Correspondence

AIDS 2003, **17**:2001–2013

Ability to generate synthetic peptides that immunologicaly mimic HIV-1 tat regulatory protein

The problem of generating broadly cross-reactive neutralizing antibody responses that specifically target immunogenic regions of HIV-1 remains to be solved [1]. The use of synthetic peptides generated with techniques based on pattern property algorithmic procedures concerning the primary structures of various members of a closely related protein family has been suggested as one potential solution to this problem. Fourier transformation analysis of the primary structures of various members of a closely related protein family has been suggested as one potential solution to this problem. Characteristic periodic features within the amino acid sequences of related polypeptides or proteins can be compared as digital arrays using discrete Fourier transformation of numerical representations of their amino acid sequences, employing different amino acid parameters as descriptors of their molecular properties [2]. With such generic informational analysis methods, regions of similar secondary structure, such as amphipathic α-helices and β-sheets, or regions encompassing other physicochemical or protein-ligand binding properties, can be identified. In more recent investigations, we have shown that several 20-mer peptides (DDALYDDKNWDRAPQRCYYQ) derived by Fourier transformation analysis of HIV-1 and sharing no sequence homology with the parent proteins, were able to generate antisera (B1) that specifically cross-reacted with HIV-1 envelope proteins [3].

Following the demonstration of the important role of extracellular Tat in HIV-1 replication and in the modulation of cellular functions, vaccination against Tat was proposed as a protective weapon against AIDS [4]. In this study, we investigate the capacity of these Fourier transformation derived antibodies to recognize the fragment representatives of regulatory protein Tat. The ability of the anti-B1 peptide sera to bind specifically to Tat protein was examined using enzyme-

