

Correspondence

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Possible allergic cross-reaction to didanosine and tenofovir in an HIV-1-infected woman

A 25-year-old woman tested positive for HIV-1 during a screening blood test. Her CD4 cell count was 234 cells/ μ l (14%) and 311 cells/ μ l (14%) in two consecutive controls a few weeks apart, whereas HIV RNA was 56 822 copies/ml and 34 000 copies/ml, respectively. The baseline genotype showed the absence of resistance mutations and she started a once-a-day regimen including tenofovir plus emtricitabine and efavirenz. After 10 days she developed a diffuse rash with fever and glossitis. Efavirenz was discontinued but her clinical conditions worsened over the following 3 days, so both tenofovir and emtricitabine were stopped, with a dramatic resolution of symptoms within 24 h. After 10 days the patient was restarted on a completely different regimen of zidovudine plus didanosine and ritonavir-boosted fos-amprenavir as both efavirenz and tenofovir might have played a role in the allergic reaction and the patient was distressed over the event.

After one week the patient again presented with a diffuse rash and the treatment was discontinued. She restarted 7 days later with only zidovudine and didanosine and within a few days the rash appeared again. So the recurrence of rash after rechallenge was reasonably caused

by didanosine. The patient was admitted to hospital for re-exposure to medications under clinical observation. She was restarted on zidovudine and atazanavir and, after 8 days, lamivudine and low-dose ritonavir was added to the regimen. The patient was well, except for mild hyperbilirubinemia, for the following 5 months.

At that time, HIV RNA was below 50 copies/ml, the CD4 cell count was 475 cells/ μ l and the regimen was simplified with zidovudine plus lamivudine and efavirenz. Three months later the patient was well and no adverse event occurred with the latter regimen. Figure 1 shows the clinical events and viro-immunological response according to the HIV regimens.

The patient developed two separate adverse reactions after exposure to two completely different regimens: tenofovir plus emtricitabine and efavirenz and zidovudine plus didanosine and ritonavir-boosted fos-amprenavir, which suggests that she is allergic to at least two different drugs. Both tenofovir [1] and didanosine [2], according to large-scale clinical trials, are generally well-tolerated drugs. Peripheral neuropathy and pancreatitis are the most common side effects associated with didanosine [2],

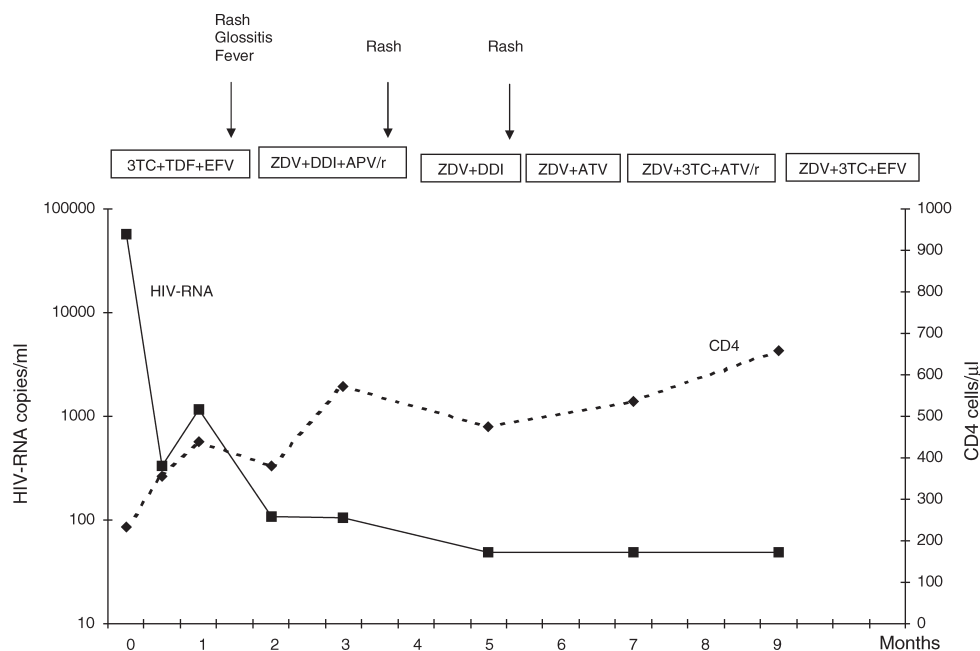


Fig. 1. Clinical events and viro-immunological response according to HIV regimen. APV/r, Ritonavir-boosted amprenavir; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; DDI, Didanosine; EFV, efavirenz; TDF, tenofovir; 3TC, lamivudine; ZDV, zidovudine.

although its enteric-coated formulation is much better tolerated. On the contrary, renal complications are the most frequently reported toxicities associated with tenofovir [3,4]. Both didanosine [5] and tenofovir [1,3] may cause allergic reactions such as rash, as virtually all medications can do, although these events have been rarely described, despite their intensive use over many years.

In our patient, the allergic reaction to didanosine has been confirmed after rechallenge with the same drug, whereas allergy to zidovudine and efavirenz has been ruled out after subsequent rechallenge with both agents.

Treatment with lamivudine and ritonavir-boosted atazanavir never caused any reaction after prolonged exposure.

Emtricitabine may have theoretically caused the first cutaneous reaction, as this event has been reported in trials with emtricitabine [6]. A rash caused by emtricitabine is, however, unlikely if we consider its rarity and the successful rechallenge with lamivudine, which is structurally very similar to emtricitabine. The reaction to the first patient's regimen was interpreted as being caused by tenofovir.

