Research Letters

AIDS 2013, **27**:1353–1359

Adipokines and vascular health in treated HIV infection: an obesity paradox?

Chris T. Longenecker[a,b], Whitney Dunn[b], Ying Jiang[b], Sara M. Debanne[b] and Grace A. McComsey[a,b]

We examined the relationship between plasma adipokine concentrations and ultrasound measures of vascular health in 100 HIV-infected adults on antiretroviral therapy. Leptin was positively correlated with flow-mediated dilation of the brachial artery and negatively with carotid intima–media thickness. These relationships were independent of traditional risk factors and trunk fat in women but not men. Neither adiponectin nor resistin was associated with either measure of vascular health.

Changes in body fat composition in HIV-infected patients on antiretroviral therapy (ART) are associated with adverse cardiometabolic risk factors [1] and altered levels of circulating adipocytokines [2,3]. Adipokines are known to exert direct effects on endothelial cells and vascular function *in vitro* [4–7], although larger epidemiologic studies have failed to demonstrate a consistent relationship between plasma adipokine concentrations and cardiovascular disease (CVD) in humans [8,9]. Little is known about the relationship between adipokines and CVD risk in HIV. In this study, we sought to examine the relationship between adipokines and measures of vascular health among HIV-infected patients on stable ART.

Plasma concentrations of leptin, adiponectin, and resistin were measured by ELISA in 100 HIV-infected adults, on stable ART, with HIV-1 RNA less than 1000 copies/ml and low-density lipoprotein (LDL)-cholesterol 130 mg/dl or less. The study was approved by the Institutional Review Board of University Hospitals Case Medical Center (Cleveland, Ohio, USA) and written informed consent was obtained from each subject. Scatter plots, *t*-tests, Spearman correlations, and multivariable linear regression were used to examine the association of adipokines with regional fat distribution (trunk and limb fat), pericardial and periaortic fat volumes, common carotid artery intima–media thickness (CIMT), and endothelial function measured by brachial artery flow-mediated dilation (FMD). Fat distribution was measured by dual-energy X-ray absorptiometry (DEXA) in the anteroposterior view using Lunar Prodigy Advance (GE Healthcare, Waukesha, Wisconsin, USA). Pericardial and thoracic periaortic fat volumes were quantified as described previously [10] from a computed tomography scan of the chest (Somatom Sensation 64; Siemens Medical Solutions, USA). Semiautomated edge detection software (Medical Imaging Applications LLC, Coralville, Iowa, USA) was used to measure mean–mean common carotid artery far wall CIMT [11]. Flow-dependent endothelial function testing was performed by brachial artery ultrasound using a 5-min forearm occlusion method as previously described [12]. All vascular ultrasound and perivascular fat measurements were performed by a single blinded reader (C.T.L.). Non-normally distributed variables (including the adipokine concentrations, FMD, CIMT, and perivascular fat volumes) were log-transformed for all analyses. All statistical tests were two-sided with a 0.05 significance level.

Overall, the study population was 77% men and 70% African–American. Median [interquartile range (IQR)] age and BMI were 47 (42–53) years and 27 (24–31) kg/m^2, respectively; although BMI was higher in women compared with men [32 (26–37) kg/m^2 versus 26 (23–29) kg/m^2, $P < 0.001$]. Compared with men, women had 2.2-fold higher limb fat and 1.6-fold higher trunk fat ($P < 0.001$) by DEXA. Overall, median (IQR) CD4 cell count of 633 (453–854) cells/μl and 81% had HIV-1 RNA less than 50 copies/ml. Fifty percent were on a protease inhibitor; however, only 4% were currently taking a thymidine analog nucleoside reverse transcriptase inhibitor. One quarter of participants had metabolic syndrome [13]. Thirty percent of women were treated with antihypertensive medication, 4% were taking aspirin, and 83% had HIV-1 RNA less than 50 copies/ml. Of the women with detectable viremia ($n = 4$), all had less than 200 copies/ml.

Leptin concentration was much higher in women compared with men [median (IQR) 55 (21–73) versus 7.0 (2.9–13)ng/ml, $P < 0.001$], whereas adiponectin and resistin concentrations were similar ($P = 0.844$ and $P = 0.345$, respectively). Leptin concentration was strongly and linearly correlated with both trunk fat ($r = 0.836$, $P < 0.0001$) and limb fat ($r = 0.862$, $P < 0.0001$), although correlations with epicardial and periaortic fat were weaker ($r = 0.399$, $P < 0.0001$ and $r = 0.267$, $P = 0.007$, respectively). Adiponectin was negatively correlated with trunk fat ($r = -0.336$, $P = 0.0006$), epicardial fat ($r = -0.300$, $P = 0.047$), and periaortic fat ($r = -0.200$, $P = 0.0008$); but not limb fat ($P = 0.108$). No correlation was observed between resistin concentration and regional or perivascular fat volumes ($P > 0.20$).