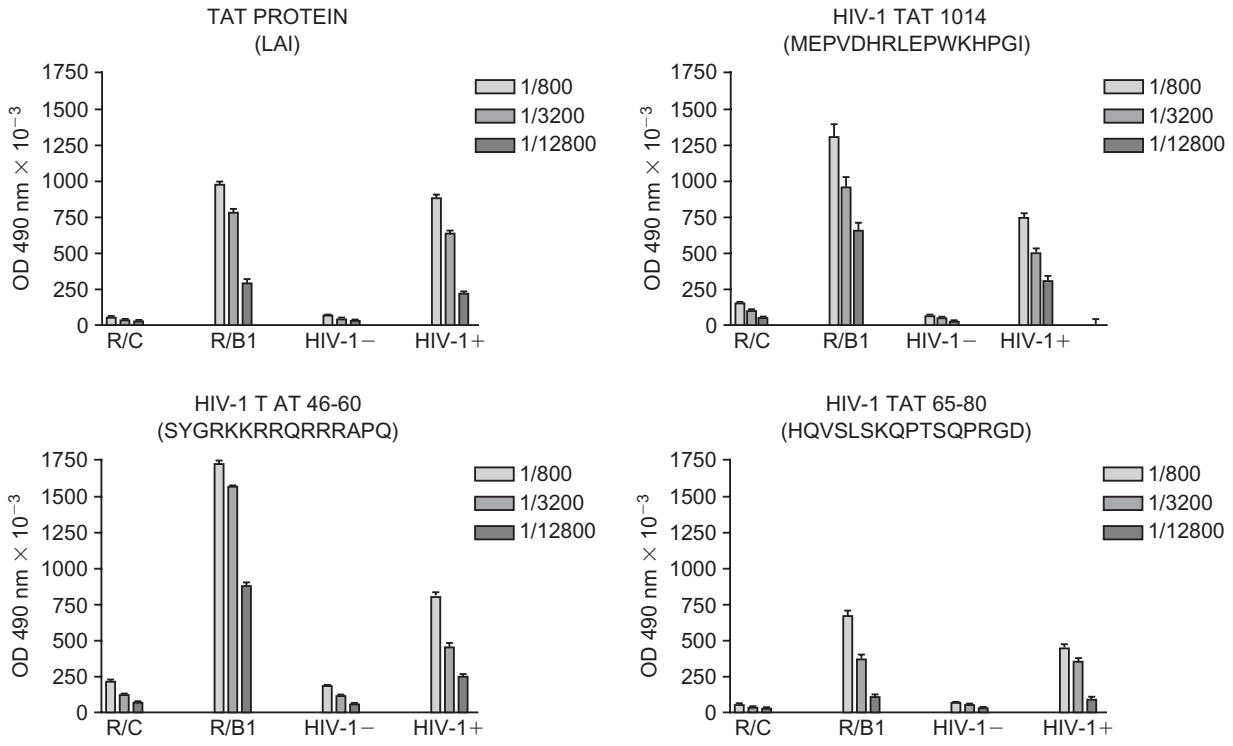

Fig. 1. Binding of antisera to Tat protein and Tat peptides. Ninety-six-well plates were coated with 50 ng Tat protein or Tat peptides as indicated. Bound antibodies were obtained by enzyme-linked immunosorbent assay. Each experiment was performed in triplicate and data are indicated as optical density (OD) plus SEM at 490 nm. Antibodies: R/C,pre-immune rabbit; R/B, B1 immunized rabbit; HIV-1−, human control serum; HIV-1+, slow progressor serum; boxes, serum dilution.

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linked immunosorbent assay procedures with the synthetic peptides and the whole protein derived from HIV-1_{LAI} isolate. Immune and pre-immune sera were tested from the NZ white rabbit. Immune sera were selected on the basis of high titres against the immunizing peptide [3]. We also assessed sera from a healthy seronegative donor and from a slow progressor HIV-1-seropositive individual and pre-immune rabbit serum as controls.

The ability of anti-B1 and control antisera to recognize Tat protein and the various synthetic peptides was determined by enzyme-linked immunosorbent assay using 96-well plates (Costar, Cambridge, MA, USA) coated with 50 ng of Tat protein (CNRS, Marseille, France) or peptides (ANRS, Paris, France). The results of these assays are shown in Fig. 1. As is evident from the data, antisera raised against B1 showed strong reactivity with full-length Tat protein (HIV-1_{LAI} isolate) as well as with all three Tat peptides ($Tat_{1–14}$, $Tat_{46–60}$ or $Tat_{65–80}$). The largest immune response was observed with Tat protein, the proline-rich (1–14) and basic core (46–60) regions compared with the 65–80 domain (30, 50 and 100% increase in OD mean value, $P < 0.005$). In contrast, sera from seronegative individuals as well from pre-immune rabbits exhibited low binding with antigens. More interestingly, slow progressor serum showed a higher titre comparable to anti-B1 serum (Fig. 1).

The studies presented here have therefore shown that by using a protein pattern algorithm based on Fourier transformation analysis methods, it was possible to develop synthetic peptides that replicated multiple epitopic regions of the HIV-1 Tat protein, despite the fact that these peptides share no sequence homology with the parent proteins. In subsequent papers we will describe the results of investigations addressing the ability of anti-peptide sera to neutralize HIV-1 in in-vitro virus neutralization assays. Our observations may thus provide a potential advance in vaccine research by providing a novel strategy to develop a synthetic AIDS vaccine beneficial to a broad-based immunity.

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Jean-Michel Biquard[a], Jean-Pierre M'Bika[b], Velibor Krsmanovic[c] and Ammar Achour[b], *[a]Laboratoire d'Hématologie, Faculté de Médecine St Antoine, 75012 Paris, France; [b]Université René Descartes Paris V, Laboratoire Des Interférons et de la Sarcolectine, Centre Biomédical des Saint Pères 45, 75270 Paris Cedex 06, France; and [c]Laboratoire de Biologie Moleculaire, Centre de Génétique Moléculaire et Cellulaire, CNRS UMR 106, Université Claude Bernard Lyon I, 69622 Villeurbanne Cedex, France.*

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HIV (AIDS), maternal malaria and prolactin

The dual infection of HIV and maternal malaria has been the subject of recent and intensive investigation [1–3]. The back-to-back reports coming from the Kenyan laboratory of Ayisi *et al.* [4] and Van Eijk *et al.* [5] exhibited interesting data that require further examination. The findings that 'the typical gravidity-specific pattern of malaria in pregnancy disappeared in HIV-seropositive women' [5] (p. 595), and that 'HIV-seropositive women with malaria were twice as likely to have anaemia than HIV-seronegative women with or without malaria' [4] (p.585) certainly present us with an enigma when viewed against the single pathology of malaria in pregnancy.

