Comparison of Metabolic Abnormalities and Clinical Lipodystrophy 48 Weeks After Switching from HAART to Trizivir™ Versus Continued HAART: The Trizal Study

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Purpose: To analyze the evolution of clinical lipodystrophy (LD) and metabolic abnormalities in patients continuing to receive HAART versus patients switched to Trizivir™ (zidovudine, lamivudine, abacavir) after 48 weeks. **Method:** Patients treated with HAART >6 months with plasma HIV-1 RNA viral load (VL) <400 copies/mL and <50 copies/mL at screening were randomly assigned to continue HAART (103 patients) or to receive Trizivir™ (106 patients). Clinical LD was evaluated using a standardized patient questionnaire only at baseline, weeks 4 and 8, and then every 8 weeks until Week 48. Laboratory evaluation was performed every 4 weeks. **Results:** The proportion of patients exhibiting ≥1 LD symptom at baseline was 40% in the Trizivir™ arm and 50% in HAART arm (difference not significant). After 48 weeks, the prevalence was 28% and 42% respectively (p = .03), and the median number of LD symptoms per patient was 2 in the Trizivir™ arm and 4 in the continued HAART arm (p = .016). Median decreases in cholesterol levels over the 48-week study period were greater in the Trizivir™ arm than in the continued HAART arm (–0.80 vs. –0.44 mmol/L; p < .001). Median triglyceride levels decreased in the Trizivir™ arm but increased in the continued HAART arm (–0.17 and +0.01 mmol/L; p = .006). Suppression of VL was maintained in most patients with no differences between the two arms. **Conclusion:** A switch from "standard" HAART to Trizivir™ was associated with an improvement in clinical LD and blood lipid abnormalities after 48 weeks. **Key words:** *lipids, lipodystrophy, Trizivir™*

In developed countries, the availability of highly active antiretroviral therapy (HAART) has led to dramatic decreases in morbidity and mortality due to HIV-1 infection.[1] However, as early as 1997, clinicians noticed morphological changes and metabolic complications in some patients treated with such regimens.[2] These changes, resulting from fat distribution abnormalities, have now been reported in 17%–84% of cases according to cohort studies and represent a major challenge for long-term compliance.[3,4] They also have a considerable negative impact on patient psychology and constitute a visible symptom of HIV-1 seropositivity with all the repercussions on everyday life that implies. Besides these morphological changes, metabolic complications such as hyperlipidemia have also been reported, although consequences in terms of cardiovascular risk are not fully known at present. These complications have been linked to protease inhibitor (PI) use; studies performed on noninfected volunteers receiving PIs found these patients to have increased cholesterol and triglyceride levels within a few weeks of initiation.[5,6] More recently, some authors have suggested that mito-

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chondrial toxicity related to the use of nucleoside analogues could be one of the factors leading to fat redistribution, namely fat atrophy.[7,8] Consequently, alternative PI-sparing regimens have been developed over the past few years to decrease pill burden, increase adherence, and limit long-term metabolic complications. Because many patients have already received standard HAART regimens, these new combinations have also been studied as switch strategies, aimed at limiting the problems encountered with HAART without compromising its efficacy. The Trizal study was a randomized, multicenter, open-label trial in patients with adequate viral suppression that compared the efficacy and tolerance of continued HAART versus a switch to Trizivir™ (containing fixed doses of zidovudine, lamivudine, and abacavir; GlaxoSmithKline, Marly-le-Roi, France). This report provides the results of a substudy conducted during the trial to assess changes in metabolic abnormalities and clinical lipodystrophy (LD) through 48 weeks of follow-up.

METHOD

Population

The study was randomized, open label, and multicenter. Patients were included if they had received a triple drug regimen for at least 6 months and had a documented history of plasma HIV-1 RNA <400 copies/mL, plus plasma RNA <50 copies/mL within 14 days of enrollment. The initial treatment consisted either of a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) + one PI, two NRTIs + one nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), or three NRTIs. Patients who had received two NRTIs as first-line therapy before moving to triple therapy were included if their plasma RNA was <400 copies/mL at that time. A CD4+ T-cell count <100/mm^3 or the presence of > grade 1 hematologic abnormalities were exclusion criteria.