Leptin concentration was positively correlated with FMD ($r = 0.336$, $P = 0.0006$) and negatively with CIMT

($r = -0.304$, $P = 0.002$). These relationships were stronger in women compared with men (Fig. 1a). In multivariable models that adjusted for age, smoking, trunk fat, and baseline brachial artery diameter (for FMD only), leptin remained positively associated with FMD and negatively associated with CIMT in women ($P = 0.018$ and $P = 0.022$, respectively) but not men ($P = 0.565$ and $P = 0.748$, respectively). Neither

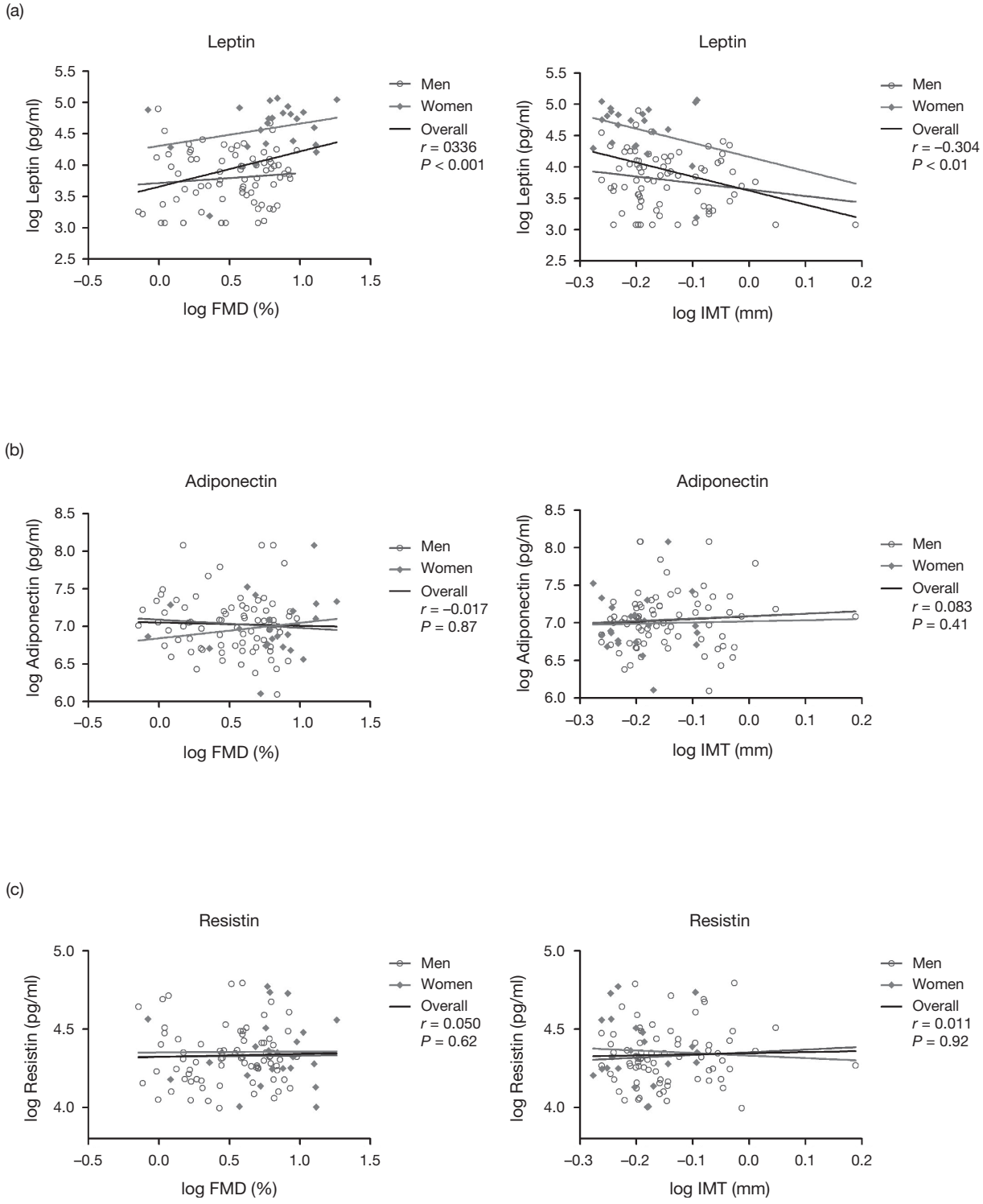

Fig. 1. Relationship between three adipokines and markers of vascular structure and function. (a) Leptin was positively correlated with flow-mediated dilation (FMD) of the brachial artery and negatively with common carotid artery intima–media thickness (IMT). (b) Adiponectin was not correlated with FMD or IMT. (c) Resistin was not correlated with FMD or IMT.

adiponectin nor resistin was associated with FMD or CIMT (Fig. 1b and c).