Tenofovir disoproxil fumarate is an ester pro-drug of the nucleotide reverse transcriptase inhibitor tenofovir, it is a nucleotide analogue of adenosine 5'-monophosphate with activity against HIV reverse transcriptase. Didanosine, which is also known by the chemical name 2',3'-dideoxyinosine, competes with the naturally occurring nucleoside deoxy-adenosine triphosphate for the active binding site on HIV reverse transcriptase. Both

agents share similarity in their structural formula. This chemical similarity may provide an explanation for a possible cross-sensitivity between these two drugs. This event, which is certainly uncommon, may have a relevant clinical implication as it drastically limits the options for the nucleotide reverse transcriptase inhibitor backbone, which is still the cornerstone of any anti-HIV regimens [7].

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Atazanavir-containing renal calculi in an HIV-infected patient

Approximately 7% of an atazanavir (Reyataz; Bristol–Myers Squibb, Princeton, New Jersey, USA) dose is excreted as unchanged drug in the urine and the solubility of atazanavir increases with acidity [1]. These properties are similar to those of indinavir, which is more soluble in acid solutions and of which 19% is excreted as unchanged drug in the urine. Indinavir is associated with precipitation in the urine and clinical sequelae in 4–43% of patients [2–4]. Conversely, there have been only two recent case reports of atazanavir-associated urolithiasis in the literature [5,6]. We report here another case of renal calculi containing significant amounts of atazanavir in an HIV-infected patient.

The patient was a 51-year-old man who was found to be HIV positive in 1989. His antiretroviral history included: zidovudine from January 1993 to July 1994; stavudine from July 1994 to April 1996; and triple therapy with

stavudine, lamivudine, and indinavir beginning in April 1996. Ritonavir was added to indinavir in March 1999 (800 mg/100 mg twice a day). In November 2003, the patient switched from boosted indinavir to atazanavir/ritonavir (300 mg/100 mg) because of patches of dry and scaly skin and flank discomfort (although no kidney stones). From December 2003 to March 2005, his flank discomfort and skin problems resolved, and he had no new medication-related complaints. His HIV markers were stable over the course of this medical treatment. His CD4 cell nadir was 399 cells/ μ l in January 1995. Since then and up to now his CD4 cell count has ranged between 400 and 700 cells/ μ l. His viral load has been undetectable since starting triple drug therapy in April 1996. His other medications and concomitant health issues include cetirizine 10 mg as needed for allergy symptoms and oxycodone/acetaminophen and sumatriptan nasal spray as needed for migraines.

The history of the present nephrolithiasis episode began in March 2005, 1.5 years after indinavir was stopped and atazanavir–ritonavir was begun. The patient presented with severe right flank pain requiring hospitalization. His urine pH was 6 and urinalysis was unremarkable. A non-contrast computed tomography scan of the abdomen and pelvis demonstrated right hydroureteronephrosis with some perinephric stranding, but no calculi. As a result of continuing pain, an intravenous pyelogram was obtained. This also showed right-sided hydroureteronephrosis with dilation to the distal ureter, but no stones or filling defects could be seen. Shortly after this examination he passed seven calculi, measuring 2–5 mm each. Chemical analysis of these stones revealed ‘crystals of undetermined origin’. The patient continued to pass stones for the next 10 months, and he complained of urinary urgency, frequency and nocturia. Repeat chemical analyses showed ‘organic matter consistent with cellulose’. The stones did not contain critical amounts of calcium, uric acid, cystine, or struvite. In January 2006, the patient was diagnosed with gout. Allopurinol (300 mg/day) was begun and his urine was alkalinized with oral UroCitK (potassium citrate). His production of stones increased on this regimen.

In February 2006, we considered that atazanavir might be precipitating in the urine based on the increase in stone production with urine alkalinization and the factors mentioned in the introduction. We asked the patient to save several stones for the analysis of atazanavir (Fig. 1).

We separately analysed three stones for their atazanavir content. Briefly, each stone was weighed (mg) and placed into a centrifuge tube. Methanol was added to create a volume ratio of 1 mg/ml. This stone/methanol mixture was sonicated for 30 min and the residual debris was removed by centrifugation. The stone solution was injected onto our validated high-performance liquid chromatography–ultraviolet method for protease inhibitors. This method undergoes twice-yearly proficiency testing.

The initial total weights of the three stones were 4.53, 6.72, and 9.20 mg. Each stone contained a significant

amount of atazanavir by weight (41, 44, and 49%). Ritonavir was also present in the stones at less than 1%. Initially, it appeared that indinavir might be present in trace amounts that were below the quantifiable limit. We verified the presence of each protease inhibitor by liquid chromatography–mass spectrometry, however, and indinavir was not detectable whereas atazanavir and ritonavir were confirmed.

On the basis of these results, the patient replaced atazanavir/ritonavir with efavirenz. By May 2006, his rate of stone passage had decreased substantially.

In summary, the substantial level of atazanavir in the renal calculi of this patient (approximately 40–50% by weight) plus the reduction in stone passage after switching from atazanavir to efavirenz suggests that atazanavir played an important role in the presence of these stones [4]. This is the third case report of atazanavir-containing renal calculi in an HIV-infected patient [5,6]. One other report suggested that atazanavir caused a case of acute interstitial nephritis, which was considered a hypersensitivity-like reaction to the drug [7]. Given the rarity of atazanavir-associated renal problems, we speculate that our patient had an unusual physical or biochemical predisposition that led to these stones. The history of indinavir use and the presence of gout stand out as possible factors contributing to this potential predisposition.