Previously, I suggested that the hormone prolactin be studied as having a possible role in the severe anaemia witnessed in human malarial infection (increased prolactin is seen in patients with anaemia undergoing dialysis) [6]. Moreover, because prolactin has now been seen to play a role immunomodulating T helper type 1 cytokines, I hypothesized that prolactin, as a pregnancy-related hormone, plays a role in the T helper cell types 1/2 disequilibrium that is witnessed in maternal malaria [7], even prompting the question, 'Is prolactin the missing piece of the maternal malaria puzzle?' [7] (p. 1314).

To date, a significant literature exists linking hyperprolactinaemia to HIV infection [8,9]. Regarding the findings and issues of parity, concerning the dual infections of HIV and maternal malaria, it should be kept in mind that following a normal uninfected first pregnancy, reduced levels of circulating prolactin and decreasing nocturnal and diurnal prolactin surges occur in the subsequent pregnancies of women and rats [10]. Could it be that in these dual infections we are witnessing a hyperprolactinaemia in the multigravidae?

Roy Douglas Pearson, *University of Toronto, Gerstein Science Information Centre, 9 Kings College Circle, Toronto, Ontario, Canada, M5S 1A5.*

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Urinary pH in HIV-infected adults in Ivory Coast and in France

In industrialized countries, indinavir-related side-effects include urinary stones in 4–12% of patients [1]. Recent data suggest that urinary stones may occur less frequently in sub-Saharan patients taking indinavir [2–4]. The risk of urinary stones increases with urinary pH. In water, indinavir solubility is 100 mg per milliliter at pH 3.5 and 0.03 mg per milliliter at pH 6.0, and immediate precipitation occurs at pH above 6.5 whatever the concentration [5]. Whereas urinary pH from adults living in industrialized countries has long been shown to be usually acid [6], data on urinary pH in sub-Saharan African adults are scarce. We made a preliminary study to compare the urinary pH between HIV-infected adults living in Abidjan, Ivory Coast and in Paris, France.

In June 2002, consecutive adults consulting in two HIV outpatient clinics in Abidjan and in Paris were asked to participate in the study. Exclusion criteria were diuretic treatment, pregnancy, and ongoing symptoms, including diarrhoea, vomiting, urogenital symptoms, diabetes mellitus, and fever. Age, sex, geographical origin, last available CD4 cell count, drugs taken within the past week, body weight, body height and date of menstruation in women were recorded through standardized questionnaires. Urine samples were collected to measure pH, leukocytes, albumin, erythrocytes, nitrite and urine density using a reagent urinary strip (Multistix 8 SG; Bayer Corporation, USA).

A total of 189 patients were included in the study (Abidjan: 91, Paris: 98). All patients in Abidjan were of sub-Saharan African origin. In Paris 52, 11 and 37% of patients were of sub-Saharan African, north-African, and European origin, respectively. Overall, there were statistical differences between Abidjan and Paris in terms of the percentage of men (30 versus 61%, $P < 0.001$), mean body mass index (21.8 versus 23.4 kg/m^2, $P < 0.001$), mean time from last available CD4 cell count (117 versus 76 days, $P < 0.001$), last available CD4 cell percentage (18.0 versus 22.3%, $P = 0.005$), and the percentage of patients receiving antiretroviral multitherapy (34 versus 66%, $P < 0.001$) or cotrimoxazole (70 versus 30%, $P < 0.001$). The difference was not statistically significant for the following variables: mean age (35.9 versus 38.1 years, $P = 0.07$), last available CD4 cell count (352 versus 410 cells/mm^3, $P = 0.13$), and percentage of patients receiving indinavir (10 versus 5%, $P = 0.21$). In patients receiving antiretroviral treatment in Abidjan, 58% received a two nucleoside reverse transcriptase inhibitors (NRTI) plus one protease inhibitor regimen, 26% a two NRTI plus one non-nucleoside reverse transcriptase inhibitor regimen, 0% a three NRTI regimen, and 16% other regimens (versus 55, 31, 5 and 9% in Paris, respectively).

Overall, the mean urinary pH was 6.32 [standard deviation (SD) 0.66] in Abidjan and 5.91 (SD 0.94) in Paris ($P < 0.001$). There was no significant difference

Table 1 Variables associated with urinary pH.

