

Correspondence

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Seven years of chronic hepatitis C virus infection in an HIV-infected man without detectable antibodies

After infection with hepatitis C virus (HCV), in 50% of cases anti-HCV antibodies will be detectable within 5–10 weeks [1–3]. The development of antibodies may be somewhat prolonged in HIV-coinfected individuals: median time from HCV infection to seroconversion has been estimated to be 10–13 weeks among HIV-infected men who have sex with men (MSM) [4,5]. Anecdotal evidence suggests that seroconversion in HIV-infected individuals may be severely delayed: Thomson *et al.* [4] reported an interval of 3.3 years between the first positive HCV-RNA test and the first positive antibody test in one patient, although testing frequency was not reported. Waning of HCV-specific antibodies (i.e. seroreversion) has been reported among HIV-positive and HIV-negative patients, after spontaneous or treatment-induced clearance of acute [5,6] or chronic [7,8] infection. In an HIV-infected patient with progressive immunosuppression, seroreversion was reported despite continuous HCV replication. However, HCV antibodies became detectable again after antiretroviral therapy (ART) was initiated [9]. Here, we report a case without documented seroconversion and/or hepatitis (reflected by elevated transaminases) despite being infected with HCV for almost 7 years.

A 61-year-old bisexual man, known to use noninjecting drugs (amphetamines and cocaine), was diagnosed with HIV in 1997. Possibly related to his drug use, he infrequently visited our outpatient clinic, and was poorly adherent to ART prescribed. In 2010, he presented with onycholysis and blistering of the skin suspect for porphyria cutanea tarda (PCT) but, because of

incompliance, no definite diagnosis could be made. After his third clinical admission because of a candida esophagitis in July 2013, he decided to improve his lifestyle, and started taking ART, which resulted in an undetectable HIV viral load. Between 2008 and the last recorded visit in 2014, his CD4 cell count varied between 30–190 cells per mL. Urine analysis showed that he indeed had PCT, which is highly associated with HCV infection [10]. Concurrently, his alanine transaminase (ALT) level was slightly elevated for the first time in years (i.e. 66 U/l), and the patient was tested positive for HCV RNA and negative for HCV antibodies, which is suggestive of an acute infection. Presence of antibodies was tested with the DiaSorin LIAISON XL HCV Ab assay. He denied injecting drug use and did not have sexual intercourse for the past 4 years. Sequence analysis showed infection with HCV genotype 1a. Stored samples were tested and demonstrated that HCV RNA was already detectable from January 2008 onwards. The last HCV RNA negative sample dated from August 2007. All samples were antibody-negative. The slight ALT elevation (from 18 U/l in August 2007 to 41 U/l in January 2008) fits the time frame of infection (Fig. 1).

The fact that during 7 years of chronic HCV infection there was never any sign of HCV antibodies (or hepatitis) is remarkable. Several reports already showed that acute HCV infections can easily be missed by using antibody testing only, due to the seroconversion window period [1–5]. Seronegative HCV infection has been reported earlier among immunocompromised patients [11,12], but

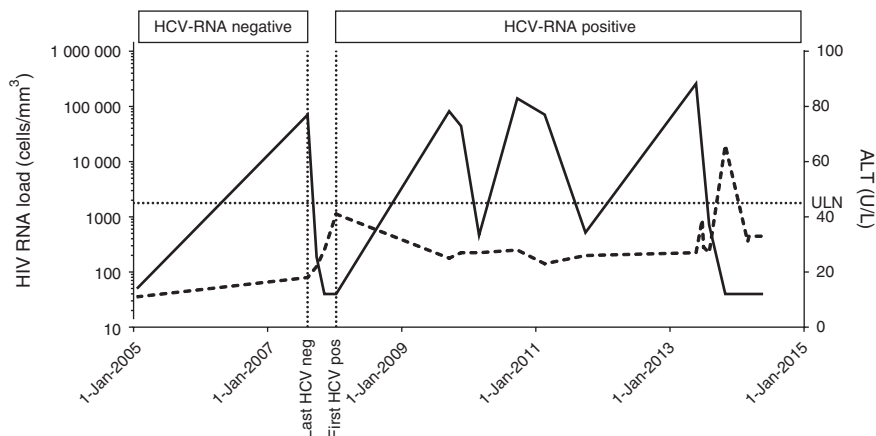


Fig. 1. Graph showing hepatitis C virus (HCV)-RNA status, HIV viral load (solid line), and alanine transaminase (ALT) concentration (dashed line) of a 61-year-old, HIV-infected man with a 7-year documented seronegative chronic HCV infection (from 2005 till present). Poor adherence to antiretroviral therapy until July 2013 is indicated by the fluctuating HIV viral load. The dotted horizontal line shows the upper limit of normal (ULN) ALT concentration (45 U/l).