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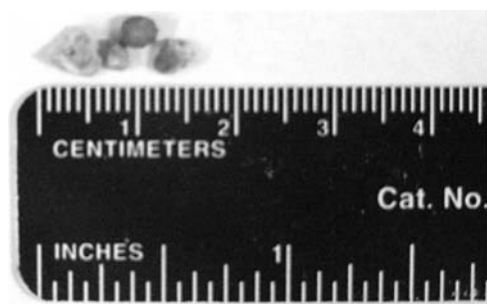


Fig. 1. Renal calculi in which the atazanavir content was 40–50% by weight.

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'Forced treatment interruptions' and risk of HIV resistance in countries adopting law enforcement against marginalized populations

To date, in many countries, marginalized HIV-infected populations, such as ethnic minorities, migrants, those exchanging sex for survival and injecting drug users (IDU) have been excluded or have been delayed from receiving appropriate care [1,2]. A limited supply of antiretroviral therapy (ART) and the suggestion that these populations may be less adherent to ART than other HIV transmission categories have been extensively used to justify such limited access. Nevertheless, these attitudes of denying access to care for these populations is still the dominant rule in many countries, despite it having been shown that 'pretreatment' information is less predictive of adherence than patient's experience with treatment [3], and that IDU can adhere to ART as closely as other transmission groups if they receive adequate comprehensive care including substitution treatment [4,5]. In addition, for those individuals living with HIV and receiving ART, the experience of prison as well as encounters with the police have already been shown to be highly associated with reduced adherence to ART [5,6] and with virological failure [7].

The introduction of fixed dose combinations (FDC) based on nevirapine has greatly contributed to the scaling up of ART in developing countries, even among those minorities who have long been excluded from HIV care.

The results reported by Oyugi *et al.* in this issue indicate that interrupting nevirapine-based treatments 48 h may induce drug resistance. Such interruptions have a greater impact than reduced adherence on drug resistance. These results could have major public health implications in countries where police harassment and drug law enforcement are massively used against marginalized populations. The scaling up of ART in such settings may be problematical as it may expose these groups to recurrent 'forced interruptions'.

How these law enforcement police forces can have a negative impact on HIV prevention and can even increase HIV prevalence has been widely documented not only in developed countries [8] but also in many eastern European and Asian countries [9].

In China and Vietnam, drug use is still considered a social threat, and there are periodic crackdowns during which large numbers of drug users are arrested and sent to rehabilitation or detoxification centres that are still unable to offer them 'comprehensive' care [9]. In Kazakhstan,

which has the third highest per capita prison population in the world, where one third are drug users, Human Rights Watch research reports that IDU and sex workers are frequently arrested without any suspicion of specific illicit acts [10].

In many countries where ART is or will be available as FDC, the presence of police enforcement, resulting in the excessive use of arbitrary detentions and 'forced treatment interruptions' is addressed especially towards drug users and sex workers who often make up the vast majority of HIV-infected individuals.

Depending on ART coverage, on the frequency of incarceration episodes, and on the prevalence of HIV in such 'bridging groups', the occurrence of HIV-resistant strains in these populations may become so sharply elevated that the public health benefits of ART scale-up are weakened and may result in a call for a large availability of multiple line treatment regimens. Such a policy may result in an uneven and dangerous paradox, and compromise the success of any national public health policy for HIV prevention and care.

The existence of cooperation between law enforcement agencies and public health institutions becomes the only constructive preamble for a successful scale-up that would also be accessible and effective for marginalized populations.

This effort is crucial to maintain the public health benefits brought about by the introduction of ART that have been demonstrated in order to reduce HIV transmission by lowering viral load and instigating safe behaviours even in low income countries.

The emergence of HIV-resistant strains to FDC regimens should also be faced by solving the dilemma between police abuse and access to and retention in HIV care for IDU, sex workers and all possible victims of legal harassment.

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D-dimer levels are markedly raised in HIV-related thrombotic thrombocytopenic purpura

The association between HIV infection and thrombotic thrombocytopenic purpura (TTP) has been apparent since the late 1980s [1]. The incidence of TTP in HIV-infected individuals has been estimated to be 15–40 times that in the general population [2]. In South African hospitals it is now by far the commonest cause of TTP.

Successful treatment depends on the early institution of plasma infusion or plasmapheresis, and it is often necessary to make the diagnosis in the presence of microangiopathic haemolytic anaemia and thrombocytopenia alone before the full diagnostic pentad of features (including renal failure, neurological symptoms and fever) has emerged [3]. This requires the exclusion of other possible causes for the clinical picture, including disseminated intravascular coagulopathy (DIC). The absence of abnormalities on a DIC screen is therefore quoted as an important diagnostic criterion. However, although other coagulation parameters appear normal, we have frequently observed extremely high D-dimer levels in patients with HIV-related TTP. We therefore analysed the results of coagulation screening in patients with HIV-related TTP and compared these with the findings in HIV-negative patients with TTP.

The HIV status and results of DIC screens performed on consecutive patients diagnosed with TTP at the Johannesburg hospital and associated teaching hospitals between August 2002 and January 2005 were reviewed. Patients were identified from records of haematology consults received during this period. The diagnosis of TTP required at least the presence of microangiopathic haemolytic anaemia and thrombocytopenia in the

absence of other possible causes. Laboratory data were retrieved from the hospital computer system. The HIV status was confirmed on enzyme-linked immunosorbent assay testing.

Twenty-two patients with HIV-related TTP and three patients with idiopathic TTP were identified. Two patients with pregnancy-related TTP who suffered spontaneous abortions before assessment were excluded, as alterations in coagulation parameters in these patients were not solely dependent on the TTP process. The median haemoglobin and platelet levels at diagnosis were 5.2 g/dl and $11 \times 10^9/l$, respectively, for patients with HIV-related TTP and 8.0 g/dl and $19 \times 10^9/l$, respectively, for patients with idiopathic TTP. The median international normalized ratio, partial thromboplastin time and antithrombin levels were normal and were not significantly different between the two groups (international normalized ratio 1.13 versus 1.12, partial thromboplastin time 31.5 versus 31.5 s, antithrombin 103 versus 108 IU). However, the median D-dimer level was significantly higher in the HIV-related TTP group (3.73 mg/l, range 0.95–6.95, versus 0.28 mg/l, range 0.22–0.3, $P = 0.0058$; Fig. 1).

