2. Burchell AN, Gardner SL, Mazzulli T, Manno M, Raboud J, Allen VG, *et al*. **Hepatitis C virus seroconversion among HIV-positive men who have sex with men with no history of injection drug use: results from a clinical HIV cohort.** *Can J Infect Dis Med Microbiol* 2015; **26**:17–22.
3. Centers for Disease Control and Prevention. **Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men – New York City, 2005–2010.** *MMWR Morb Mortal Wkly Rep* 2011; **60**:945–950.
4. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, *et al*. **Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours.** *AIDS* 2007; **21**:983–991.
5. Ingiliz P, Steininger K, Schuetze M, Dupke S, Carganico A, Krznaric I, *et al*. **Acute hepatitis C virus (HCV) infection in the setting of HIV coinfection: a single-centre 10-year follow-up.** *J Int AIDS Soc* 2014; **17 (4 Suppl 3)**:19638.
6. Martin TC, Martin NK, Hickman M, Vickerman P, Page EE, Everett R, *et al*. **Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM.** *AIDS* 2013; **27**:2551–2557.
7. Matthews GV, Pham ST, Hellard M, Grebely J, Zhang L, Oon A, *et al*. **Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C.** *Clin Infect Dis* 2011; **52**:803–811.
8. Nishijima T, Shimbo T, Komatsu H, Hamada Y, Gatanaga H, Oka S. **Incidence and risk factors for incident Hepatitis C infection among men who have sex with men with HIV-1 infection in a large Urban HIV clinic in Tokyo.** *J Acquir Immune Defic Syndr* 2014; **65**:213–217.
9. European ATNAHCICP. **Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference.** *AIDS* 2011; **25**:399–409.
10. Dorward J, Garrett N, Scott D, Buckland M, Orkin C, Baily G. **Successful treatment of acute hepatitis C virus in HIV positive patients using the European AIDS Treatment Network guidelines for treatment duration.** *J Clin Virol* 2011; **52**: 367–369.
11. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, *et al*. **Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.** *N Engl J Med* 2004; **351**:438–450.
12. Matthews GV, Hellard M, Haber P, Yeung B, Marks P, Baker D, *et al*. **Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in Acute Hepatitis C.** *Clin Infect Dis* 2009; **48**:650–658.
13. Vogel M, Page E, Matthews GV, Guiguet M, Dominguez S, Dore GJ, *et al*. The use of week 4 HCV-RNA after acute HCV infection (AHC) to predict chronic HCV infection. 17th Conference on Retroviruses and Opportunistic Infections; 2010 February 16–19.
14. Karageorgopoulos DE, Allen J, Bhagani S. **Hepatitis C in human immunodeficiency virus co-infected individuals: is this still a 'special population'?** *World J Hepatol* 2015; **7**: 1936–1952.
15. European Association for Study of L. **EASL Clinical Practice Guidelines: management of hepatitis C virus infection.** *J Hepatol* 2014; **60**:392–420.
16. Basu P, Shah NJ, John N, Aloysius M, Brown R. *Sofosbuvir and ledipasvir versus sofosbuvir and simeprevir combination therapy in the management of acute hepatitis C: a randomized open label prospective clinical pilot study. SLAM C study. Interim data*. San Francisco, California: The liver meeting 2015: American Association for the Study of Liver Diseases; 2015.
17. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, *et al*. **Sofosbuvir plus ribavirin without interferon for treatment of acute hepatitis C virus infection in HIV-1 infected individuals (SWIFT-C).** *The liver meeting 2015: American Association for the Study of Liver Diseases*. San Fransisco, California, 2015.
18. Martinello M, Gane EJ, Hellard M, Sasadeusz J, Shaw D, Petoumenos K, *et al*. **Sofosbuvir and ribavirin for six weeks is not effective among people with acute and recently acquired HCV infection: the DARE-C II study.** *The liver meeting 2015: American Association for the Study of Liver Diseases*. San Francisco, California, 2015.

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A pilot trial of pentoxifylline on endothelial function and inflammation in HIV-infected patients initiating antiretroviral therapy

Systemic and vascular inflammation are thought to be the key mechanisms underlying the increased risk of cardiovascular disease (CVD) in those with HIV infection [1,2]. Antiretroviral therapy (ART) reduces, but does not necessarily normalize, systemic inflammation [3]. As such, adjunctive strategies to further reduce inflammation may be helpful in mitigating the risk of CVD in HIV.