at least part of these patients probably had an acute infection and antibodies would have been detectable later on. In addition, patients in these studies were tested with second-generation anti-HCV assays, thereby increasing chances of false-negativity [13]. The case we describe shows that chronic HCV infection may also be missed when only third-generation serologic assays are used. Among HIV-infected MSM, testing for acute HCV is thus ideally performed using HCV RNA testing when there is suspicion of infection, especially since subtle ALT elevations are easily missed when monitored infrequently.

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There are no conflicts of interest.

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Acute pancreatitis associated with dolutegravir and lamivudine/abacavir administration

A 16-year-old African-American male was admitted to hospital with recurrent pneumonia. He had been treated for pneumonia 1 month before. His cough, however, persisted and was associated with fever and back pain. Chest radiographs showed bilateral lower lobe infiltrates with a small left pleural effusion. Social history was pertinent for unprotected sexual intercourse with males and females. He denied alcohol use. An HIV-1 RNA level documented 800 900 copies/ml with a CD4⁺ T-cell count of 15 cells/μl. His respiratory status improved, and he was discharged on co-trimoxazole treatment with plans to initiate combination antiretroviral therapy (cART) as an outpatient.

Four days after discharge, he was readmitted with fever and rigors. Evidence of acute kidney injury was noted (creatinine of 2.3 mg/dl), with hyponatremia (130 mmol/l) and transaminitis (alanine aminotransferase 167 U/l, aspartate aminotransferase 233 U/l). He was diagnosed with an adverse reaction to co-trimoxazole, which was discontinued, and he was started on atovaquone prophylaxis. Following negative HLA-B*5701 testing, and a genotype consistent with wild-type virus, he was initiated on dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC). The hospital course was complicated by herpes simplex virus esophagitis and nonspecific gastritis. Despite treatment with parenteral acyclovir,

abdominal pain acutely worsened, and 11 days after initiating cART, he was diagnosed with acute pancreatitis with an amylase of 384 U/l and lipase of 2189 U/l. Repeat CD4⁺ T-cell count documented 11 cells/ μ l, with a HIV-1 RNA level of 7900 copies/ml. Abdominal computed tomography demonstrated mild fullness of the pancreatic head without focal mass. Following development of pancreatitis, DTG/ABC/3TC were discontinued. Clinical pancreatitis resolved over 3 days, with improving laboratory biomarkers and symptom resolution. After clinical resolution, he was initiated on elvitegravir, cobicistat, emtricitabine and tenofovir (EVG/COBI/FTC/TDF). Two months after discontinuing the initial antiretroviral regimen, amylase and lipase normalized and he was asymptomatic. He was adherent to EVG/COBI/FTC/TDF, reflected in continuing virologic suppression with a recent CD4⁺ T-cell count of 81 cells/ μ l.

Acute pancreatitis is a known complication of HIV infection, specifically with older nucleoside antiretrovirals [1,2] and prophylactic medications including co-trimoxazole and pentamidine [1]. Pancreatitis with ABC/3TC is very rarely reported: in postmarketing surveillance in Japan, two patients developed acute pancreatitis while receiving ABC/3TC [3].

Dolutegravir has a half-life of 14 h, making it a viable once-daily drug that is efficacious in suppressing plasma HIV-1 RNA level without inducing resistance to this and other integrase inhibitors [4,5]. Combined with ABC/3TC, it provides effective treatment for individuals who have difficulty adhering to more complex regimens, and is one of the new first-line agents as per the US guidelines [6,7]. Known side effects of dolutegravir include nausea, diarrhea, fatigue, vomiting, back pain and headache [8,9]. In the SPRING-2 trial comparing two integrase inhibitors, dolutegravir and raltegravir, none of the patients experienced serious dolutegravir-associated adverse events [8]. The FLAMINGO study noted that one treatment-naïve adult developed pancreatitis while receiving dolutegravir, but did not publish additional risk factors in this individual or details about severity [9].

