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Skin rash associated with atazanavir: report of three cases

Atazanavir is a new azapeptide inhibitor of HIV protease suitable for patients with marked lipodystrophy. Rash is reported in 6% of patients treated with atazanavir, but no cutaneous reactions have so far been reported in detail [1]. We describe three cases of cutaneous reactions to atazanavir.

Case 1

A 40-year-old man was admitted to our unit on 30 August 2004 for diffuse macular rash, jaundice and arthralgia. He had been HIV seropositive since 1991 and was infected by hepatitis B virus in September 2002. He had received various antiretroviral drugs (zidovudine, lamivudine, stavudine, nelfinavir and nevirapine) since 1997, and had been treated with ritonavir (100 mg per day), indinavir (800 mg per day), lamivudine (300 mg per day) and tenofovir (245 mg per day) since September 2002. On 20 August 2004, indinavir was replaced (because of ingrowing toe nail and skin dryness) with atazanavir (300 mg per day). On admission, physical examination showed a diffuse pruritic macular erythematous rash and afebrile subclinical jaundice. The total bilirubin level was 28 mg/l. No other biological abnormalities were found. The HIV-RNA level was undetectable and his CD4 cell count was 612 cells/ μ l. The atazanavir serum concentration was 324 ng/ml (expected range > 600 ng/ml after 24 h). As the symptoms were mild, the treatment was continued and the rash disappeared spontaneously. No other adverse effects occurred during more than one year of follow-up.

Case 2

A 33-year-old man presented to our department on 28 August 2004 with a diffuse macular rash. Eleven days before symptom onset he had started a regimen of atazanavir (400 mg per day), didanosine (400 mg per day) and lamivudine (300 mg per day) after a 5-month treatment-free period. HIV infection had been diagnosed in 1999, and he had had chronic hepatitis of unknown origin since 2003. He received multiple antiretroviral drugs (didanosine, stavudine, efavirenz, zidovudine, lamivudine and nevirapine) between 1999 and March 2004, with no adverse effects. On admission, physical examination showed a diffuse macular rash and jaundice.

The total bilirubin level was 202 mg/l, without cholestasis; the serum alanine transferase level was 63 IU/l and the aspartate aminotransferase level was 40 IU/l; the blood cell count and C-reactive protein level were normal. His HIV-RNA level was 4.97 log₁₀ copies/ml and CD4 cell count was 246 cells/ μ l. The atazanavir plasma concentration was 899 ng/ml. The rash disappeared within 48 h, but the treatment was discontinued after 3 days because of the persistent hyperbilirubinemia and pre-existing chronic hepatitis.

Case 3

A 40-year-old man was admitted to our department on 9 September 2004 with a diffuse maculopapular rash. He had been HIV seropositive since 1993 and had received multiple antiretroviral drugs (zidovudine, didanosine, stavudine, indinavir, lamivudine, saquinavir, ritonavir, abacavir, tenofovir and lopinavir); the only noteworthy adverse effect had been a cutaneous reaction to nevirapine 2 years before. Because of viral escape, he started to take a combination of atazanavir (300 mg per day), lopinavir (100 mg per day) and lamivudine (300 mg per day) on 31 August 2004. On admission, physical examination showed a generalized pruritic maculopapular rash. Laboratory tests were normal. His HIV-RNA level was 4.05 log₁₀ copies/ml and his CD4 cell count was 471 cells/ μ l. An antihistamine was prescribed. The patient was seen 48 h later and the antiretroviral treatment was discontinued because the rash had worsened, but there was no mucous membrane involvement nor fever.

Discussion

Adverse cutaneous reactions are a treatment-limiting adverse effect of antiretroviral drugs, and are mainly seen with reverse transcriptase inhibitors (nevirapine, abacavir and efavirenz).

Two factors point to the probable responsibility of atazanavir in the three cutaneous reactions described here. First, the mean interval between atazanavir introduction and clinical onset was 10 days in all three cases; and second, the antiretroviral drugs combined with atazanavir at the onset of rash had previously been well tolerated.