In this contemporary cohort of HIV-infected men and women on ART without clinical lipoatrophy and with limited use of thymidine analogs, higher plasma leptin concentration appears to be associated with healthier arterial structure and function measured by carotid ultrasound and brachial artery FMD. In women, these relationships were independent of several traditional CVD risk factors and visceral adiposity. These results suggest the possibility of an obesity paradox in this population of HIV-infected women with regards to CVD risk.

Although obesity is generally associated with poor vascular health and CVD risk in the general population [14,15], examples of CVD obesity paradoxes do exist [16,17]. Some prior studies of HIV-infected patients have reported similarly paradoxical results. In the Women's Interagency Health Study, higher BMI was associated with lower prevalence of CIMT more than 1.5 mm despite a positive association with overall mean CIMT [18]. The Study of Fat Redistribution and Metabolic Change in HIV infection did not report associations of IMT with measures of adiposity [19]; however, in separate analyses, higher subcutaneous adipose tissue (SAT) was associated with higher leptin, paradoxically higher adiponectin [2], and lower Framingham risk [20]. In a study of endothelial function that included a small number of women ($n = 27$), both SAT and leptin concentration were positively correlated with FMD, although the relationship was attenuated in multivariable models [21]. Finally, we have previously described a positive correlation between BMI and FMD independent of other risk factors in a majority male population [22].

This study is limited by a relatively small sample size and cross-sectional design, although these limitations are shared by most studies of endothelial function in HIV. Therefore, our study was not powered to explore all possible confounders. Our participants had little clinical lipoatrophy and favorable LDL cholesterol levels, which reflects current trends in the HIV-infected population; however, this makes comparisons with older studies more difficult.

In conclusion, previous studies in HIV have linked SAT to higher leptin and lower cardiovascular risk [2,20]. In this ultrasound study of vascular health, these relationships appear to persist in an obese HIV-infected population with a low prevalence of clinical lipoatrophy, particularly among women. This unexpected observation merits further investigation in longitudinal studies.

Acknowledgements

This project was supported by an award from the National Institutes of Health NR012642. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health. The study is registered with clinicaltrials.gov, number NCT01218802.

Conflicts of interest

C.T.L. has received a virology fellow research grant from Bristol-Myers Squibb. S.M.D. currently serves on a DSMB of a Johnson and Johnson study. G.A.M. has served as a scientific advisor or speaker for Bristol-Myers Squibb, GlaxoSmithKline, Tibotec, and Merck, has received research grants from Bristol-Myers Squibb, GlaxoSmithKline, and Gilead Sciences, and is currently serving as the DSMB Chair for aPfizer-sponsored study. W.D. and Y.J. have no disclosures.

[a]University Hospitals Case Medical Center, and [b]Case Western Reserve University, Cleveland, Ohio, USA.

Correspondence to Grace A. McComsey, MD, Professor of Pediatrics and Medicine, Case Western Reserve University, 11100 Euclid Ave, Cleveland,OH 44106, USA.
Tel: +1 216 844 3607; fax: +1 216 844 3926;
e-mail: grace.mccomsey@case.edu

Received: 18 December 2012; revised: 13 February 2013; accepted: 20 February 2013.

References

1. Gandhi RT, Sax PE, Grinspoon SK. **Metabolic and cardiovascular complications in HIV-infected patients: new challenges for a new age.** *J Infect Dis* 2012; **205 (Suppl 3)**:S353–S354.
2. Kosmiski LA, Bacchetti P, Kotler DP, Heymsfield SB, Lewis CE, Shlipak MG, *et al*. **Relationship of fat distribution with adipokines in human immunodeficiency virus infection.** *J Clin Endocrinol Metab* 2008; **93**:216–224.
3. Veloso S, Escote X, Ceperuelo-Mallafre V, Lopez-Dupla M, Peraire J, Vilades C, *et al*. **Leptin and adiponectin, but not IL18, are related with insulin resistance in treated HIV-1-infected patients with lipodystrophy.** *Cytokine* 2012; **58**: 253–260.
4. Knudson JD, Dincer UD, Zhang C, Swafford AN, Koshida R, Picchi A, *et al*. **Leptin receptors are expressed in coronary arteries, and hyperleptinemia causes significant coronary endothelial dysfunction.** *Am J Physiol Heart Circ Physiol* 2005; **289**:H48–H56.
5. Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, Wu D, *et al*. **Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells.** *Diabetes* 2007; **56**:1387–1394.
6. Ouchi N, Kihara S, Arita Y, Kazuhisa M, Kuriyama H, Okamoto Y, *et al*. **Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin.** *Circulation* 1999; **100**:2473–2476.
7. Li Y, Wang Y, Li Q, Chen Y, Sun SZ, Zhang WD, *et al*. **Effect of resistin on vascular endothelium secretion dysfunction in rats.** *Endothelium* 2007; **14**:207–214.
8. Ronti T, Lupattelli G, Mannarino E. **The endocrine function of adipose tissue: an update.** *Clin Endocrinol (Oxf)* 2006; **64**:355–365.
9. Koh KK, Park SM, Quon MJ. **Leptin and cardiovascular disease: response to therapeutic interventions.** *Circulation* 2008; **117**: 3238–3249.