This study confirmed our clinical impression that high D-dimer levels, in the absence of any other abnormalities in coagulation parameters, appear to be a consistent feature of HIV-related TTP. In our experience this finding is often helpful in suggesting the diagnosis. The D-dimer levels appear to be significantly higher than those in patients with idiopathic TTP although the small numbers of HIV-negative patients in this study limits the reliability of the comparison. It is possible that the very

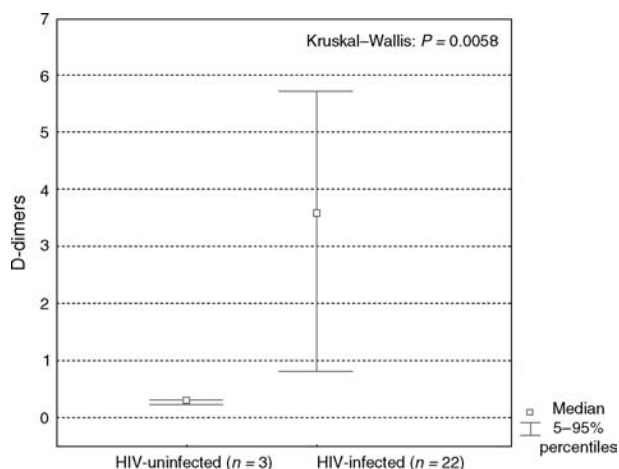


Fig. 1. Median D dimer levels in HIV-negative ($n = 3$) compared with HIV-positive ($n = 22$) patients with thrombotic thrombocytopenic purpura.

high D-dimer levels noted in patients with HIV-related TTP reflect differences in the pathogenesis.

It is becoming increasingly clear that a deficiency of ADAMTS13, a von Willebrand factor (VWF)-cleaving protease, although contributory is not sufficient in itself to precipitate an episode of TTP [4]. Endothelial cell injury is likely to play a key role in initiating and sustaining HIV-related TTP. Direct infection of endothelial cells by the virus itself has been documented [5], and the release of cytokines such as TNF- α and IL-1 β or proteins secreted by the HIV-infected cells has been shown to increase monocyte-endothelial cell interactions and cause the detachment of endothelial cells [6]. VWF release is taken as a marker of endothelial cell injury, and VWF levels have been shown to be markedly elevated in HIV infection, with higher levels correlating significantly with disease progression and increased viral load [7].

Florid VWF release as well as loss of the natural anti-thrombotic properties of the endothelium as a result of endothelial cell injury could certainly cause platelet deposition and microvascular thrombosis. Activation of coagulation pathways and subsequent fibrinolysis as a result of this process would give rise to the raised D-dimer levels noted. If extensive enough, the platelet deposition and microvascular thrombosis may be sufficient in

isolation to result in the clinical picture of TTP. Concomitant ADAMTS13 deficiency (acquired either through the presence of autoantibodies, as is typically described [8], or as a result of the consumption of the enzyme through the overwhelming release of VWF, as has been demonstrated in association with the use of 1-deamino-8-D-arginine vasopressin; desmopressin [9]) would result in the accumulation of ultralarge VWF multimers, which may be important in sustaining the process.

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Thrombosis of a drug-eluting stent after almost 2 years in an HIV-infected patient

Late thrombosis of drug-eluting stents (DES) has been reported to occur up to 26 months after implantation [1]. Stent thrombosis is a life-threatening emergency, and risk factors for late thrombosis in DES are the premature discontinuation of antiplatelet therapy, renal failure, bifurcation lesions, diabetes and low ejection fraction

[1-3]. Whether HIV-positive patients are more prone to stent thrombosis than individuals without HIV infection is unknown [4].

We describe the occurrence of a stent thrombosis 23 months after DES implantation, and 6 weeks after

the discontinuation of clopidogrel in an HIV-infected patient under HAART.

Case report

A 61-year-old male patient was admitted in October 2005 because of an acute anterior wall infarction. As a result of angina pectoris diagnosed in November 2003, coronary angiography had been performed and two polymer-based paclitaxel-eluting stents were implanted in the proximal part of the left anterior descending artery. A combination therapy with acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) was initiated. Because of hypercholesterolemia pravastatin (20 mg/day) was started. The patient continued to smoke two to three cigarettes a day. Clopidogrel was discontinued after 21 months for exceeding the recommended therapy duration of 6–12 months.

In November 2003, he was diagnosed as being HIV infected, possibly as a result of non-tested blood transfusions that he had received 15 years previously. He denied using illicit drugs and anabolic steroids. The patient was without HIV-related symptoms and had a CD4 cell count of 263 cells/ μ l and a plasma viral load of 5.6 log. In June 2004, HAART was initiated, consisting of stavudine extended release 100 mg, tenofovir 245 mg and efavirenz 600 mg all administered once a day. HAART was well tolerated, and 4 months later the patient's viral load was suppressed below the level of detection and his CD4 cell count had risen to 337 cells/ μ l. In May 2005, stavudine was substituted by lamivudine 300 mg as a result of early signs of polyneuropathy.