These were the only three cutaneous adverse reactions observed among 323 patients treated with atazanavir in our department since March 2004, giving a prevalence rate of approximately 1%. The rash was sufficiently severe to warrant treatment withdrawal in only one case.

Clinicians must be aware of adverse cutaneous reactions to atazanavir, which may require treatment discontinuation.

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Research design determines what can be known about modes of HIV transmission

We commend Becker and colleagues [1] for assessing one type of potential exposure to HIV, medical injections, rarely examined in HIV epidemiology in India and other developing nations. However, their interpretation of their results is at odds with the evidence they presented, and their research design severely limits the inferences about transmission that can be drawn from the study.

Remarkable proportions of their respondents reported receiving medical injections in the past year (68%) and ever (95%). Becker and colleagues [1] observed a dose-dependent association between the number of medical injections received and prevalent HIV infection (e.g. adjusted odds ratio for 10+ versus no injections in the past year 2.3, 95% confidence interval 1.2–4.3). Clearly, this is a meaningful relationship, and it is consistent with other research in India [2,3]. However, Becker and colleagues [1] concluded that ‘... data from this study do not provide evidence for an association between HIV infection and medical injections’ (p. 1335).

Becker and colleagues [1] dismissed the association by suggesting that it represents HIV-infected individuals seeking more medical care, and thus injections, as a consequence of HIV-related illnesses. Whereas this is possible [4], Becker and colleagues [1] presented no data to support the contention. In the absence of identified incident infections and measures of why respondents received injections at particular points in time, there is no empirical basis for interpreting the temporal order of this association.

Given the prevailing assumption that most HIV transmission in India and other poor countries is through penile–vaginal sex, it is important for Becker and colleagues [1] to show results for analogous analyses of sexual behavior as a correlate of HIV infection. The appropriate benchmark with which to compare their results on medical injections is the association between penile–vaginal sex (ever in lifetime, frequency in the past year, and number of opposite sex partners in the past year) and prevalent HIV infection, including adjustments for

the same demographic covariates used in their published analyses and the corresponding measure of medical injections. The measures of penile–vaginal sex should not reflect condom use or partner type, because their measures of medical injections did not capture the riskiness of those exposures or the settings in which they occurred [5].

As we have noted previously [6,7], many other types of parenteral exposures (e.g. dentistry, tattooing, scarification, injection drug use, surgery, blood transfusion, phlebotomy, etc.) are important to consider for HIV transmission; Becker and colleagues [1] apparently did not assess any of these. To our knowledge, no study on HIV epidemiology in India has yet included a thorough inventory of both sexual and parenteral exposures. Other barriers to understanding the modes of HIV transmission in India and sub-Saharan Africa are the lack of any systematic analysis of HIV contact tracing or risk networks (especially with respect to incident infections), investigation of the place and time dimensions of transmission, and sequencing of HIV DNA in relation to any of these kinds of data [8]. Without such fundamental evidence on the structure and context of transmission, it is not possible to determine the important modes of transmission with confidence.

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Response to Brewer *et al.* regarding our article 'Association between medical injections and HIV infection in a community based study in India'

We thank Dr Brewer and colleagues for their interest in our study. As they point out, we did observe an association between the number of medical injections reported to have been received in the past year and the risk of HIV infection. On univariate analysis, this was significant for women reporting five or more injections in the past year, and for men, 10 or more injections. On multivariate analysis, the association was statistically significant only among women who reported receiving five or more injections, although there was a trend towards an association for men reporting 10 or more injections. As Brewer and colleagues indicate, causal inferences cannot be drawn from a cross-sectional study, and it is possible that individuals may either have acquired HIV infection on account of receiving unsafe injections, or have first acquired HIV and then received injections related to illness. Only prospective studies or other studies that measure incidence can tease out causality in these relationships.