Laboratory Determinations

In each participating center, it was recommended that patients give blood samples in the morning after 12 hours overnight fasting. All laboratory analyses were performed in the same central laboratory.

HIV-1 RNA in plasma was measured using the Roche Amplicor assay (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. Lymphocyte subsets were measured on freshly isolated peripheral blood mononuclear cells (PBMC) using flow cytometry and monoclonal antibodies (Becton Dickinson, Franklin Lakes, New Jersey, USA). Serum glucose, cholesterol, and triglyceride levels were measured by standard clinical laboratory methods as previously described.[9]

Evaluation of LD Clinical Symptoms

LD at baseline, Weeks 4 and 8, then every 8 weeks until Week 48 was reported by patients according to a consensus definition[10] with standardized questionnaires on peripheral atrophy (facial wasting, arm wasting, limb wasting, buttock fat loss, prominent veins), fat accumulation (buffalo hump, breast enlargement, abdominal fat changes), and possible LD-related symptoms (dry skin, dry lips, ingrown toenails, body hair loss, erectile dysfunction, loss of libido). Body weight was recorded at the same time points. Anthropometric measurements, dual-energy X-ray absorptiometry (DEXA), and CT scan were not used in this study.

Statistical Analysis

The primary study objective was virological failure (defined by HIV-1 RNA ≥400 copies/mL on two consecutive occasions, or premature discontinuation of randomized study treatment) and was compared using intent-to-treat analysis (switching or missing = failure). Distribution of HIV-associated fat redistribution symptoms was assessed in both treatment arms by chi-square test. The median number of symptoms per participant was compared using a Wilcoxon rank sum test. Percentages of participants in each arm with at least one emergent symptom or at least one resolved symptom were compared by chi-square test. Percentages of participants in each arm with at least one emergent symptom without simultaneous resolution of other symptoms or with resolution of at least one symptom without simultaneous emergence of other symptoms were compared by chi-square test. Weight, CD4+ T-cell count, serum glucose, cholesterol, and triglycerides in each arm were compared

using a Wilcoxon rank sum test. A p value <.05 was considered as significant in each analysis.

RESULTS

Population

A total of 219 patients were randomized, and 209 were included in the trial (106 in the Trizivir™ arm and 103 in the continued HAART arm). Five patients in each arm did not initiate treatment due to incompatibility with entry criteria. The median age of the 209 patients enrolled was 38 years (range, 20–82). Eighty-eight percent were white Caucasians, 9% were black, and 2% were American Hispanics. Most cases had asymptomatic HIV-1 infection with a median CD4+ T-cell count of 494 cells/mm^3. The median time on HAART before study entry was 26 months. The baseline characteristics of the population are shown in **Table 1**. No differences were found between the two arms at baseline in terms of demographics or laboratory parameters.

Forty-five percent of patients were receiving stavudine (d4T) at baseline versus 38% in the Trizivir™ and continued HAART arms, respectively.

Treatment Efficacy

Forty-six (22%) participants met the treatment failure criteria over the 48-week study period: 23 in the Trizivir™ arm and 23 in the continued HAART arm. This corresponded to virological failure in 6 cases (Trizivir™, 5; continued HAART, 1) and switch in 40 cases (Trizivir™, 18; continued HAART, 22). Using intent-to-treat analysis, we found that 75% of patients in the Trizivir™ arm versus 69% in the continued HAART arm had plasma HIV-1 RNA <50 copies/mL at Week 48 (difference not significant).[11]

Median increases from baseline in CD4+ T cell counts were 26 cells/mm^3 in both arms. Between screening and Week 48, two patients (one in the Trizivir™ arm and one in the continued HAART arm) progressed from CDC group A to group B.