	Number of patients		Univariate analysis		Multivariate analysis	
	pH < 6 (n = 40)	pH ⩾ 6 (n = 149)	OR (95% CI)	*P*	OR (95% CI)	*P*
Centre						
Ivory Coast	2	89				
France	38	60	0.04 (0.008–0.15)	< 0.001	0.08 (0.02–0.39)	0.002
Sex						
Male	27	60				
Female	13	89	3.08 (1.47–6.45)	0.003	1.55 (0.62–3.88)	0.35
Age (years)						
> 37	26	74				
< 37	14	75	1.88 (0.91–3.89)	0.09	0.84 (0.30–2.31)	0.73
Geographical origin						
Sub-Saharan Africa	18	124				
North Africa	6	5	0.12 (0.03–0.44)	0.001	0.35 (0.07–1.72)	0.20
Europe	16	20	0.18 (0.08–0.41)	< 0.001	0.71 (0.25–1.98)	0.51
Body mass index						
> 22 kg/m^2	28	73				
< 22 kg/m^2	12	76	2.43 (1.15–5.14)	0.02	1.87 (0.74–4.75)	0.19
CD4 cell count						
> 200 cells/mm^3	35	107				
< 200 cells/mm^3	5	42	2.75 (1.01–7.49)	0.05	1.39 (0.40–4.84)	0.61
Drugs						
No indinavir	36	139				
Indinavir	4	10	0.65 (0.19–2.18)	0.48	–	–
No cotrimoxazole	37	89				
Cotrimoxazole	3	60	8.31 (2.45–28.20)	0.001	3.78 (0.93–15.29)	0.06
Leukocyturia						
No	37	118				
Yes	3	31	3.24 (0.94–11.21)	0.06	1.41 (0.32–6.14)	0.65
Albuminuria						
No	26	64				
Yes	14	85	2.47 (1.19–5.10)	0.01	1.42 (0.58–3.48)	0.44

CI, Confidence interval; OR, odds ratio.

in terms of urine density (1.020 versus 1.019, $P = 0.63$), the presence of nitrite (2 versus 0%, $P = 0.23$) and the presence of erythrocytes (5 versus 9%, $P = 0.67$). There were significantly more samples with leucocyturia (16 versus 1%, $P = 0.003$) and albuminuria (26 versus 5%, $P < 0.001$) in Abidjan than in Paris. As shown in Table 1, the variables associated with a urinary pH less than 6 in univariate analyses were the city (Paris), sex (male), older age, origin other than sub-Saharan Africa, higher body mass index, higher CD4 cell count, the absence of cotrimoxazole treatment, and the absence of albuminuria. In multivariate analysis, the only variable that remained associated with the urinary pH was the city.

When considering only patients of sub-Saharan African origin, the mean urinary pH was 6.32 for those living in Abidjan and 5.92 for those living in Paris ($P < 0.001$). When considering only patients living in Paris, the mean urinary pH was not significantly different between patients of sub-Saharan (5.92) and European origin (6.0) ($P = 0.70$).

Further studies should confirm these findings, and explore whether they could be caused by dietary or genetic differences. In our study, patients from sub-Saharan and European origin living in Paris had similar urinary pH, reinforcing the dietary hypothesis. In an old report of urinary pH values in women living in Uganda, the mean pH was significantly higher in women of Ugandan origin than in women of European origin, which could be consistent with both hypotheses [7].

In all cases, a higher urinary pH in African adults living in sub-Saharan Africa is not likely to explain the lower frequency of indinavir-related urinary stones in subsub-Saharan Africa. Apart from a high urinary pH, the other mechanism causing urinary stones is the concentration of the drug or its metabolites in urine [1]. Genetic differences in the metabolism of indinavir could be hypothesized to be associated with the different frequency of indinavir-associated urinary stones, as suggested by a recent study showing an increasing risk of urinary stones in Caucasian patients in a cohort of HIV-infected adults in the USA [8].

Emmanuel Mortier[a], Siaka Toure[b], Catherine Seyler[b], Martine Bloch[a] and Xavier Anglaret[b,c], *[a]Department of Internal Medicine, Hospital Louis Mourier, AP-HP, Colombes, France; [b]Programme Pac-ci, Abidjan, Côte*

d'Ivoire; and [c]Unité INSERM 593, Université Victor Segalen Bordeaux 2, Bordeaux, France.

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Antiretroviral therapy in a primary care clinic in rural South Africa

Data from studies demonstrating potential models for the delivery of antiretroviral therapy (ART) have shown ART to be effective in resource-limited settings [1,2]. It is unclear whether these models can be generalized to other settings, as data on the use of ART in primary care, non-research settings are not available.