To address the issue raised by Brewer and colleagues of sexual behaviour as a risk factor for HIV infection, we examined the relationship between HIV infection and individuals reporting two or more lifetime sex partners. On univariate analysis, this relationship was statistically significant for men [odds ratio (OR) 2.7, 95% confidence interval (CI) 1.6–4.7] and for women (OR 3.4, 95% CI 1.0–12.3). We also developed a logistic regression model with HIV infection as the outcome, and the independent variable of interest being individuals reporting two or more lifetime partners. We controlled for injections received in the previous year in addition to the other variables controlled for in our initial analysis [1]. On multivariate analysis, there was a trend towards an

association among men, with men who reported multiple partners being 1.8 times more likely to be infected with HIV ($P = 0.07$). However, there was no significant association observed among women. A potential limitation of these data is the underreporting of risk behaviours, particularly among women. Other studies that we have conducted in the same area in India have shown that more anonymous forms of collecting behavioural information yield a much greater response with respect to reported risky sexual behaviours than face to face interviews [2]. In any case, population-based longitudinal studies are required, using more detailed and accurate measures of sexual and parenteral exposures, to assess their relationships with the risk of HIV infection in these settings.

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Unexpected improvement of sexual dysfunction during atazanavir therapy

We read with interest the report by Bernal E *et al.* about two patients on HAART who experienced improvement of sexual dysfunction when switched to an atazanavir-containing regimen [1].

The authors state that, to their knowledge, there are no data suggesting a differential effect of any particular antiretroviral drug or regimen on the clinical course of HIV-related sexual dysfunction. In 2001 we published

our experience with 16 men with complaints of sexual dysfunction while treated with a protease inhibitor regimen who switched to a nevirapine-containing regimen [2]. Thirteen (81.3%) of them reported that their libido increased and 12 (86%) of them that their erectile function improved after the switch. On the other hand, we also observed other patients who developed sexual dysfunction after starting a nevirapine-containing regimen.

Sexual dysfunction potentially related to antiretroviral therapy, is a topic that so far has received very little scientific attention. It is, however, for many patients an important complaint. We suggest that questions about sexual dysfunction should be included as part of quality of life questionnaires that should be administered during randomized clinical trials evaluating new antiretrovirals. Only in this way we will be able to demonstrate a clear link between sexual dysfunction and the use of any particular antiretroviral drug.

Dramatic interaction between levothyroxine and lopinavir/ritonavir in a HIV-infected patient

Drug interaction with HAART is a major concern especially in the case of protease inhibitors (PIs), which potentially interact with numerous drugs metabolized by cytochrome P450 3A4. A dosage adjustment of the drug may be necessary, depending on the specific antiretroviral agents being used. Here we report on a case of dramatic interaction between PI and levothyroxine associated with hypothyroidism that probably involved an interaction on the glucuronyl transferase.

A 58-year-old woman was followed up in our department for a HIV infection revealed by symptomatic primary infection 8 years ago. HAART was initiated at the time of the primary infection and was stopped 12 months later. Due to T CD4+ cell decrease, HAART was re-introduced 3 years later, based on a zidovudine, lamivudine and lopinavir/ritonavir combination. The patient exhibited an immunological and virological response with T CD4+ cell count at 840 cells/ μ l and plasma HIV RNA below 50 copies/ml.

Her other medical feature consisted of a multinodular euthyroid benign goitre that was diagnosed at the age of 51. Five years after its discovery, a thyroid radionuclide scintigraphy showed a nodule that was suggestive of cancer. A cytopunction was performed and this confirmed a thyroid papillary carcinoma T1N0M0 according to the TNM International Classification. In June 2003, the patient underwent a total thyroidectomy, followed by post-surgical radioiodine therapy. A substitution by levothyroxine was therefore introduced. During the following months, routine hormonal tests showed a persistent hypothyroidism defined by an increase in

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thyroid stimulating hormone (TSH) serum level and a decrease in free serum T4 level (85 mIU/l and 4.8 pmol/l, respectively) associated with clinical symptoms of hypothyroidism. The abnormal results of the thyroid hormonal tests persisted despite the increase in daily dose of levothyroxine up to 225 μ g/day and the introduction of liothyronine. The patient did not take any other medication apart from the HAART, had no digestive symptoms and did not report any lack in adherence to the substitutive hormonotherapy. On the basis of a possible interaction between protease inhibitors and levothyroxine, the lopinavir/ritonavir-containing HAART was withdrawn. Two months later the TSH and T4 serum concentrations had returned to normal level and remain stable. Eight months later her CD4 cell count had decreased to 321 cells/ μ l and so we decided to re-introduce lopinavir/ritonavir in association with zidovudine and lamivudine. The biological blood test performed 1 month later showed a recurrence of hypothyroidism with TSH serum level increase to 42 mIU/l. A switch from lopinavir/ritonavir to nelfinavir was not associated with a return to normal values of thyroid hormone tests. Finally, normalization of thyroid test was obtained when we decided to stop the protease inhibitor and to introduce a combination of three nucleoside reverse transcriptase inhibitors (Table 1).