10. Yun CH, Lin TY, Wu YJ, Liu CC, Kuo JY, Yeh HI, *et al*. **Pericardial and thoracic peri-aortic adipose tissues contribute to systemic inflammation and calcified coronary atherosclerosis independent of body fat composition, anthropometric measures and traditional cardiovascular risks.** *Eur J Radiol* 2012; **81**:749–756.
11. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et al*. **Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine.** *J Am Soc Echocardiogr* 2008; **21**:93–111; quiz 89–90.
12. Longenecker CT, Hileman CO, Carman TL, Ross AC, Seydafkan S, Brown TT, *et al*. **Vitamin D supplementation and endothelial function in vitamin D deficient HIV-infected patients: a randomized placebo-controlled trial.** *Antivir Ther* 2012; **17**:613–621.
13. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. **Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition.** *Circulation* 2004; **109**:433–438.
14. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, *et al*. **Body weight and mortality among women.** *N Engl J Med* 1995; **333**:677–685.
15. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. **Body-mass index and mortality in a prospective cohort of U.S. adults.** *N Engl J Med* 1999; **341**:1097–1105.
16. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, *et al*. **Obesity paradox in patients with hypertension and coronary artery disease.** *Am J Med* 2007; **120**:863–870.
17. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, *et al*. **The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox?.** *J Am Coll Cardiol* 2002; **39**:578–584.
18. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, Lazar J, *et al*. **Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men.** *AIDS* 2008; **22**:1615–1624.
19. Grunfeld C, Delaney JA, Wanke C, Currier JS, Scherzer R, Biggs ML, *et al*. **Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study.** *AIDS* 2009; **23**:1841–1849.
20. Lake JE, Wohl D, Scherzer R, Grunfeld C, Tien PC, Sidney S, *et al*. **Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study.** *AIDS Care* 2011; **23**:929–938.
21. Dube MP, Shen C, Mather KJ, Waltz J, Greenwald M, Gupta SK. **Relationship of body composition, metabolic status, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects.** *AIDS Res Hum Retroviruses* 2010; **26**:847–854.
22. Hileman CO, Longenecker CT, Carman TL, Milne G, Labbato DE, Storer NJ, *et al*. **Elevated D-dimer is independently associated with endothelial dysfunction: a cross-sectional study in HIV-infected adults on antiretroviral therapy.** *Antivir Ther* 2012; **17**:1345–1349.

DOI:10.1097/QAD.0b013e3283606c11

Efficacy and tolerance of telaprevir in HIV-hepatitis C virus genotype 1-coinfected patients failing previous antihepatitis C virus therapy: 24-week results

Karine Lacombe[a,b,c], Nadia Valin[b], Hind Stitou[d], Joël Gozlan[e], Vincent Thibault[f], Anders Boyd[c], Jean-Marie Poirier[g], Jean-Luc Meynard[b], Marc-Antoine Valantin[d,h], Julie Bottero[a,b,c] and Pierre-Marie Girard[a,b,c]

The efficacy and tolerance of telaprevir (TVR) was examined in 20 mostly cirrhotic HIV-hepatitis C genotype 1 (HCV-G1)-infected patients failing previous treatment with pegylated-interferon and ribavirin (PR). HCV-RNA less than 12 IU/ml was observed in 35.3% of patients at W2, 55.0% at W4, 65.0% at W12 and 55.0% at W24. All patients with virological failure ($n = 9$) exhibited V36M/R155K mutations. Early virological response was a determinant of HCV-RNA less than 12 IU/ml at W24 ($P < 0.001$). No grade 3–4 dermatological side-effects were reported. TVR-PR tritherapy appeared to be rather effective and well tolerated among difficult-to-treat HIV-HCV-G1 patients.