In a single-arm, open-label, 8-week, pilot study, we reported that pentoxifylline (PTX) reduced circulating levels of IFN-γ-induced protein 10 and soluble vascular cell adhesion molecule-1 and improved endothelial function [measured as flow-mediated dilation (FMD) of the brachial artery] in HIV-infected patients not receiving ART [4]. However, in a randomized, placebo-controlled trial of PTX in a similarly untreated population, we did not confirm that PTX reduced inflammation or improved endothelial function [5]. In fact, PTX unexpectedly led to significantly increased circulating soluble tumor necrosis factor-1 (sTNFR1) levels compared with placebo in this trial. However, the potential effects of PTX on FMD and inflammation in a population initiating ART are unknown. Thus, we conducted a randomized, placebo-controlled, single-center pilot trial of PTX 400 mg thrice daily given for 48 weeks in patients concurrently initiating ART (ClinicalTrials.gov NCT00864916).

The eligibility criteria, procedures, and methods in the current study were similar to our previous trial in patients not receiving ART [5]. Participants were instructed to start ART, as chosen by the primary HIV provider, and the study drug together at study entry. Study visits occurred at weeks 0, 8, 24, and 48. No restrictions were made on the ART components or initial $CD4^+$ cell count. The primary endpoint was change in brachial artery FMD, measured using B-mode ultrasound after 5 min of forearm cuff occlusion to a supra-systolic pressure, as previously described [5]. All scans were performed by a certified sonographer and read at the University of Wisconsin, the brachial artery reactivity testing reading center for the NHLBI HIV-CVD collaborative, by a single reader [5]. This trial was approved by the Indiana University Institutional Review Board; all participants provided their written, informed consent. The use of PTX for the purpose of reducing

inflammation and improving endothelial function is unlabeled and considered investigational.

Linear mixed effects models were constructed to evaluate changes in FMD and the circulating biomarkers both between groups and over time. Additional models were constructed to evaluate the effects of individual biomarkers (listed in Table 1), baseline brachial artery diameter, $CD4^+$ cell count, and HIV-1 RNA levels on changes in FMD. We also constructed linear mixed effects models assessing treatment group by week interactions and including HIV-1 RNA levels at each study visit as a covariate. Two-sided *P* values less than 0.05 were considered statistically significant.

We enrolled 19 participants (10 in the PTX group and 9 in the placebo group). At weeks 8, 24, and 48, the numbers of participants remaining in the PTX and placebo arms were, respectively, 9 and 7, 8 and 6, and 4 and 5. The baseline characteristics of the enrolled participants are shown in Table 1. The two study groups were balanced. The majority of the study participants were black men with over half being current smokers. Table 1 shows the baseline brachial artery diameter, FMD, and nitroglycerin-mediated dilation (NTGMD) values at each time point. The changes in FMD (SD) in the PTX vs. the placebo groups at weeks 8, 24, and 48 were, respectively, −3.60% (2.54%) vs. 1.91% (2.46%), 0.72% (3.71%) vs. 1.07% (1.77%), and 0.01% (3.22%) vs. 2.23% (1.42%). In all models constructed comparing these changes in FMD, even after adjustment for changes in HIV-1 RNA levels, we did not find significant differences between the PTX and placebo groups at any time point. There were also no significant changes between groups or over time in all models for NTGMD.

In our models assessing the changes in the circulating biomarkers, we found smaller declines from baseline in

Table 1. Baseline (week 0) characteristics of the study groups and vascular measures during the trial.