This current study was designed to describe patients prescribed ART in a private primary care clinic in rural Kwazulu-Natal, South Africa. A retrospective chart review was undertaken in January and February 2002 to describe demographic variables, financing mechanisms, current drug usage patterns, adherence (as measured from drug prescription renewals) and effectiveness of therapy, as reflected by changes in the CD4 cell count and viral load.

Seventy-two patients were prescribed ART through the clinic between March 1999 and the study period. Seventy out of the 72 patients (97.2%) were black and two were white (2.8%). Forty-two patients (58.3%) were women. The median age at diagnosis was 33 years (6 months to 55 years). Employment data was available for 43 patients: 26 out of 43 (60%) were teachers, 12 (28%) were skilled labourers and five (12%) were policemen. Fifty-four patients (75%) were tested for HIV after presenting with clinical signs of infection, six (8%) were tested because of contact (three patients), pregnancy (two patients) or for insurance (one patient). The reasons for testing were unknown in 12 cases. Tuberculosis (12 patients), lymphadenopathy (eight patients), weight loss (eight patients) and shingles (eight patients) were the most common presenting conditions. Twenty-five patients (44%) with charted reasons for testing presented with an AIDS-defining illness. The median haemoglobin level was 10.4 g/dl (range 6.6–15.7) in women and 12.8 g/dl (range 6.9–15.3) in men. The median CD4 cell count was 245 cells/mm^3 (range 23–650) and the median viral load was 102 917 (range $<$ 400 to $>$ 750 000) copies/ml. (Table 1).

Sixty-two patients (86%) had a medical aid scheme that covered ART, and 10 paid for their drugs out of pocket. In the medical aid group, insurers refused ART to seven patients because their CD4 cell count was greater than 350 cells/mm^3. Eight patients were not started as their insurance had expired or no longer covered ART.

Table 1. Patient characteristics at initial visit.

Sex (N = 72)	
Male	30
Female	42
Age (years)	33 (0.5–55)
Race (N = 72)	
Black	70
White	2
Employment (N = 43)	
Teacher	26
Skilled labour	12
Policeman	5
Haemoglobin (mg/dl)	
Male	12.8 (6.9–15.7)
Female	10.4 (6.6–16.1)
CD4 cell count (cells/μl)	245 (23–650)
Viral load (copies/ml)	102 917 ($<$ 400 to $>$ 750 000)
Payment mechanisms	
Medical aid	62
Cash	10
Follow-up data	
Drug regimen (N = 57)	
Triple therapy	31
Dual nucleoside therapy	17
Hydroxyurea-containing therapy	7
Single nucleoside therapy	2
Adherence (N = 36)	
$>$ 90%	8
80–90%	4
70–80%	3
$<$ 70%	21
Viral load $<$ 400 copies/ml	12 (33%)
CD4 cell count (cells/μl)	315 (21–647)

Of the remaining 57 patients, 31 (55%) received triple therapy, 17 (30%) received double therapy, seven (12%) received a hydroxyurea-containing regimen, and two (3%) received single nucleoside therapy. The most commonly prescribed regimen was zidovudine, lamivudine and efavirenz (37%). No patients without medical aid received triple therapy.

Adherence data were available for 36 patients and were based on the number of prescriptions filled. Eight patients (22%) were more than 90% adherent and 21 (58%) were less than 70% adherent. The reasons for non-adherence were rarely known, but included patients thinking that a month of therapy was sufficient, sharing with a spouse and medical aid funds being exhausted.

Follow-up data were available for 37 patients (two on single therapy, eight on double therapy, six on hydroxyurea regimens, and 21 on triple therapy). Twelve patients (32%) achieved a viral load of leas than 400 copies/ml. The CD4 cell count at a mean of 217 days after initiation of therapy increased 70 cells/mm above baseline ($P < 0.05$). Haemoglobin levels were unchanged from the initial visit and no liver function abnormalities were noted in the 15 patients who were tested after the initiation of ART.

This study describes the use of ART in a real life primary care setting in rural Africa, and reveals a number of barriers to effective ART in an area with relatively advanced infrastructure and monitoring. First, patients presented late in the course of their disease; almost half had CD4 cell counts of less than 200 cells/mm^3. Second, only 55% received treatment that followed the World Health Organization (WHO) guidelines for resource-limited settings [3], no patients without insurance received recommended therapy. Third, adherence was poor when measured by prescription refill. The possible reasons suggested here include medical aid funds being exhausted for the year, poor patient education about ART, and a lack of provider training and expertise. Finally, the virological and immunological responses were suboptimal, which may be the result of inadequate combinations of antiretroviral drugs or poor adherence.