Direct antiviral agents (DAAs) targeting hepatitis C virus (HCV) protease activity have triggered a major shift in treating HCV genotype 1 (G1) infection. In HCV-HIV coinfected patients, boceprevir (BOC) or telaprevir (TVR) with pegylated-interferon (pegylated-interferon and ribavirin) has led to a 30% increase in sustained virological response rates in treatment-naive patients [1,2]. However, these results may not apply to more difficult-to-treat populations, such as cirrhotic, HIV-infected patients failing previous treatment with pegylated-interferon and ribavirin [3]. The primary objective of the study herein was to evaluate the efficacy and tolerance during 24 weeks of TVR-based tritherapy in HIV-HCV G1-coinfected patients previously treated with pegylated-interferon and ribavirin.

From December 2011 to May 2012, HIV-HCV G1-infected patients receiving TVR [1125 mg three times daily (t.i.d.) with efavirenz (EFV); 750 mg t.i.d. with raltegravir (RAL), atazanavir (ATZ), or without antiretroviral (ARV) therapy], PegIFNα2 (180 μg/week), and ribavirin (1000 mg/day < 75 kg, 1200 mg/day ≥75 kg) were recruited from two outpatient clinics in Paris, France (Hôpital Saint-Antoine, Hôpital Pitié-Salpêtrière). All patients had provided signed informed consent, in accordance with the Helsinki Declaration. At inclusion, response to previous pegylated-interferon and ribavirin treatment was defined according to European AIDS Clinical Society guidelines [4]. HCV-RNA was measured using the Abbott RealTime HCV assay (detection limit: <12 IU/ml) and Il28B polymorphism using the LightMix Il28B kit. In patients failing TVR-based therapy [5], amino acid substitutions in HCV protease were examined by direct sequencing following PCR-amplification of the NS3 encoding region, between nucleotides 3309 and 4054 [6]. A sequence editing program was used (Seqscape; Applied Biosciences, Les Ulis, France) and substitutions associated with TVR resistance further confirmed with the 'Geno2pheno (hcv)' tool (http://www.geno2pheno.org). In ARV-treated patients, EFV/ATZ/RAL trough concentrations were measured after a 12-h fast by high-performance liquid chromatography at TVR initiation (C_{min0}), and then twice after TVR initiation (week 4 = C_{min1}, week

Table 1. Baseline and follow-up characteristics of the study population, stratified by hepatitis C virus response at week 24.

	Total $n=20$	HCV-VL at W24 <12 IU/ml $n=11$	>12 IU/ml $n=9$	P^1
Demographic characteristics				
Age (years)[a]	52 (49–54)	50 (48–52)	53 (50–57)	0.1
Sex ratio male/female (% male)	18/2 (90)	10/1 (91)	8/1 (89)	0.9
BMI (kg/m^2)[a]	20.9 (20.1–23.4)	20.6 (19.5–23.8)	21.1 (20.6–21.7)	0.4
HIV characteristics				
Estimated HIV-infected duration (years)[a]	22.8 (17.8–25.4)	22.0 (15.4–25.5)	24.7 (20.6–25.4)	0.4
Nadir CD4$^+$ cell count per μl[a]	146 (86–236)	156 (88–273)	139 (80–181)	0.6
CD4$^+$ cell count per μl[a]	449 (279–568)	444 (282–573)	454 (254–562)	0.9
HIV-RNA VL copies/ml[a]	20 (20–20)	20 (20–20)	20 (20–34)	0.6
HIV-RNA VL <50 copies/ml*	15 (75)	9 (82)	6 (67)	0.6
ARV regimens*				0.5
None	2 (10)	1 (9)	1 (11)	
ABC+3TC+ATZ	1 (5)	1 (9)	0	
FTC+TDF+ATZ	8 (40)	4 (36)	4 (44)	
FTC+TDF+EFV	2 (10)	0	2 (22)	
FTC+TDF+RAL	5 (25)	4 (36)	1 (11)	
FTC+TDF+RAL+ETR	1 (5)	1 (9)	0	
RAL+MVC	1 (5)	0	1 (11)	
HCV parameters				
Estimated HCV infection duration (years)[a]	15.4 (11.2–18.3)	15.6 (9.8–18.4)	14.5 (12.6–16.4)	0.7
HCV-RNA VL $\log_{10}$ IU/ml[a]	6.11 (5.44–6.47)	5.78 (4.86–6.22)	6.25 (6.14–6.60)	0.07
HCV-RNA VL >800 000 IU/ml*	12 (60)	5 (45)	7 (78)	0.2
Viral hepatitis characteristics				
HCV genotypes* [$N=19$]				0.5
1a	17 (89)	8 (80)	9 (100)	
1b	2 (11)	2 (20)	0	
Il28B polymorphism*				0.8
CC	6 (30)	4 (36)	2 (22)	
CT/TT	14 (70)	7 (64)	7 (78)	
HBsAg-positive serology*	1 (5)	1 (9)	0	0.9
Previous HCV treatment response				0.6
Relapse	3 (15)	1 (10)	2 (22)	
Partial response	7 (35)	5 (45)	2 (22)	
Non response	10 (50)	5 (45)	5 (56)	
METAVIR fibrosis level*				0.06
F0–F2	4 (20)	4 (36)	0	
F3	1 (5)	1 (9)	0	
F4	15 (75)	6 (55)	9 (100)	
Characteristics during follow-up				
Lead-in phase (4-week PR)				
Yes	2 (10)	0 (0)	2 (22)	0.7
HCV response[b]				
RVR*	11 (55)	8 (73)	3 (33)	0.2
EVR	13 (65)	11 (100)	2 (22)	<0.001
eRVR*	10 (50)	8 (73)	2 (22)	0.07
Biochemical response				
ALT (IU/ml)[a]	40 (28–59)	35 (26–51)	49 (30–106)	0.4
AST (IU/ml)[a]	40 (33–50)	37 (25–47)	47 (39–122)	0.06
HIV characteristics at last visit				
HIV-RNA undetectability*	17 (85)	9 (82)	8 (89)	0.9
CD4$^+$ cell count per μl[a]	276 (209–365)	242 (202–299)	289 (228–375)	0.5
Adverse events[c]				
Anemia*	1 (5)	1 (9)	0	0.9
Thrombopenia*	4 (20)	2 (18)	2 (22)	0.9
Leukopenia*	4 (20)	3 (27)	1 (11)	0.6
Neutropenia*	1 (5)	0	1 (11)	0.5
Rash*	0	0	0	–