In October 2005, the patient arrived at the hospital 10 h after the sudden onset of chest pain. His blood pressure was 90/60 mmHg. A complete blood cell count was within normal ranges. Blood chemistry revealed increased levels of fasting glucose (8.16 mmol/l, normal 3.9–6.1 mmol/l), potassium (5.6 mmol/l, normal 3.5–5.5 mmol/l), creatine phosphokinase (1409 U/l, normal up to 170 U/l) and lactate dehydrogenase (432 U/l, normal up to 247 U/l). Serum cholesterol, high-density and low-density lipoprotein cholesterol levels showed normal results in contrast to elevated triglyceride levels (2.41 mmol/l, normal < 1.8 mmol/l). Activity of antithrombin III, protein C, factor XI and factor VIII, and levels of protein S antigen, activated protein C-resistance ratio and homocysteine were all normal. Tests for lupus-sensitive activated partial thromboplastin time, dilute Russell viper venom time and beta 2-glycoprotein antibody were negative, as well as mutation screening for 1.691 G→A and 20.210 G→A. An oral glucose tolerance test was normal. The electrocardiogram showed sinus tachycardia 125/min,

negative T-waves in V₁–V₃ and ST elevations in V₂–V₆. Coronary angiography revealed a complete thrombotic occlusion of the DES in the left anterior descending artery. A stent-in-stent implantation of a polymer-based paclitaxel-eluting stent was performed after recanalization. Clopidogrel medication was recommended indefinitely. Creatine phosphokinase peaked up to 9575 U/l. Echocardiographically and by radionuclide ventriculography a large akinesia of the left ventricular apex, the anterior wall and the middle and apical region of the interventricular septum was found. The further course was complicated by pulmonary congestion. Therapy with angiotensin-converting enzyme inhibitors, beta antagonists and diuretics was started. At the time of writing the patient was still in heart failure New York Heart Association class III and the implantation of a cardiac defibrillator was being considered.

In the absence of acknowledged risk factors, the case raises the question as to whether either HIV infection or HAART contributed to the stent thrombosis. Impaired endothelial function that results in decreased flow-mediated dilation may be caused either by the HIV infection itself or by HAART [5,6]. In addition, endothelial cells have been reported to be direct targets of certain HIV-1 isolates [7]. HAART decreases the morbidity and mortality of HIV infection but is associated with the premature manifestation of coronary artery disease [8]. Endothelial cells possibly play an important role in this process [9].

The degree of endothelialization of the DES remains unknown because of the lack of an intravascular ultrasound investigation. Coagulation studies showed normal results, making stent thrombosis caused by an underlying coagulation disorder unlikely [10]. A case-control study demonstrated altered neo-intima formation after DES resulting in an increasing risk of late stent thrombosis in HIV-infected patients [4].

In HIV-infected patients with DES, lifelong therapy with acetylsalicylic acid and clopidogrel is recommended. Because of the bleeding risk of this combination therapy, bare metal stents instead of DES should be considered in HIV-infected patients.

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Nodular regenerative hyperplasia of liver as a consequence of ART

We found the report of Mallet *et al.* [1] regarding the occurrence of nodular regenerative hyperplasia (NRH) in HIV patients tantalizing, particularly because we were recently confronted with a similar clinical conundrum in an HIV patient.

A 27-year-old white homosexual man presented to the HIV clinic and complained of generalized weakness, upper abdominal pain/distension, daily heartburn, non-bloody diarrhea and excessive flatulence that had its onset 3 days after starting nevirapine, and exacerbated further when the dose of nevirapine was increased from 200 to 400 mg a day. He was previously doing well on a triple nucleoside analogue regimen including didanosine 250 mg and emtricitabine 200 mg/tenofovir 300 mg a day, with an undetectable HIV viral load and a CD4 cell count of 249 cells/ μ l, but nevirapine was substituted for didanosine 4 weeks before his current presentation in order to give diversity to his antiretroviral regimen. His past medical history was significant for gastroesophageal reflux disease, psoriasis and bipolar disorder. Besides the antiretroviral drugs, he used over-the-counter omeprazole, dovonex 0.005% ointment and fluocinolone 0.01% cream as needed. He had used alcohol in moderate amounts during the past 6 years, using up to 13 units of alcohol on a weekly basis. He did not have any history of intravenous drug use. His physical examination revealed stable vital signs and moderate diffuse upper abdominal tenderness and no rashes.

His complete blood count, albumin and prothrombin time were normal. His liver function tests showed an alkaline phosphatase level of 165 U/ml (38–126), an aspartate aminotransferase level of 126 U/ml (14–36), an alanine aminotransferase level of 109 U/ml (9–52) and a total bilirubin level of 0.6 mg/dl (0.2–1.3). Before starting

nevirapine, his alkaline phosphatase level was 110 IU/ml, the aspartate aminotransferase level was 75 IU/ml, the alanine aminotransferase level was 79 IU/ml and the bilirubin level was 0.3 mg/dl. The hepatic viral serologies, hepatitis C virus RNA, hepatitis B virus DNA, antinuclear antibody, antimitochondrial antibody and anti-liver-kidney microsomal antibody were all negative. The F actin antibody was weakly positive, whereas ceruloplasmin and iron saturation were within the normal limits.

He underwent a computed tomography scan of the abdomen after the administration of oral and intravenous contrast that showed splenomegaly, perisplenic varices and no ascites. An upper gastrointestinal endoscopy showed grade two esophageal varices and minimal portal gastropathy. Biopsies of the antrum and duodenum showed mild inflammation. A transvenous liver biopsy performed a month after his initial presentation showed mild zone III sinusoidal dilation, patchy hepatocellular necrosis and congestion. His free hepatic venous pressure was 9 mmHg, wedged hepatic venous pressure was 17 mmHg and the hepatovenous gradient was 8 mm. An echocardiogram showed normal heart function. A magnetic resonance angiography of the abdomen showed no evidence of portal, splenic, superior mesenteric or hepatic venous obstruction.