We report on acute pancreatitis in an immunocompromised HIV-infected adolescent temporally associated with DTG/ABC/3TC administration. He had no underlying alcohol use, anatomical abnormality or gall bladder disease. Although HIV infection is a known cause of acute pancreatitis, this patient's viral load had dropped precipitously shortly after commencing cART. A low CD4⁺ T-cell count (<50 cells/ μ l) has also been associated with pancreatitis [10]. However, once the antiretroviral regimen was discontinued, he experienced both clinical and laboratory evidence of improvement without discontinuing or adjusting his other medications at a time when the CD4⁺ T-cell count was just

11 cells/ μ l. Thus, it seems unlikely that the pancreatitis was related to HIV itself.

With the development of novel antiretrovirals and fixed-drug combinations that allow once-daily administration, clinicians should be aware of potential side effects associated with these new antiretroviral combinations. Progress with depot formulations should proceed with caution, since newer therapies may not have been fully evaluated for postmarketing serious adverse effects.

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Changes in kidney function in patients with suppressed HIV RNA who substitute their protease inhibitor with atazanavir/ritonavir

Atazanavir (ATV) is a protease inhibitor licensed for the treatment of HIV infection, and one of the preferred agents for first-line therapy in the UK [1]. The use of ATV, however, has been associated with a number of kidney syndromes, including acute interstitial nephritis [2,3], chronic kidney disease (CKD) [4], rapid decline in estimated glomerular filtration rate (eGFR) [5], proximal kidney tubular dysfunction [6,7] and nephrolithiasis [8,9]. The risk factors for ATV-associated kidney dysfunction remain to be defined.

There is a paucity of data on renal biomarkers in patients switching from other ritonavir-boosted protease inhibitor (PI/r) to ATV/r. Most clinical trials focussed on lipid profiles and bilirubin and did not report data on renal function [10,11]. A change in the London HIV Consortium treatment guidelines in 2010 allowed us to study the effects of ATV/r on renal function of individuals with suppressed HIV viral loads switching protease inhibitor therapy. Patients deemed suitable for protease inhibitor switching were invited to consent to storage of fasted plasma, serum and urine samples at their routine clinic visits at baseline (preswitch), and 2–4 and 24–48 weeks postswitch. These samples were stored at -70°C until analysis for urinary total protein, albumin, retinol-binding protein (RBP) [12] and phosphate, and for serum cystatin C (CysC) concentrations. This observational study was approved by the BioBank Ethics Committee.

The current analyses focus on individuals who were on two nucleoside reverse transcriptase inhibitor (NRTI, with no subsequent change in NRTI) and a non-ATV ritonavir-boosted protease inhibitor for more than 6 months prior to switching protease inhibitor. Routinely collected serum creatinine data were used to calculate eGFR slopes (CKD-EPI-creatinine [13]) pre and postswitch (reflecting exposure to non-ATV PI/r and ATV/r, respectively). For those individuals with stored samples, estimated GFR (CKD-Epi-creatinine and CKD-EPI-CysC), tubular function [RBP expressed as a ratio with urinary creatinine (RBPCR)] and the ratio of the maximum rate of tubular phosphate reabsorption to eGFR (TmPO_4/GFR) at 2–4 weeks and 24–48 weeks

were compared with baseline. Preswitch and 2–4 and 24–48 weeks postswitch data were compared using the one-way repeated-measures analysis of variance, Friedman [14] or Skillings–Mack tests [15]. To determine whether switching to ATV/r had an effect on eGFR slope, pre and postswitch eGFR slopes were calculated and compared using a linear mixed effects model [16].

Overall, 159 individuals were identified as being on a non-ATV protease inhibitor containing regime at baseline. Twenty-eight (17.6%) were on lopinavir (LPV)/r monotherapy and were not switched. Of the remaining 131 individuals on triple therapy, 52 switched to ATV/r between November 2010 and April 2013. Reasons for not switching PI included current pregnancy, viral nonsuppression, age less than 18 years and patient unwillingness to change protease inhibitor regime. One patient also switched NRTI backbone at the time of protease inhibitor switch and three had HIV RNA levels more than 400 copies/ml; these were excluded from the analyses. Of the 48 remaining individuals, 47 had at least three creatinine measurements pre and postswitch on protease inhibitor therapy and were included in the eGFR slope analyses, and 30 provided samples for biomarker analysis. The mean age of the patients was 42.6 (SD 7.2) years, 44% were female and 73% were of black ethnicity. The median time since HIV diagnosis was 7.6 [interquartile range (IQR) 3.1–13.1] years, and the median CD4^+ cell count was 594 (491–781) cells/ μl . Thirty patients (63%) received tenofovir disoproxil fumarate (TDF) as part of their antiretroviral regimen; preswitch protease inhibitor exposure consisted of LPV/r ($n = 35$), fosamprenavir/r ($n = 7$), saquinavir/r (SQV/r, $n = 4$) and darunavir/r (DRV/r, $n = 2$). Patients included in the renal biomarker analyses had similar characteristics as those included in the eGFR slope analysis, with the exception that they were more likely to be men (56.7 vs. 22.2%) who acquired HIV through sex with men (36.7 vs. 5.6%) and be on TDF vs. a non-TDF containing regime (80.0 vs. 33.3%, $P < 0.01$ for all).