3TC, lamivudine; ABC, abacavir; ALT, alanine transaminase; ARV, antiretroviral; AST, aspartate transaminase; ATZ, atazanavir; EFV, efavirenz; eRVR, extended rapid virological response; ETR, etravirine; EVR, early virological response; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MVC, maraviroc; RAL, raltegravir; RVR, rapid virological response; TDF, tenofovir; VL, viral load.

[a]Median (25–75th%tile).

[b]Defined per European AIDS Clinical Society guidelines [4].

[c]All laboratory adverse events were grade 3–4: anemia (hemoglobin <8 g/dl), thrombopenia (platelet count <50000/μl), leukopenia (<2000/μl), and neutropenia (<750/μl).

[1]Comparing patients with versus without response at week 24 (W24); significance determined using a Kruskal–Wallis test for continuous variables and Pearson χ^2test or Fisher's exact test for categorical variables.

*n (%).

$12 = C_{min2}$). Variation in concentrations before and after TVR initiation was defined as $[(C_{min1}+C_{min2})/2]/C_{min0}$. Adverse events were graded according to AIDS Clinical Trial Group classification [7]. Platelet, leukocyte or erythropoietin growth factors, and blood transfusions were permitted.

The virological endpoints were the proportions of patients with undetectable HCV-RNA at W2, W4, W12, and W24. Analysis on treatment response was intention-to-treat (ITT). Determinants of HCV-RNA less than 12 UI/ml at W24 were compared between treatment response groups, while no *P* value adjustments for multiple comparisons were made. Statistical analysis was performed using STATA (v11.2; College Station, Texas, USA) and significance was determined as $P < 0.05$.

Baseline characteristics are presented in Table 1, stratified by W24 response. A previous null response was observed in 50% of patients and 75% were cirrhotic. The proportion of patients with undetectable HCV-RNA was 35.3% at W2, 55.0% at W4, 65.0% at W12, and 55.0% at W24; and 50% had extended rapid virological response (undetectable HCV-RNA at W4 and W12) [4]. Following stopping rules, nine patients ended treatment early: W4 = 3, W12 = 3, W24 = 3. One patient terminated treatment at W8 due to psychiatric adverse events despite rapid virological success. Undetectable HCV-RNA at W12 was the only significant determinant among those with versus without treatment response ($P < 0.001$). All nine patients with virological failure harbored genotype 1a, with TVR-resistant variants appearing at the time of failure. Six double amino acid substitutions at positions V36M+R155K were the only mutations observed prior to W24. HCV population sequencing for those harboring resistant variants at the end of TVR treatment showed different mutation patterns with a potentially lower genetic barrier to TVR resistance (V36L+Q80K+R155K, R155K, or V36M+T54A).