Upon his initial presentation to the HIV clinic, nevirapine was stopped for a week, with some improvement of his symptoms, and was restarted again. Finally, because of persistent and worsening abdominal pain requiring narcotic analgesics, all antiretroviral agents, including nevirapine, were stopped 8 weeks after his initial presentation, and a second liver biopsy was performed that showed progressive changes of sinusoidal dilatation, hepatocellular congestion, patchy hepatocyte atrophy

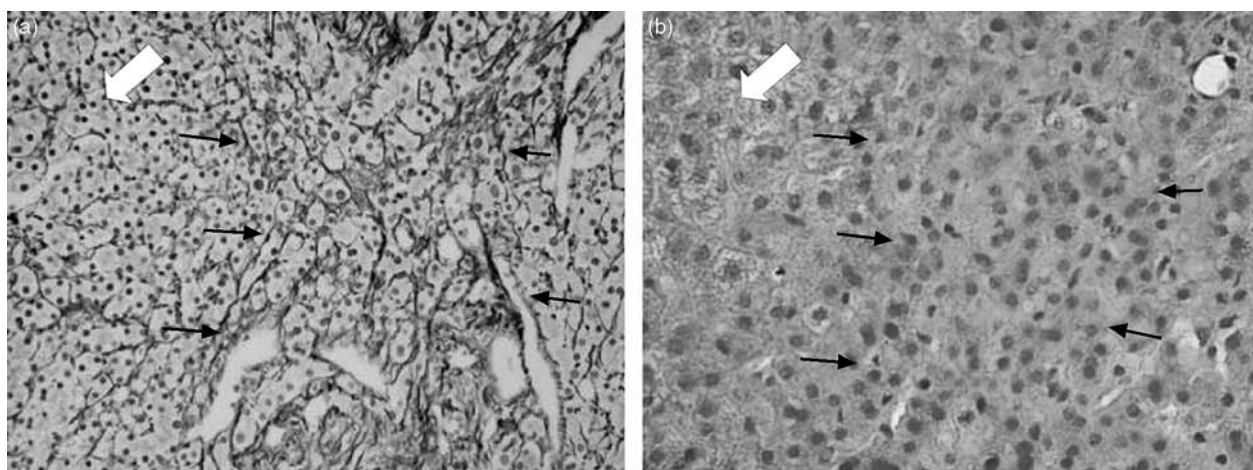


Fig. 1. Liver biopsies of the patient. (a) Reticulin stain shows an area (indicated by black arrows) of trabecular atrophy resulting in compression of reticulin fibres. Compare with normal liver (white arrow). Reticulin stain, original magnification 200 $\times$. (b) Hematoxylin and eosin stain shows an area (indicated by black arrows) of trabecular atrophy that corresponds with the area of compressed reticulin fibres in (a). Compare with normal liver (white arrow). Hematoxylin and eosin stain, original magnification 200 $\times$.

and reticulin compression, as well as hepatocellular necrosis without fibrosis compared with his previous biopsy (Fig. 1a and b). Four months after his initial presentation and 2 months after being off antiretroviral drugs, his abdominal pain had improved significantly and he had stopped using narcotic analgesics.

The present case is similar to case number 3 reported by Mallet *et al.* [1], in which no evidence of nodular architectural change of the liver was seen but putative changes of hepatic congestion were present. Although the present case was also exposed to didanosine like all the cases of Mallet *et al.* [1], his symptoms and subsequent documentation of portal hypertension occurred only after stopping didanosine and starting nevirapine, supporting the theory that portal hypertension was related to nevirapine and not didanosine. Moreover, Mallet *et al.* [1] reported a cross-sectional analysis of their cases, whereas this individual case provides a longitudinal follow-up of the patient when he was on didanosine for 4 years, and only after he was switched from didanosine to nevirapine did he experience the onset of symptoms and manifestation of portal hypertension. Nonetheless, five patients in the series of Mallet *et al.* [1] were not exposed to nevirapine, raising other possibilities for the cause of portal hypertension. It is unclear from the report by Mallet *et al.* [1] whether heart failure could have been a cause of sinusoidal dilatation or perisinusoidal fibrosis in any of their patients. Other causes of NRH in HIV patients reported in the literature include IL-2 therapy [2] in a didanosine-exposed individual and visceral leishmaniasis [3]. Finally, whether hepatotoxicity of antiretroviral therapy resulting in NRH occurs through a dose-dependent or idiosyncratic mechanism remains unclear.

Mallet *et al.* [1] suggested that because of the risk of inducing hepatic encephalopathy after portosystemic shunting procedures, liver transplantation should be considered for those who have refractory ascites and its associated complications. Many reports of successful portosystemic shunting in NRH patients have been reported [4–6], however, which did not cause refractory encephalopathy even many years after the creation of such shunts. Mallet *et al.* [1] correctly pointed out that NRH does not result in hepatocellular dysfunction, and therefore medical therapy and portosystemic shunting should be considered before liver transplantation, which should be reserved for a subset of patients with severe symptoms and no hope of the reversibility of NRH [7–9].

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***Rhodotorula mucilaginosa*: an unusual cause of oral ulcers in AIDS patients**

A vast majority of patients with AIDS present with oral manifestations [1]. The essential risk factors that influence the development of such oral manifestations are the low number of CD4 lymphocytes, xerostomia, and a lack of antiretroviral therapy [2]. The most common oral lesion seen in HIV disease is oropharyngeal candidiasis [1]. Here we present a case of an HIV-positive patient who presented with oral ulcers caused by *Rhodotorula mucilaginosa*, which to our knowledge has not been reported in the literature.