Subclinical hypothyroidism in HIV-infected patients has already been investigated [1–3] as several retrospective studies report an increase in its prevalence among HIV-infected patients, especially those treated with HAART. Thyroid dysfunction during HIV infection may result from different mechanisms: auto-immunity, infectious

Table 1. Change in thyroid hormone tests, CD4 cell count and plasma viral load during the follow-up.

Month-year	6-2003	9-2003	12-2003	02-2004	04-2004	07-2004	08-2004	11-2004	01-2005	05-2005	06-2005	08-2005	09-2005	11-2005
TSH ^a (mIU/l)	2	85.1	50.6	47.5	4.1	0.1	0.1	42.9	21.5	18.1	9.7	1.1	0.1	0.5
T4 (pmol/l)	11.8	3.7	7.6	8.5	12.2	17.0	17	10.6	9.6	8.5	7.6	13.4	14.3	14.2
T3 (pmol/l)	4.8	2.4	3.2	3.2	6.8	9.2	5	4.4	4.4	5.1				
CD4 cell count (cells/ μ l)	634	554	608	608	447	315	321	482	545	473		572		709
Plasma HIV-RNA (log copies/ml)	< 1.7	< 1.7	< 1.7	< 1.7	4.4	4.8	4.8	1.9	< 1.7	< 1.7		< 1.7		< 1.7
↑ Thyroidectomy ← ZDV + 3TC + LPV/r → ← ZDV + 3TC + LPV/r → ← ZDV + 3TC + ABC → ← STOP Antiretroviral drugs → NFV														

^aTSH range of normal values (0.20–5.10 mIU/l); serum free T4 range of normal values (11.0–24.0 pmol/l); serum free T3 range of normal values (2.5–7.0 pmol/l). ZDV, zidovudine; 3TC, lamivudine; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; ABC, abacavir.

thyroiditis, drug reaction, or tumour [4]. In our case the loss of levothyroxine efficacy observed, seemed to result essentially from an increase of its inactivation, as a potential digestive malabsorption of this drug was easily ruled out. The imputability of lopinavir/ritonavir in the enhanced L-T4 degradation was demonstrated by the normalization and deterioration in TSH level after withdrawal and re-introduction of this drug. Perturbation of hormonal test results in a HIV patient treated with HAART and levothyroxine has already been reported [5,6]. Tseng *et al.* [5] have described a similar case of a patient stabilized on levothyroxine for an auto-immune thyroiditis induced by interferon therapy. One month after the introduction of ritonavir 600 mg twice daily, his TSH serum level increased to 18 mIU/l and the patient became lethargic. Increasing his levothyroxine dose to 0.25 mg daily reduced his TSH to 7.35 mIU/l. Lanza-fame *et al.* [6] described a case of a HIV-infected patient receiving levothyroxine, who developed a pharmacological hyperthyroidism after the introduction of an indinavir-containing antiretroviral regimen.

PIs are metabolized by the cytochrome P450 3A4 and may interact with other drugs metabolized through this pathway [7]. PIs are also the inducer of several metabolizing enzymes including glucuronyl transferase [8]. This latter enzyme plays a major role in the metabolism of levothyroxine.

Inactivation of thyroid hormone is indeed separated in two pathways [9]: the inner ring diiodination by enzymes of the diiodinase family in liver and peripheral tissues and the conjugation of the phenolic hydroxyl group with sulphate or glucuronic acid in liver. Acting as an inducer of the glucuronyl transferase, ritonavir could increase conjugation of L-thyroxine and thus promote its inactivation leading to hypothyroidism. Up to now, no interaction between protease inhibitor and diiodinase has been described.