HIV-RNA was detectable (>20 copies/ml) for three ARV-treated patients at baseline (range: 31–42 copies/ml), 0 at W12, and one at W24 (50 copies/ml). Median (interquartile range, IQR) $CD4^+$ cell counts dropped in both ARV-treated [W0: 410/μl (275–550), W24: 259/μl (202–375)] and ARV-naive patients (dropping to 289–293/μl at W24). Variation of trough concentrations ranged as follows: EFV = −46.6–17.5, ATZ = −7.2–65.3, and RAL = −93.7–688.0, observing a substantial decrease in one RAL-treated patient suspected of nonadherence (detectable HIV-RNA and $C_{min} = 31$ ng/ml at W24).

The following grade 3–4 adverse events occurred during treatment: thrombopenia (20%), leukopenia (20%), anemia (5%), and neutropenia (5%). Accordingly, a substantial drop in platelet count and hemoglobin was observed, requiring the use of growth factors in 11 patients (erythropoietine: $n = 11$, eltrombopag: $n = 5$) and iterative blood transfusions in two patients. No grade 3–4 dermatological side-effects were reported.

In this well defined cohort, 55% responded to TVR-containing tritherapy after 24 weeks. This rate is lower than that found in previous reports in HIV-HCV-coinfected patients, with rates reaching upward of 71% in treatment-naive and less frequently cirrhotic patients [8]. In HCV-G1-monoinfected patients with higher prevalence of bridging fibrosis or cirrhosis, both early and W24 response rates in previous partial or nonresponders were closer to what was observed in our study [9,10]. Smaller studies have reported no difference in early treatment response according to HIV status [11]. Recent drugs, such as sofosbuvir, have also shown similar early-treatment HCV kinetics between treatment-naive HIV-HCV and HCV-infected patients [12]. Patients experiencing virological failure exhibited the V36M+R155K double mutant, common in genotype 1a-infected individuals experiencing 'on-treatment' failure [13,14]. As expected, no 1b subtype-infected patient selected this mutation. Although baseline resistance was not assessed, it is rather uncommon and cannot rule out TVR therapeutic success [15,13]. Hematologic tolerance also appeared to be reasonable, as both rates of grade 3–4 hematological adverse events and/or use of growth factors seemed to be lower than those in cirrhotic HCV G1-monoinfected patients [1,10,16]. Importantly, no grade 3 or 4 rash was reported in our study, compared to 7.4% among HCV-monoinfected patients [16] and a 5% discontinuation rate due to rashes [10]. Better TVR tolerance among HIV-HCV-coinfected patients may be due to the lack of immune-mediated skin reactions via HIV-induced immunosuppression [17,18]. Taken together, HIV coinfection is probably not a detrimental factor toward virological response to DAAs.

In conclusion, combined TVR-PR exhibited comparatively good efficacy and tolerability, to monoinfected patients, in a difficult-to-treat population of HIV-infected patients with chronic G1 hepatitis C. Notwithstanding the small number of patients, this population is generally excluded from clinical trials, bringing into light barriers to current anti-HCV therapy. As HIV-infected, cirrhotic patients failing previous HCV therapy have a high risk of developing end-stage liver disease and may not be able to wait for newer drugs to become available, TVR may represent an appropriate therapeutic strategy.

Acknowledgements

Conflicts of interest

There are no conflict of interest.

[a]*Université Pierre et Marie Curie,* [b]*Service de Maladies Infectieuses et Tropicales, Hôpitaux Universitaires de*

l'Est Parisien, Hôpital Saint-Antoine, [c]Inserm UMR-S707, [d]Service de Maladies Infectieuses et Tropicales, Groupe Hospitalier Pitié-Salpétrière, [e]Service de Bactériologie-Virologie, Hôpitaux Universitaires de l'Est Parisien, Hôpital Saint-Antoine, [f]Service de Bactériologie-Virologie, Groupe Hospitalier Pitié-Salpétrière, [g]Service de Pharmacologie, Hôpitaux Universitaires de l'Est Parisien, Hôpital Saint-Antoine, and [h]Inserm UMR-S943, Paris, France.

Correspondence to Dr Karine Lacombe, MD, PhD, Service de Maladies Infectieuses et Tropicales, Hôpital Saint-Antoine, 184 rue du Fbg Saint-Antoine, 75012 Paris, France.
Tel: +33 1 49283137; fax: +33 1 49282149;
e-mail: karine.lacombe@sat.aphp.fr

Received: 23 January 2013; revised: 13 March 2013; accepted: 13 March 2013.