LD Clinical Symptoms

At baseline, 40% of patients in the Trizivir™ arm versus 50% in the continued HAART arm complained of at least one LD symptom (difference not significant). These symptoms comprised either fat accumulation symptoms only, fat atrophy symptoms only, or a combination of both (**Table 2**). The

Table 1. Baseline characteristics of the included population

Characteristic	Trizivir™ (n = 106)	Continued HAART (n = 103)
Male, %	80	83
Median age, years	39.5	37
Median weight, kg	68	71
CDC group C, %	20	15
Median CD4, cells/mm^3	482	504
Median months on HAART (range)	27 (8–29)	24 (6–44)
HAART at entry, %		
2 NRTIs + 1 PI	62	63
2 NRTIs + 1 NNRTI	19	19
3 NRTIs	17	17
1 NRTI + 1 NNRTI + 1 PI	2	0
Median triglycerides, mmol/L	1.6	1.6
Median cholesterol, mmol/L	5.9	5.6

Note: NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

Table 2. Evaluation of clinical lipodystrophy at baseline in the two study arms

	Trizivir™ (*n* = 106)	Continued HAART (*n* = 103)
Patients with lipodystrophy symptoms, *n* (%)	42 (40)	51 (50)
Classification of symptoms, *n* (%)		
Fat accumulation	6 (6)	7 (7)
Fat atrophy	12 (11)	16 (16)
Fat accumulation and atrophy	9 (8)	16 (16)
Lipodystrophy-related symptoms only	15 (14)	12 (12)
Median number of symptoms/patient	2	3

median number of LD symptoms per patient was similar at baseline in both groups (2 in the Trizivir™ arm and 3 in the continued HAART arm; $p = .139$).

At 48 weeks, the proportion of patients with at least one LD symptom was 28% in the Trizivir™ arm versus 42% in the continued arm. The difference between the two arms at Week 48 was statistically significant ($p = .03$). The evolution from baseline to Week 48 in the Trizivir™ arm was not statistically significant ($p = .07$). At Week 48, the median number of LD symptoms per participant with at least one symptom was two in the Trizivir™ arm versus four in the continued HAART arm ($p = .016$).

Subsequent evaluations were performed to exclude possible LD-related symptoms. The proportion of participants exhibiting at least one emergent LD symptom at Week 48 versus baseline was lower in the Trizivir™ arm (13%) than in the continued HAART arm (23%), although the difference did not reach statistical significance ($p = .076$). The proportion of participants having at least one LD symptom resolved at Week 48 versus baseline was higher in the Trizivir™ arm (67%) than in the continued HAART arm (42%), although this difference was barely significant ($p = .059$). At 48 weeks in the Trizivir™ arm, the emergence of at least one new LD symptom without other symptom resolution was observed in 12% of participants; this incidence reached 20% in the continued HAART arm ($p = .13$). At 48 weeks in the Trizivir™ arm, the resolution of at least one LD symptom without other symptom emergence was observed in 63% of participants compared to 34% of participants in the continued HAART arm ($p = .029$).

No significant difference was observed in median body weight changes in either treatment group (data not shown).

Evolution of Blood Glucose and Lipid Levels

At Week 48, median changes in blood glucose levels from baseline were +2.00 mg/dL in the Trizivir™ arm and +0.50 mg/dL in the continued HAART arm ($p = .492$). Median total blood cholesterol levels over the 48-week study period decreased in both groups, although this decrease was significantly greater in the Trizivir™ arm than in the continued HAART arm (respectively, –0.80 and –0.44 mmol/L; $p < .001$; **Figure 1**). Median blood triglyceride levels over the 48-week study period decreased in the Trizivir™ arm and increased slightly in the continued HAART arm (respectively, –0.17 and +0.01 mmol/L; $p = .006$; **Figure 2**).

Because participants were not systematically fasting during visits, the evolution of both triglyceride and glucose levels was also analyzed on fasting samples only (52 cases in the Trizivir™ arm and 51 in the continued HAART arm). Conclusions were similar regarding all sample analyses, although a more pronounced difference was observed in median triglyceride changes between the two arms (–0.10 vs. +0.18 mmol/L, respectively; $p = .010$).