Drug interactions are a major and frequent problem in HIV-infected patients. PIs could increase thyroid hormone inactivation through an induction of the glucuronyl transferase. This mechanism may be not univoque. TSH levels should be carefully monitored in patients receiving levothyroxine and ritonavir. Further studies are warranted to explore the pharmacological interaction between these drugs in order to improve the treatment of HIV-infected patients with hypothyroidism and for a better comprehension in drugs interaction.

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Haemolytic anaemia associated with efavirenz

Immune-mediated hypersensitivity reactions, such as skin rashes and drug-induced hepatitis, are well documented with the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretroviral drugs [1,2]. We report here a case of immune-mediated haemolytic anaemia associated with HAART that resolved upon switching the efavirenz component of the HAART to lopinavir/ritonavir and a brief course of corticosteroid therapy. This is the first case of haemolytic anaemia associated with efavirenz to be described in the literature.

A 36-year-old woman with World Health Organization Stage 3 HIV disease was commenced on stavudine 30 mg 12 hourly, lamivudine 150 mg 12 hourly and nevirapine 200 mg daily on 10 May 2005. Her CD4 cell count was 217 cells/ μ l, HIV viral load 21 000 copies/ml and her alanine aminotransferase (ALT) normal. She had no previous history of drug allergy or atopy. She was also taking co-trimoxazole 800/160 mg daily and vitamin B complex two tablets daily. Fourteen days later, 2 days after the dose of nevirapine was increased to 200 mg 12 hourly, she presented with a systemic hypersensitivity reaction to nevirapine. She had a widespread morbiliform rash associated with facial angio-oedema, but no mucosal ulceration. She had an associated eosinophilia (1.0×10^9 /l; normal range, $0-0.45 \times 10^9$ /l) and hepatitis (ALT 343 U/l (normal range, $0-40$ U/l), alkaline phosphatase 225 U/l (normal range, $40-120$ U/l), lactate dehydrogenase (LDH) 1111 U/l (normal range, $266-500$ U/l) and total bilirubin 3μ mol/l (normal range, $0-21 \mu$ mol/l). All drugs were stopped. The rash resolved and laboratory values returned to normal over 1 week.

She recommenced stavudine 30 mg 12 hourly, lamivudine 150 mg 12 hourly and efavirenz 600 mg daily at her primary care antiretroviral clinic on 1 August 2005. Co-trimoxazole was not recommenced. She was referred to our hospital on 2 September 2005 for investigation of

'frank haematuria'. She was afebrile with a pulse rate of 70 b.p.m. and blood pressure of 129/70 mmHg. She was pale, but her skin rash had not recurred. Her urine was noted to be dark reddish-brown in colour. Urine dipstick showed 4+ haemoglobin and microscopy showed debris, but no cells. Haemoglobin (Hb) was 4.6 g/dl (normal range, 12–15 g/dl), mean corpuscular volume 88 fl (normal range, 79–99 fl), LDH 6570 U/l, haptoglobin < 0.2 g/l (normal range, 0.3–2.0 g/l) and polyspecific direct antibody test (Coombs test) positive. Her ALT was 57 U/l. Renal function and white cell and platelet counts were normal. Peripheral smear revealed no fragments. Her eosinophil count was normal (0.06×10^9 /l).

A diagnosis of immune-mediated haemolytic anaemia was made. In light of her previous reaction to nevirapine, it was hypothesized that this may be another immune-mediated NNRTI drug reaction. The efavirenz was switched to lopinavir/ritonavir 400/100 mg 12 hourly. Stavudine and lamivudine were continued. She was transfused on two occasions and prednisone 40 mg daily was commenced. Her haemolysis resolved over the next 2–3 weeks. Over the next month, the prednisone was weaned then discontinued. One month after stopping prednisone she is well with no evidence of haemolysis (see Table 1 for clinical details).