References

1. Sulkowski M, Sherman K, Soriano V, Rockstroh J, Dieterich D, Girard P, *et al.* **Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV co-infected patients: SVR24 final study results.** *The 63rd Annual Meeting of the Association for the Study of Liver Diseases*; 9–13 November 2012, Boston, MA, USA.
2. Sulkowski M, Pol S, Cooper C, Fainboim H, Slim J, Rivero A, *et al.* **Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-co-infected patients: end of treatment (week-48) interim results.** *Conference on Retroviruses and Opportunistic Infections*, Abst. #47; 5–8 March 2012; Seattle, USA.
3. Lacombe K, Rockstroh J. **HIV and viral hepatitis coinfections: advances and challenges.** *Gut* 2012; **61 (Suppl 1)**:i47–i58.
4. EACS. European AIDS Clinical Society, Guidelines – Version 6; October 2011.
5. Thomas DL, Bartlett JG, Peters MG, Sherman KE, Sulkowski MS, Pham PA. **Provisional guidance on the use of hepatitis C virus protease inhibitors for treatment of hepatitis C in HIV-infected persons.** *Clin Infect Dis* 2012; **54**:979–983.
6. Colson P, Brouk N, Lembo F, Castellani P, Tamalet C, Gerolami R. **Natural presence of substitution R155K within hepatitis C virus NS3 protease from a treatment-naive chronically infected patient.** *Hepatology* 2008; **47**:766–767.
7. ACTG. http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf. (last accessed: 03/26/2013)
8. Sherman K, Rockstroh J, Dieterich D, Soriano V, Girard P, McCallister S, *et al.* **Telaprevir combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfected patients: 24-week treatment interim analysis** [abstract LB-8]. 62nd *Annual Meeting of the American Association for the Study of Liver Disease (AASLD)*. San Francisco, USA; 4–8 November 2011.
9. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, *et al.* **Telaprevir for retreatment of HCV infection.** *N Engl J Med* 2011; **364**:2417–2428.
10. Colombo M, Fernández I, Abdurakhmanov D, Ferreira P, Strasser S, Urbanek P, *et al.* **Treatment of hepatitis C genotype 1 patients with severe fibrosis or compensated cirrhosis: the International Telaprevir Early Access Program. Abstract #LB15.** *The 63rd Annual Meeting of the Association for the Study of Liver Diseases*; 9–13 November, Boston, MA, USA; 2012.
11. Moreno A, Bárcena R, Quereda C, Pérez-Elías M, García-Hoz M, Casado J, *et al.* **Does HIV infection reduce initial safety and efficacy of boceprevir (BOC) or telaprevir (TPV)-based initial therapy in cirrhotic patients in the 'real life'? Abstract S07.** *The 63rd Annual Meeting of the Association for the Study of Liver Diseases*; 9–13 November, Boston, MA, USA; 2012.
12. Rodriguez-Torres M, Gonzalez M, Rossi S. **HIV/HCV coinfected and HCV monoinfected patients have similar early HCV viral kinetics with the potent HCV nucleotide polymerase inhibitor sofosbuvir (SOF). Abstract H1921a.** *52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2012)*; 9–12 September, San Francisco, USA; 2012.
13. De Meyer S, Dierynck I, Ghys A, Beumont M, Daems B, Van Baelen B, *et al.* **Characterization of telaprevir treatment outcomes and resistance in patients with prior treatment failure: results from the REALIZE trial.** *Hepatology* 2012; **56**:2106–2115.
14. Kieffer TL, De Meyer S, Bartels DJ, Sullivan JC, Zhang EZ, Tigges A, *et al.* **Hepatitis C viral evolution in genotype 1 treatment-naive and treatment-experienced patients receiving telaprevir-based therapy in clinical trials.** *PLoS One* 2012; **7**:e34372.
15. Bartels DJ, Zhou Y, Zhang EZ, Marcial M, Byrn RA, Pfeiffer T, *et al.* **Natural prevalence of hepatitis C virus variants with decreased sensitivity to NS3.4A protease inhibitors in treatment-naive subjects.** *J Infect Dis* 2008; **198**:800–807.
16. Hezode C, Dorival C, Zoulim F, Larrey D, Pol S, Cacoub P, *et al.* **Safety and efficacy of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in 455 cirrhotic non responders. Week 16 analysis of the French Early Access Program (ANRS CO20-CUPIC) in real-life setting.** *The 63rd Annual Meeting of the Association for the study of Liver Diseases*; 9–13 November, Boston, MA, USA; 2012.
17. Picard O, Cacoub P. **Dermatological adverse effects during genotype-1 hepatitis C treatment with the protease inhibitors telaprevir and boceprevir. Patient management.** *Clin Res Hepatol Gastroenterol* 2012; **36**:437–440.
18. Cacoub P, Bourliere M, Lubbe J, Dupin N, Buggisch P, Dusheiko G, *et al.* **Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals.** *J Hepatol* 2012; **56**:455–463.

DOI:10.1097/QAD.0b013e32836138d0