-naïve patients. Data from the current study demonstrate that antiviral response to SQV/r is durable, and that long-term treatment is well tolerated in routine clinical management.

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