This patient had manifest with one NNRTI hypersensitivity reaction in the form of a nevirapine-induced skin rash with angio-oedema and systemic features. She was recommenced on an efavirenz-containing regimen although international and local guidelines recommend that all NNRTI drugs be avoided in a patient who has had a severe skin reaction on nevirapine because of potential cross-reactivity [3,4]. When she presented with haemolytic anaemia on her new regimen, we hypothesised that there may have been an association between her previous episode of nevirapine hypersensitivity and this subsequent

Table 1. Clinical course, laboratory investigations and management of the case.

Month	Date	Clinical details	Hb (g/dl)	LDH (U/l)	Dipstix	Prednisone	Transfusion
May	10	Started D4T, 3TC, NVP					
June	2	NVP reaction. HAART stopped	11.2				
Aug	1	Started D4T, 3TC, EFV					
September	2	Haemolytic anaemia	4.6		++++		3 units
	5	EFV changed to Lop/RTV	7.9		++++		
	6		8	6570			
	14	Prednisone commenced	3.3	3599		40 mg/day	3 units
	20		11.8	1565	+++	40 mg/day	
October	26		12.8	955	Nil	30 mg/day	
	4		12.5	568		20 mg/day	
	11		12.8	665	Nil	10 mg/day	
	18	Prednisone discontinued	11.9	679			
	27		11.7	595	Nil		
November	24		12.4	614	Nil		

D4T, Stavudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; Lop/RTV, lopinavir/ritonavir; Hb, haemoglobin (normal range, 12–15 g/dl); LDH, lactate dehydrogenase (normal range, 266–500 U/l); Dipstix, quantification of haemoglobin in urine using dipstix.

haemolytic anaemia while on efavirenz. Thus we switched her efavirenz to lopinavir/ritonavir. Given the long half-life of efavirenz (40–55 h after multiple dosing [5]) we did not anticipate an immediate response. The resolution of the haemolysis 2–3 weeks after withdrawal of efavirenz (when negligible amounts of the drug are present in the plasma) and the non-recurrence of haemolysis following rapid withdrawal of prednisone make an auto-immune aetiology unlikely. Rather the clinical course suggests this was a drug-induced haemolytic anaemia related to efavirenz. We felt that a rechallenge of efavirenz to strengthen the evidence for a causal relationship between efavirenz and the haemolytic anaemia did not warrant the risk given the availability of alternative agents.

Cross-reactivity between nevirapine and efavirenz is described. The rate of recurrence of skin rash with efavirenz after a nevirapine skin rash was reported in one retrospective study to be 40% [6]. It is unclear whether this particular case represents an unusual manifestation of cross-reactivity or two distinct hypersensitivity episodes.

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Leishmania–HIV co-infection: An emerging problem in India

Leishmaniasis is emerging as third most frequent opportunistic infection in AIDS patients in various parts of the world particularly in *Leishmania* endemic countries where in 25–70% of adult cases of visceral leishmaniasis or kala-azar are found to be HIV co-infected [1]. The *Leishmania*–HIV co-infection has serious implications for patient management as the visceral strains can manifest in

atypical forms localizing to mucus membranes and skin while dermatophic strains can cause visceral disease [2,3].

So far, 33 countries have reported HIV–*Leishmania* co-infections. Of the first 1700 co-infections reported to the World Health Organization until 1998, 1440 cases were

from south-western Europe, mainly Spain (835) followed by Italy (229); France (259); and Portugal (117) [4]. In the Americas, most co-infections are reported from Brazil [5]. In Africa, the number of cases is expected to rise but the actual figures are not available [6].

In Asia, it is likely that a number of cases are missed due to the poor reporting system and lack of diagnostic facilities. In India, the first co-infection was reported in 1999 from the sub-Himalayan (Kumaon) region [7]. Later five more reports of *Leishmania*–HIV co-infection were published [2,8–11].