The median (IQR) duration of follow up on PI/r-containing regimens was 3.8 (1.7–7.3) and 1.8 (1.5–2.1)

Table 1. Renal biomarkers in 30 patients who switched from nonatazanavir protease inhibitor/ritonavir to atazanavir/ritonavir-containing antiretroviral regimens.

		Visit 1 (baseline)	Visit 2 (2–4 weeks)	Visit 3 (24–48 weeks)	P
eGFR (creatinine)	Mean (SD)	108 (21)	108 (23)	108 (22)	0.3
eGFR (CystatinC)	Median (IQR) ml/min/1.73 m ²	129 (119–153)	128 (108–147)	138 (105–188)	0.6
PCR	Median (IQR) mg/mmol	9.4 (6.7–13.7)	10.4 (6.9–16.1)	9.2 (7.2–12.2)	0.6
ACR	Median (IQR) mg/mmol	0.9 (0.5–1.1)	0.7 (0.5–1.0)	1 (0.4–1.7)	0.8
RBPCR	Median (IQR) µg/mmol	1.0 (0.4–3.7)	1.2 (0.5–2.6)	1.2 (0.6–3.3)	0.2
TmPO ₄	Median (IQR) mmol/l	0.8 (0.7–0.9)	0.9 (0.8–0.9)	0.9 (0.8–1.0)	0.4

ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PCR, protein/creatinine ratio; RBPCR, retinol-binding protein expressed as a ratio with urinary creatinine.

years pre and postswitch, respectively, and the median number of eGFR measurements during this period was 33 (17–42) and 7.5 (6–9), respectively. The median (IQR) eGFR was 118 (100–126) at the start of PI/r therapy and 113 (90–126) ml/min/1.73 m² at the time of ATV switch. The crude eGFR slopes [95% confidence interval (95% CI)] were –0.7 (–1.1 to –0.3) preswitch and –0.6 (–4.2 to 3.0) ml/min/1.73 m²/year postswitch. Using mixed effect models adjusted for age, ethnicity and CD4⁺ cell count, there was no significant difference between the pre and postswitch eGFR slope [1.1 (–1.5 to 3.6) ml/min/1.73 m²/year, *P* = 0.4].

In the subset of patients with stored samples, there was no statistically significant difference from baseline in eGFR (based on creatinine and cystatin C measurements), proteinuria (protein/creatinine ratio), albuminuria (albumin/creatinine ratio), RBPCR or TmPO₄/GFR at either weeks 2–4 or weeks 24–48 postswitch (Table 1).

In this observational study of patients with well controlled HIV infection, switching from a non-ATV PI/r to ATV/r-containing antiretroviral regimen did not have a demonstrable effect on renal glomerular or tubular function. Our data provide reassurance regarding the use of ATV/r in protease inhibitor experienced patients with preserved renal function and are consistent with studies in treatment-naïve patients in whom ATV/r was compared with LPV/r [17], SQV/r [18], DRV/r [19] or efavirenz [20]. By contrast, although large observational cohort studies such as EuroSIDA, Veterans Health Administration and D:A:D are able to provide risk estimates of rapid eGFR decline and/or kidney disease progression [4,5,21], these studies may be subject to channelling bias if ATV/r was preferentially prescribed to individuals at an increased risk of CKD.

Our study is limited by the relatively small sample size, duration of follow-up, lack of a control group and its observational design. It does, however, reflect real-life clinical practice. Our results endorse the London Consortium guidance to use ATV/r as the preferred protease inhibitor in people living with HIV who have preserved renal function. Our data argue against a widespread detrimental effect of ATV/r on the kidney

but are unable to exclude the possibility of a direct nephrotoxic effect in a small subset of patients.

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