Baseline characteristics		Total (*n* = 19)	PTX (*n* = 10)	Placebo (*n* = 9)	*P* value
Age (years)		36 (10.6)	38 (12.1)	34 (8.8)	0.44
Male sex, *n* (%)		16 (84%)	9 (90%)	7 (78%)	0.58
Black race, *n* (%)		12 (63%)	5 (50%)	7 (78%)	0.35
Current smoker, *n* (%)		11 (58%)	7 (70%)	4 (44%)	0.37
BMI (kg/m^2)		26.9 (6.3)	25.4 (4.1)	28.5 (8.1)	0.39
$CD4^+$ cell count (cells/μl)		230 (191)	208 (225)	252 (161)	0.56
$CD3^+CD8^+CD38^+HLA\text{-}DR^+$ cells (%)		49.4 (14.8)	52.9 (9.7)	45.0 (19.2)	0.19
HIV-1 RNA log_{10}copies/mL		4.97 (0.79)	5.10 (0.91)	4.82 (0.65)	0.45
MCP-1 (pg/ml)		346.07 (164.31)	271.02 (101.84)	429.46 (184.97)	0.06
hsCRP (mg/ml)		4.07 (9.79)	1.67 (2.26)	6.74 (13.95)	0.13
ADMA (μmol/l)		0.71 (0.19)	0.78 (0.22)	0.64 (0.12)	0.24
IL-6 (pg/ml)		3.74 (2.9)	2.86 (1.31)	4.71 (3.86)	0.26
sVCAM-1 (ng/ml)		1148.8 (379.0)	1227.7 (373.7)	1061.2 (387.1)	0.35
sTNFR1 (pg/ml)		1074.8 (317.8)	1071.2 (394.8)	1078.9 (227.6)	0.96
sTNFR2 (pg/ml)		10199.3 (4001.0)	10882.2 (3956.6)	9440.5 (4144.5)	0.45
IP-10 (pg/ml)		609.6 (244.6)	602.6 (246.9)	617.5 (256.8)	0.93
Total cholesterol (mg/dl)		135.5 (24.2)	130.7 (23.4)	140.8 (25.5)	0.36
HDL-C (mg/dl)		35.8 (10.2)	36.4 (12.2)	35.2 (8.2)	0.93
LDL-C (mg/dl)		77.3 (21.6)	70.9 (21.1)	84.5 (21.0)	0.18
Triglycerides (mg/dl)		111.3 (66.9)	116.7 (78.6)	105.3 (55.2)	0.95
HOMA-IR		1.74 (1.06)	1.75 (0.89)	1.73 (1.32)	0.97
Urine protein/creatinine (g/g)		16.96 (16.93)	9.34 (5.48)	25.43 (21.39)	0.09
Urine albumin/creatinine (mg/g)		5.0 (10.0)	2.0 (2.0)	9.0 (14.0)	0.16
Estimated GFR ($ml/min/1.73^2$)		89.6 (21.7)	89.2 (23.0)	90.1 (21.6)	0.93
Vascular parameters during the trial					
Brachial artery diameter (cm)	Week 0	0.44 (0.06)	0.43 (0.06)	0.44 (0.06)	0.56
	Week 8	0.45 (0.06)	0.45 (0.08)	0.46 (0.04)	0.57
	Week 24	0.47 (0.05)	0.46 (0.07)	0.48 (0.02)	0.43
	Week 48	0.50 (0.06)	0.50 (0.10)	0.50 (0.01)	0.90
FMD (%)	Week 0	4.27 (3.49)	4.43 (2.58)	4.07 (4.57)	0.41
	Week 8	4.24 (2.54)	4.60 (2.71)	3.77 (2.45)	0.66
	Week 24	3.91 (3.65)	4.44 (4.65)	3.16 (1.71)	0.85
	Week 48	2.81 (2.15)	2.25 (2.92)	3.36 (1.44)	0.42
NTGMD (%)	Week 0	18.21 (7.69)	18.40 (9.01)	17.95 (5.97)	0.90
	Week 8	16.64 (6.69)	16.03 (7.64)	17.5 (5.84)	0.71
	Week 24	15.11 (5.30)	16.25 (5.18)	13.52 (5.62)	0.41
	Week 48	14.21 (4.64)	11.54 (3.69)	16.88 (4.34)	0.18