Our study population comprised 100 patients with clinical suspicion of kala-azar seen or hospitalized in the last 4 years at the All India Institute of Medical Sciences, New Delhi, a tertiary care hospital. The diagnosis of leishmaniasis was made by demonstrating Leishman-Donovan (LD) bodies in the tissue of relevance followed by antibody detection using recombinant antigens from *Leishmania chagasi*, rK39 [12] and another from *Leishmania donovani*, rKE-16 [13]. The tests were performed with appropriate negative and positive controls. Positive samples were tested for HIV using standard methods and confirmed by western blot (BioRad, Maines-La-Coquette, France). The samples positive for LD bodies and anti-Leishmanial antibodies by both the antigens in qualitative screening tests were further analysed by rKE-16 quantitative ELISA using a twofold serial dilution in phosphate-buffered saline (from 1 : 100 to 1 : 4096000) to determine the end-point titers, as published previously [13].

Of 100 patients with clinical suspicion of leishmaniasis, 25 were confirmed by parasitology and serology to have leishmaniasis. Of the 25 patients, 19 (76%) were male and six (24%) were female. The age of patients ranged from 2.5 years to 61 years with overall mean of 25 ± 17.3 years. Of these only six (24%) were found to be HIV–*Leishmania* co-infected. One patient had triple infection of *Leishmania*, *Mycobacterium tuberculosis* and HIV. The anti-leishmania antibody end-point titers were found to be significantly lower in co-infected cases ($P < 0.017$) than the HIV uninfected patients (Fig. 1).

Visceral leishmaniasis is characterized by a strong humoral response in otherwise immunocompetent patients [12]. This phenomenon has been exploited to devise various non-parasitological non-specific diagnostic methods, such as aldehyde test, Sia test and albumin : globulin ratio determination [14]. In the past three decades some specific antibody detection methods have been developed which were used in this study. In 19 HIV-negative patients the anti-*Leishmania* antibody titres were found to be very high (upto 4×10^6), as reported earlier [12]. However, the antibody response in six co-infected patients was significantly ($P < 0.017$) low (Fig. 1). Similar findings have been reported by Medrona *et al.* from Spain [15]. In our patients, four of the six (66.6%)

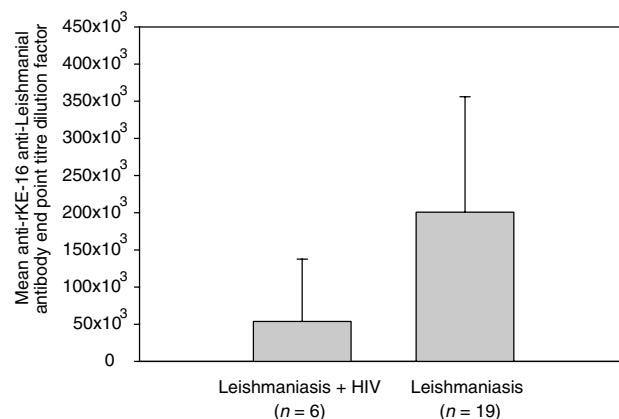


Fig. 1. Mean anti-rKE-16 anti-*Leishmania* antibody end-point titers in Leishmaniasis patients with HIV ($n = 6$) and without HIV co-infection ($n = 19$).

Leishmania–HIV co-infected patients showed end-point titers below $1 : 10 \times 10^4$ dilutions, whereas in all HIV-negative patients, the antibody titers were higher than $1 : 10 \times 10^5$.

Geographically, of six cases four were from Bihar (Eastern India), an old endemic state, and two were from Uttaranchal (North India). The latter has recently been found to be a new focus of leishmaniasis [7].

Both HIV and *Leishmania* spp. are obligate intracellular parasites. It is reported that like HIV, *Leishmania* infection causes depletion of T-helper cells [16]. HIV-related immunosuppression increases the risk of reactivating leishmaniasis by 100–1000 times in endemic areas and enhances the chances of drug resistant leishmaniasis [17].

The present study presents two major observations. First, HIV–*Leishmania* coinfection is an emerging problem in India and more awareness is required. Second, humoral response to *Leishmania* is severely compromised in HIV co-infected patients. Therefore, one may think of separate test cut-off values for making the diagnosis of leishmaniasis in HIV infected patients. It will also be advisable for manufactures of diagnostic kits and tests to mention this limitation and prepare appropriate test guidelines.