When lipid evolution in terms of changes in toxicity grades between baseline and maximum post-baseline grade through 48 weeks was investigated,

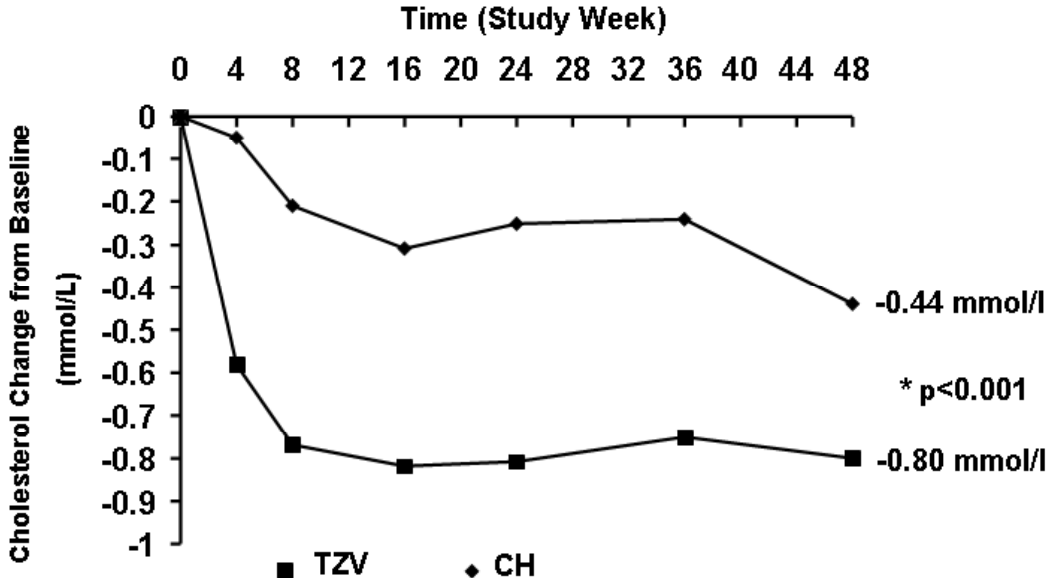

Figure 1. Evolution of blood cholesterol levels (median) from baseline to Week 48 in the two arms. TZV = Trizivir™ arm; CH = continued HAART arm.