A 45-year-old HIV-positive patient presented to the internist with complaints of non-healing oral ulcers and white patches in the mouth of 2 months' duration associated with painful swallowing and dry mouth. The patient was a known case of HIV for 6 years and his CD4 cell count at presentation was 52 cells/ μ l. He had been receiving oral fluconazole for 2 months and antiretroviral

therapy for 4 years. He was currently on saquinavir, zidovudine and lamivudine. The patient showed no improvement on the current therapy, instead the ulcers increased in size. On examination, the oral ulcers were bilateral, deep, and 1 $\times$ 1 cm in size (Fig. 1a). Swabs were obtained from the edges of the ulcers and were subjected to direct Gram staining and culture on Sabouraud's dextrose agar (SDA) and SDA with chloramphenicol in duplicate; they were then incubated at 25°C and 37°C.

On direct microscopy large round yeast cells with narrow angle budding and a thin capsule were seen. Reddish pink yeast-like creamy colonies were isolated in pure culture 5 days later on SDA at 25°C and 37°C, which showed large round budding yeast cells and no hyphae (Fig. 1b). The organism did not ferment glucose, sucrose, lactose, galactose, maltose or trehalose. On performing carbohydrate assimilation tests on yeast nitrogen base agar,

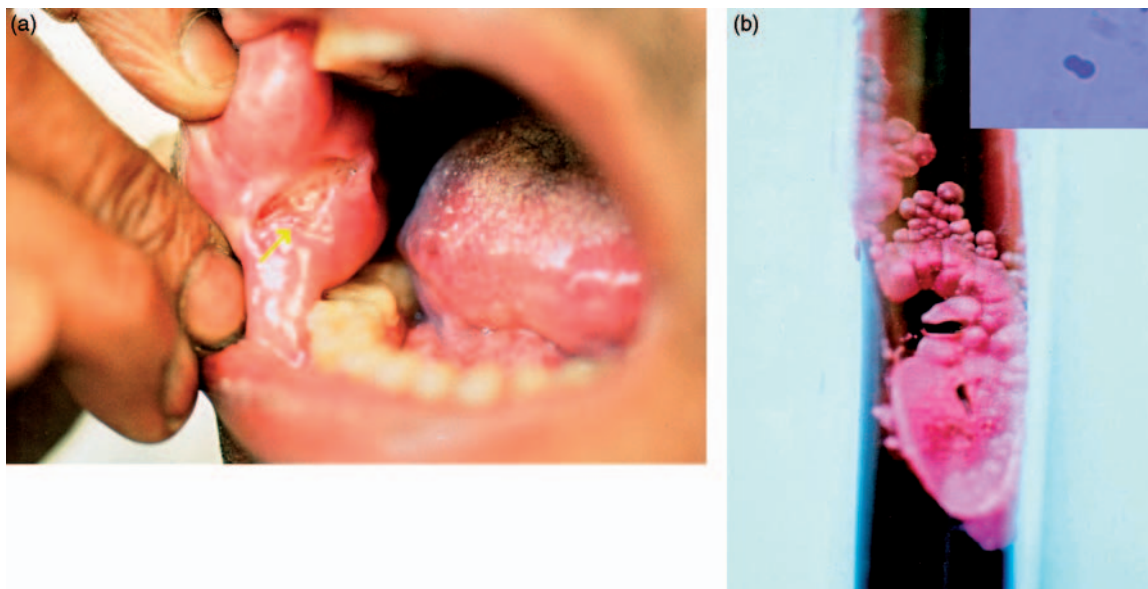


Fig. 1. Oral ulcer caused by *Rhodotorula mucilaginosa*. (a) Clinical photograph showing a deep ulcer on the buccal mucosa (arrow). (b) Reddish pink yeast-like creamy colonies of *Rhodotorula mucilaginosa* on Sabouraud's dextrose agar and (inset) Gram-stained picture of *R. mucilaginosa*.

glucose, sucrose, trehalose, D-xylose, raffinose, and D-arabinose were assimilated, whereas lactose, melibiose, galactose, maltose, cellobiose and inositol were not. Urea was hydrolysed. Repeated sampling showed similar results. Based on the above tests, a diagnosis of *R. mucilaginosa* (earlier called *Rhodotorula rubra*) oral ulcers was made. The patient was started on itraconazole thereafter and antiretroviral therapy was continued. A dramatic improvement in the symptoms was noted, with healing of the ulcers. A CD4 cell count was repeated and the count was recorded as 42 cells/ μ l with no improvement.

R. mucilaginosa is a yeast found in air, soil, lakes [3], ocean water [4], and dairy products. It can be found in shower curtains, bath tubs or tooth brushes [5]. On Gram staining it is a Gram-positive yeast and may show a thin capsule on India ink preparation. On SDA, cultures are coral pink, smooth, sometimes reticulate, rugose or corrugated, and moist to mucoid yeast like in appearance. The germ tube test is negative, hydrolysis of urea is positive, growth on cycloheximide medium is negative and growth at 37°C is variable [6]. *Rhodotorula* differs from *Cryptococcus* by its inability to assimilate inositol and the carotenoid pigment, and from *Candida* by producing pink-to-red colonies, lacking pseudohyphae and its inability to ferment sugars [5].