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HIV optimism does not explain increases in high-risk sexual behaviour among gay men of positive or negative HIV status in Sydney, Australia

Many studies have found an association between HIV optimism and unsafe sex [1–9], and Stolte *et al.* [8], in a cohort study, noted a possible causal link between optimism and unsafe sex. Yet HIV optimism does not appear to drive increases in unsafe sex over time. Elford *et al.* [1,2] and Williamson and Hart [7] concluded that the increases in unsafe sex between 1998 and 2001 in London, and between 1999 and 2002 in Glasgow and Edinburgh, respectively, could not be explained by HIV optimism alone. In light of these studies, we investigated the role of HIV optimism in relation to an increase in unprotected anal intercourse with casual partners (UAIC) in Sydney, Australia, between August 1999 and August 2002.

Our study consisted of cross-sectional community-based surveys of gay men. Men were recruited through a range of sites in Sydney including gay social venues, gay sex-on-premises venues, gay men's clinics and the Gay and Lesbian Mardi Gras Fair Day [10]. The total sample over the 3 year period comprised 3243 men aged 18 to 74 years; 3034 (94%) described themselves as homosexual and 209 (6%) as bisexual; 767 (24%) were HIV positive, 2178 (67%) were HIV negative, and 298 (9%) did not know their HIV status.

UAIC was measured as 'any UAIC' versus 'no UAIC' in the last 6 months. HIV optimism was measured using four items from a 12-item HIV optimism scale developed and

validated among gay men in Australia [10]: 'New HIV treatments take the worry out of sex'; 'The availability of treatment (PEP) immediately after unsafe sex makes safe sex less important'; 'HIV is less of a threat because the epidemic is on the decline'; 'HIV/AIDS is a less serious threat than it used to be because of new treatments'. The questions were the same at all time points (cf. Elford *et al.* [1] and Stolte and Dukers [4]). Low scores on the optimism scale represented scepticism and high scores optimism. The scale coefficient alpha was 0.80.

Between August 1999 and 2002, UAIC increased among gay men in Sydney from 32.2% to 40.5% (linear trend $P = < 0.001$). Men who reported any UAIC (1207) had higher levels of optimism than men who reported no UAIC (2036): mean optimism score 1.71 (SD, 0.56) versus 1.53 (SD, 0.52) ($P = < 0.001$). Yet optimism levels did not change significantly over the period ($P = 0.248$).

HIV status was included in the analyses. A greater percentage of HIV-positive men (58%) than other men (31%) engaged in UAIC ($P = < 0.001$), and HIV-positive men had higher optimism scores than other men: mean optimism score 1.66 (SD, 0.56) versus 1.57 (SD, 0.55) ($P = < 0.001$), as found in some previous research [5,11].

When year of survey, optimism and HIV status were entered into a multivariate logistic regression, all three variables remained significant after controlling for the

Table 1. Main effects model: variables associated with unprotected anal intercourse with casual partners in multivariate logistic regression ($n = 3243$) of the final model^a.

	Odds ratio (95% confidence interval)	P value
Year of survey	1.08(1.04–1.11)	< 0.001
Optimism	1.82(1.58–2.09)	< 0.001
HIV status (reference group HIV negative)		
Untested/unknown status	0.95(0.73–1.25)	0.730
Positive status	2.13(2.61–3.68)	< 0.001

^aModel $R^2 = 0.111$, $P = < 0.001$.

other variables. Rates of UAIC among gay men increased over time, optimism was greater among gay men who engaged in UAIC, and HIV-positive men were more likely than other men to engage in UAIC (Table 1). All possible interactions between these three main effects were tested but none was significant.

These results among Australian gay men between 1999 and 2002 support and confirm the earlier findings in England and Scotland during the same, or a similar, period [1,7]. It is noteworthy that HIV optimism itself remained essentially constant over time. If HIV optimism did explain the increase in sexual risk over time, either year of survey would not remain significant in the multivariate analysis or there would be a significant interaction between year of survey and optimism [7]. Neither of these was the case. Therefore, our results show that HIV optimism, although it is related to unsafe sex and although it predicts unsafe sex in multivariate analysis (as shown in Table 1) does not explain the *increase* in high-risk sexual behaviour *over time*.

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