Data presented as means (SD) or as *n* (%). Student's *t* tests and associated *P* values were used for comparison between the pentoxifylline and placebo groups. GFR estimated using the 2012 CKD-EPI creatinine-cystatin C combined equation. At weeks 8, 24, and 48, the numbers of participants remaining in the pentoxifylline and placebo arms were, respectively, 9 and 7, 8 and 6, and 4 and 5. ADMA, asymmetric dimethyl arginine; FMD, flow-mediated dilation; HDL-C, HDL cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high sensitivity C-reactive protein; IP-10, IFN-γ-inducible protein-10; MCP-1, monocyte chemoattractant protein-1; NTGMD, nitroglycerin-mediated dilation; sTNFR1, soluble tumor necrosis factor receptor 1; sVCAM-1, soluble vascular cell adhesion molecule-1; LDL-C, LDL cholesterol; PTX, pentoxifylline.

the PTX group vs. the placebo group in levels of monocyte chemoattractant protein-1 (MCP-1, pg/ml) [week 8: −68.18 (83.61) vs. −242.64 (180.66), $P=0.01$; week 24: −30.04 (129.17) vs. −225.71 (181.28), $P=0.027$; and week 48: −61.90 (113.69) vs. −202.02 (185.62), $P=0.077$] and IL-6 (pg/ml) [week 8: −1.27 (1.57) vs. −2.73 (3.91), $P=0.30$; week 24: −0.29 (2.23) vs. −2.28 (3.46), $P=0.033$; and week 48: −0.12 (0.41) vs. −3.13 (3.26) ($P=0.045$)] but trends toward greater declines in levels of asymmetric dimethylarginine (ADMA, μmol/l) in the PTX group compared with the placebo group [week 8: −0.27 (0.17) vs. −0.16 (0.12), $P=0.12$; week 24: −0.31 (0.19) vs. −0.15 (0.07), $P=0.03$; and week 48: −0.35 (0.25) vs. −0.18 (0.15), $P=0.06$]. There were no significant changes between groups in the other biomarkers assessed at any time point.

There was one serious adverse event in the PTX group (suicidal ideation with overdose of a nonstudy drug which did not result in death) but none in the placebo group. There was a nonsignificantly higher number of gastrointestinal adverse events (nausea, flatus, and diarrhea) with PTX (6 of 10 participants) compared with placebo (two of nine participants), none of which were treatment-limiting.

In this pilot, randomized, placebo-controlled trial, we did not find that PTX improved endothelial function in HIV-infected patients over the first year of ART. These results are in line with our previous trial in patients not receiving ART. However, in the current trial, we found that PTX may attenuate reductions in MCP-1 and IL-6 and possibly greater reductions in ADMA compared with placebo. We did not find any significant effects of PTX on sTNFR1 as we had in our previous trial of PTX in patients not receiving ART. To our knowledge, these potential effects of PTX on the proatherogenic molecules MCP-1, IL-6, and ADMA have not previously been described. Although we cannot fully explain the latter results, these data add to our previous trial in those not receiving ART showing that PTX may have mixed and potentially adverse effects on inflammatory and endothelial activation pathways. Our results are limited by the small sample size, so they must be considered exploratory as we cannot exclude the possibility a larger, longer study or one that involved patients chronically treated with ART may have found an effect of PTX on vascular function. We acknowledge that the numbers of statistical tests performed may have led to false positive findings, especially in regard to the biomarker comparisons.

Because PTX is considered safe and very well tolerated [5–7], it has been considered as an ideal anti-inflammatory agent for chronic inflammatory conditions. For this reason, it is currently being studied in trials in HIV-uninfected patients for nonalcoholic steatohepatitis, irritable bowel syndrome, chronic kidney disease, and congestive heart failure (ClinicalTrials.gov). However, the lack of improvement in endothelial function and the potentially worrisome effects on several proatherogenic inflammatory molecules in our trials should be considered before using PTX in future trials in HIV-infected patients.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, *et al*. **Inflammation, coagulation and cardiovascular disease in HIV-infected Individuals.** *PLoS One* 2012; **7**:e44454.
2. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, *et al*. **Arterial inflammation in patients with HIV.** *JAMA* 2012; **308**:379–386.
3. Wolf K, Tsakiris DA, Weber R, Erb P, Battegay M. **Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1.** *J Infect Dis* 2002; **185**:456–462.
4. Gupta SK, Johnson RM, Mather KJ, Clauss M, Rehman J, Saha C, *et al*. **Anti-inflammatory treatment with pentoxifylline improves HIV-related endothelial dysfunction: a pilot study.** *AIDS* 2010; **24**:1377–1380.
5. Gupta SK, Mi D, Dube MP, Saha CK, Johnson RM, Stein JH, *et al*. **Pentoxifylline, inflammation, and endothelial function in HIV-infected persons: a randomized, placebo-controlled trial.** *PLoS One* 2013; **8**:e60852.
6. Dezube BJ, Pardee AB, Chapman B, Beckett LA, Korvick JA, Novick WJ, *et al*. **Pentoxifylline decreases tumor necrosis factor expression and serum triglycerides in people with AIDS. NIAID AIDS Clinical Trials Group.** *J Acquir Immune Defic Syndr* 1993; **6**:787–794.
7. Sliwa K, Woodiwiss A, Kone VN, Candy G, Badenhorst D, Norton G, *et al*. **Therapy of ischemic cardiomyopathy with the immunomodulating agent pentoxifylline: results of a randomized study.** *Circulation* 2004; **109**:750–755.