There is a scarcity of papers in the literature regarding the association of *R. mucilaginosa* with oral ulcers. In a report from Taiwan [7] it was noted on endoscopy that oesophageal ulcers caused by *R. rubra* resembled ulcers caused by *Candida*. *R. mucilaginosa*, usually considered a commensal, is known to cause fungal peritonitis, endocarditis [6], fungemia [6,8–10] and meningitis [6,10] in patients undergoing chemotherapy for cancer and those with indwelling intravenous catheters [6,11], and disseminated *R. mucilaginosa* infection [9] and meningitis [12] in HIV patients. Eye infections caused by *Rhodotorula* spp. have included chronic postoperative endophthalmitis and dacryocystitis [13]. An outbreak of *R. mucilaginosa* in a neonatal intensive care unit was recently reported in preterm infants with indwelling catheters [14].

A positive direct microscopy and repeated isolation in pure culture pointed towards it being the causative agent. Studies have shown that *Rhodotorula* is susceptible to 5-fluorocytosine, is moderately susceptible to amphotericin B, miconazole, ketoconazole, and itraconazole, and is mostly resistant to fluconazole [6]. An improvement seen in the patient after a change in therapy to itraconazole emphasizes the aetiological role of the fungus in our patient.

Information on the oropharyngeal and esophageal involvement of *Rhodotorula* in patients with HIV infection

is scarce and therefore important. Although the clinical presentation is similar to infection caused by *Candida*, the response to treatment is different. The role of mycological evaluation and culture is thus increasingly important in cases not responding to conventional therapy, especially in reducing the morbidity in patients with AIDS with low CD4 cell counts.

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Psychosocial support for HIV-infected populations in developing countries: a key yet understudied component of positive prevention

Increased attention is being given to positive prevention, which emphasizes intervening with HIV-infected individuals to reduce their likelihood of infecting others, and enhancing quality of life [1,2]. Numerous published research studies have been conducted in wealthy countries on psychosocial support for individuals infected with HIV, some showing efficacy in reducing HIV risk behavior [3–5]. It is, however, unclear whether psychosocial support services will reduce HIV risk behaviors in less economically developed settings. To examine this issue we conducted a systematic review of quantitative studies in developing countries to establish an evidence base for psychosocial support services for HIV-infected clients as a behavioral risk reduction intervention.

We searched electronic databases including the US National Library of Medicine's Gateway system, PsycINFO, sociological abstracts, EMBASE, and the Cumulative Index to Nursing and Allied Health Literature. Study staff also hand-searched the table of contents of the journals *AIDS*, *AIDS and Behavior*, *AIDS Care*, and *AIDS Education and Prevention*. Studies had to meet the following inclusion criteria: (i) present quantitative data from a developing country (the World Bank categories of low-income, lower-middle income, or upper-middle income economies) [6]; (ii) include participants who have received a diagnosis of HIV or who were presumed to be HIV infected based on clinical signs and symptoms; (iii) examine an intervention that provided social or psychological support to HIV-infected individuals; (iv) employ an evaluation design comparing post-intervention outcomes using either a pre/post or multi-arm study design (including post-only exposure analysis); (v) present behavioral, psychological, social, care, or biological outcome related to HIV prevention; and (vi) appear in a peer-reviewed journal from 1990 to 2004. Two separate staff independently assessed whether citations met our inclusion criteria, and the study principal investigator made an additional review of the results. Each citation was subjected to data extraction by three independent reviewers.

The initial search identified 69 articles with titles and abstracts indicative of potentially relevant citations (Fig. 1). Only one ultimately met the criteria for inclusion. No additional citations were identified through hand-searching of journals or secondary references. The one study meeting our inclusion criteria [7] was conducted in Tanzania between 1996 and 1997 with a sample size of 154 HIV-infected, sexually active participants who were newly diagnosed. Subjects were randomly assigned to receive either standard healthcare, or standard healthcare plus ongoing individual counseling by trained staff on prevention and problem solving,

education of family members, provision of condoms, and referral to treatment. Participants were administered a baseline survey with 3 and 6-month follow-up interviews.

For the entire study group, regardless of treatment arm, the investigators found statistically significant improvements from baseline to follow-up for the following measures: sharing HIV test results with either parents or 'anyone', discussing HIV with partners, condom negotiation, use of condoms, extramarital sex (at 6 months), sexually transmitted disease, genital sores, and medical treatment seeking. There were, however, no statistically significant differences across intervention and comparison arms for any of the outcomes examined, indicating that enhanced psychosocial support was not associated with reductions in HIV risk behaviors.

Despite the frequency with which positive prevention is being promoted in developing countries, we have a limited evidence base on one of the main prevention components of this strategy. In this systematic review, we were able to identify only one study on psychosocial support for HIV-infected individuals. That single well-designed study showed no significant impact. We stress that lack of evidence should not be confused with lack of efficacy. As agencies expand positive prevention programmes in developing countries, they should concurrently evaluate their efficacy to ensure they are having the desired impact given the current lack of evidence.

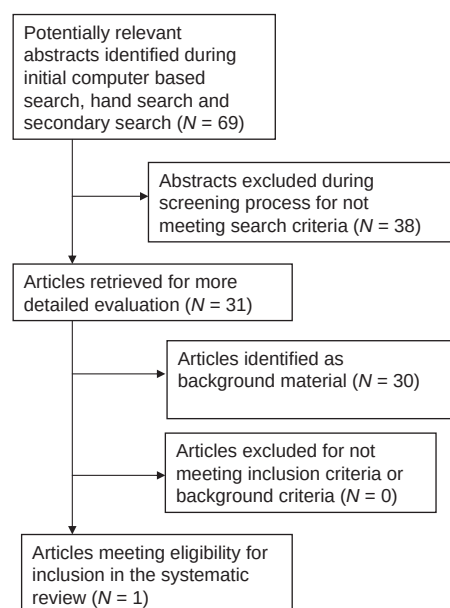


Fig. 1. Flow chart showing selection of articles for inclusion.

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