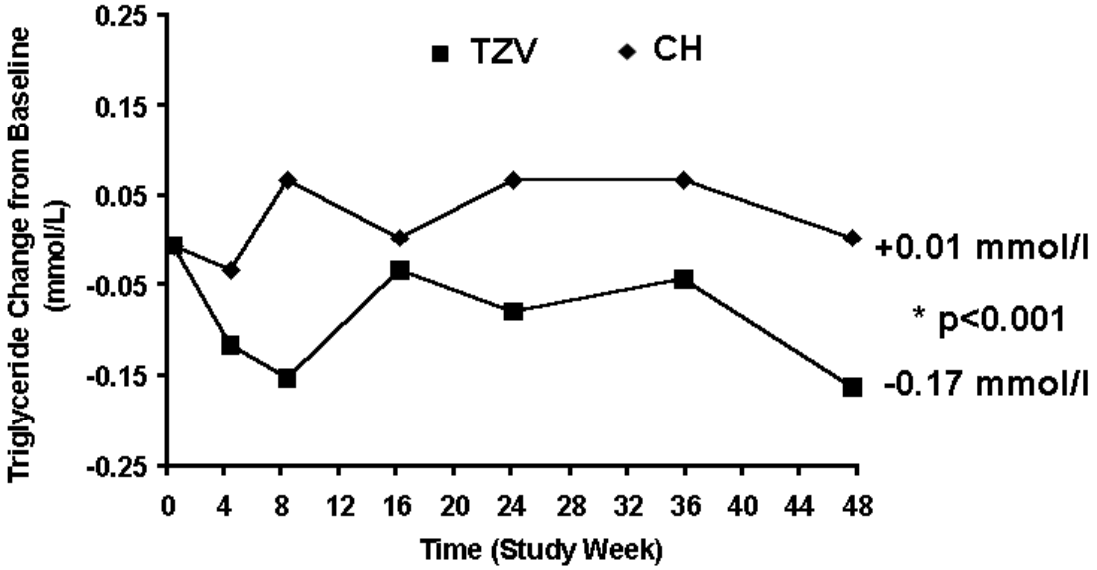

Figure 2. Evolution of blood triglyceride levels (median) from baseline to Week 48 in the two arms. TZV = Trizivir™ arm; CH = continued HAART arm.

9% of patients on Trizivir™ showed a cholesterol toxicity grade increase versus 29% on continued HAART ($p < .001$), and 40% of patients in the Trizivir™ arm showed a cholesterol toxicity grade decrease versus 10% on continued HAART ($p < .001$).

Regarding triglycerides, 25% of patients on Trizivir™ showed a toxicity grade increase versus 44% on continued HAART ($p < .01$), and 22% on Trizivir™ showed a toxicity grade decrease versus 4% on continued HAART ($p = .05$).

DISCUSSION

LD and metabolic abnormalities are increasing obstacles for the effective and safe management of HIV-1 infection.[12,13] Although the precise pathophysiological mechanisms of these complications remain to be clarified, antiretrovirals are thought to play a key role, with varying impact according to the drugs used.[14,15] Consequently, a PI-free combination that contains less toxic NRTIs for mitochondria is theoretically likely to limit or improve these anomalies.[16] We took advantage of a randomized trial that tested the virological safety of Trizivir™ switching in patients on standard HAART regimens to perform this substudy aimed at assessing the consequences of Trizivir™ switching on clinical LD and metabolic abnormalities. The impact of Trizivir™ —and in particular lamivudine and abacavir — on mitochondrial metabolism has been shown to be less than that of other NRTIs.[17] In addition, this regimen spares PI consequences on adipogenesis. For the purposes of our substudy, clinical LD was evaluated using standardized questionnaires that are easy to implement but do not provide quantitative measurements. This tool might be subject to criticism as it gives only a single-sided view of the problem, that of the patient. Moreover, different studies that address this issue have used all available tools or individual ones from the subjective clinician's perspective to the more objective CT/DEXA scans. A validated definition of HIV LD is still lacking and is needed. The use of CT and DEXA scans in several studies has proved difficult to standardize and also has led to reproducibility problems. The Australian FRAM study results should be able to clarify the utility of the different tools.[18,19] Moreover, the open-label design of our study may have impacted positively on the patients' perception of their morphologic abnormalities, more so for those patients switching therapy. Forty-eight weeks after switching to Trizivir™, we observed an important (although not statistically significant) reduction in the proportion of patients with clinical LD, dropping from 40% at baseline to 28% at Week 48, along with more frequent symptom resolution without new symptom emergence and less symptoms per patient than with continued HAART. Significant decreases in blood cholesterol and triglyceride levels were observed in the Trizivir™ arm versus the continued HAART arm. Although the clinical implications of these metabolic changes were not addressed during the trial, differences in the incidence of cardiovascular events in both groups require an extended assessment.

Various trials have studied the evolution of LD and metabolic changes after switching a PI-based therapy to a nevirapine-, efavirenz-, or abacavir-containing regimen with conflicting results. Some studies found only an improvement in metabolic abnormalities after this switch[20]; this improvement is also observed when HAART is interrupted.[21] Others observed minimal clinical changes in body fat distribution,[22] some of which were probably related to stavudine replacement.[23–25]

In conclusion, despite the current absence of specific treatments for HIV-associated LD syndromes and the metabolic complications observed with HAART, our study shows that these complications could be at least partially limited or reversed by changing the antiretroviral regimen. This change is virologically safe if patients are appropriately selected. Further studies, plus an extended follow-up using a standardized definition of HIV LD, are now required to confirm these findings.

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