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A case of hereditary coproporphyria precipitated by efavirenz

There are rare but increasing reports of exacerbations of acute porphyrias precipitated by antiretrovirals [1–3]. We describe the first report of an acute attack in a patient with hereditary coproporphyria precipitated by efavirenz-based combination antiretroviral therapy (cART) with full recovery following replacement with raltegravir.

A 25-year-old Colombian male student was diagnosed HIV-1 antibody positive on routine screening, having tested antibody negative 1 year previously. Baseline $CD4^+$ cell count was 415 cells/ml (28%) and HIV-1 viral load was 16 668 copies/ml. He was hepatitis C IgG negative and hepatitis B surface antigen negative, with no comorbidities, concomitant medication, or recreational drug use. No family history was available because the patient was adopted. He was commenced on antiretroviral therapy with tenofovir, lamivudine, and efavirenz in line with current British HIV Association guidelines [4].

He presented 2 weeks later with vomiting, constipation, and colicky umbilical and right iliac fossa pain. Clinical examination revealed mild generalised abdominal tenderness. Plasma sodium was 133 mmol/l and potassium 4.4 mmol/l. Alanine transaminase was 71 iU/l, bilirubin 11 μmol/l, alkaline phosphatase 63 iU/l, and amylase 166 iU/l. Full blood count was normal as were thyroid function, lactate, bicarbonate, 9am cortisol, glucose, creatinine, and creatine kinase. An autoimmune screen, including antinuclear antibody, anti-neutrophil cytoplasmic antibody, immunoglobulins, and complement was negative. Chest and abdominal radiographs, an abdominal ultrasound, and abdominal computed tomography were normal. He received treatment for a presumptive viral gastroenteritis with intravenous normal saline, antiemetics (cyclizine and ondansetron), and analgesia (paracetamol, ibuprofen, and morphine sulfate).

Over the subsequent 3 days, his pain worsened, and plasma sodium decreased to 118 mmol/l. Urine and plasma osmolalities were consistent with the syndrome of inappropriate antidiuretic hormone secretion, at 572 and 247 mmol/kg, respectively. He subsequently developed dark red urine, with dipstick testing showing ketones only. He additionally described transient auditory and visual hallucinations.

Urine porphobilinogen was increased, consistent with an acute attack of porphyria. Urine porphyrins were raised at 156 nmol/mmol creatinine (normal range 0–30). Stool porphyrins were increased, with a coproporphyrin isomer III : I of 13.2 (normal range <1.4). Plasma porphyrins showed a fluorescence emission peak at 620 nm. Efavirenz was switched to raltegravir, with continuation of tenofovir and lamivudine, and the patient received four infusions of haem arginate on consecutive days. His symptoms and biochemical abnormalities resolved over the following week. At 5 weeks post-initiation of cART, $CD4^+$ cell count was 503 cells/ml (27%) and viral load was less than 40 copies/ml. Subsequent genetic testing confirmed heterozygosity for c.717T>A in the *coproporphyrinogen oxidase* gene, predicted amino acid p.Cys239Ter. This is a new mutation and is a nonsense change, which would be expected to cause premature termination of translation and hence reduce enzyme activity. The identification of this pathogenic CPOX mutation confirmed hereditary coproporphyria.