Studies performed in centres with considerable support for providers and patients have shown that ART can be safe and effective in resource-limited settings [1,2]. Our study shows that when ART is introduced without adequate support for providers and patients the results can be disappointing. Discovering the reasons for success in these more controlled settings will be important. There is an immense need for operational research in antiretroviral delivery in resource-limited settings that not only advocates the use of these medications but describes ways to integrate them into existing private and public sector activities.

***Nigel Livesley*[a] *and Chester Morris*[b]** [a]*Clinical Research Fellow, Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, Canada, and* [b]*Department of Medical Microbiology, Unviersity of Manitoba, Winnipeg, Manitoba, Lecturer, Department of Community Health, University of Nairobi, Nairobi, Kenya.*

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Intensive chemotherapy with rituximab is safe and effective in AIDS non-Hodgkin's lymphoma

Spina *et al.* [1] recently presented the results of the use of rituximab (a monoclonal antibody against the CD20 B-cell antigen) and an infusional cyclophosphamide, doxorubicin and etoposide (CDE) combination in the treatment of AIDS-related non-Hodgkin's lymphoma (NHL). Coiffier *et al.* [2] also analysed the results of their randomized study of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy versus CHOP plus rituximab in non-HIV-infected patients with diffuse large B-cell NHL. Using two different standard dose regimens, both studies gave impressive and superimposable results in terms of complete remission (CR) rates and survival. The recent introduction of highly active antiretroviral therapy has improved immune function in HIV-positive patients and allowed more aggressive approaches to AIDS-related NHL (high-dose chemotherapy [3] or stem-cell transplantation [4]), which have been shown to be of interest in HIV-negative patients with aggressive NHL [5,6]. Together, these data prompted us to investigate

the feasibility and efficiency of the combination of a more aggressive chemotherapy regimen in association with rituximab in patients with AIDS-related NHL.

Six patients with aggressive AIDS-related NHL were treated with the following intensive regimen: one course of cyclophosphamide, vincristine and prednisone was used as a 'debulking' chemotherapy and was followed one week later by three courses of modified high-dose CHOP performed at 3 week intervals (cyclophosphamide 2000 mg/m^2; doxorubicin 50 mg/m^2). In order to treat or prevent central nervous system lymphoma involvement, one course of high-dose methotrexate (8000 mg/m^2, day 1) was given 3 weeks after the last CHOP course, followed 2 weeks later by high-dose cytarabine (8000 mg/m^2). Patients received five infusions of rituximab (375 mg/m^2) in association with the five intensive chemotherapy courses (CHOP $\times$ 3, methotrexate, cytarabine). Granulocyte colony-stimulating factor was used after the intensive chemotherapy courses from day 6 until neutrophil recovery. Radiotherapy was given 4 weeks after the last chemotherapy course for patients with bulky tumours at diagnosis or residual disease after treatment. All patients except one were treated by highly active antiretroviral therapy.

The median age of the patients was 41 years (range 36–76), there were four men and two women. Five patients were in first-line treatment, whereas one patient had a late relapse (> 2 years). The route of HIV contamination was heterosexual in two cases, homosexual in one, intravenous drug use in two and related to transfusion in one. The median CD4 lymphocyte count at lymphoma diagnosis was 158 cells/mm^3 (range 21–490). The median viral load at diagnosis was 32 000 copies/ml (range 0–576 000). All patients had high-grade NHL, i.e. diffuse large-cell lymphoma (three), Burkitt or Burkitt-like (two) and immunoblastic (one), and were positive for CD20. According to the Ann Arbor staging, all AIDS-related NHL were classified as stage III (three) or IV (three). According to the age-adjusted international prognostic index, one patient was stage 2 and five patients were stage 3.

On an intention-to-treat basis, patients received 95, 100, 100, and 74% of the planned doses of cyclophosphamide, doxorubicin, methotrexate and cytarabine, respectively. Grade 3 or 4 toxicity events were observed as follows: neutropenia (12), anaemia (nine), thrombocytopenia (nine), mucositis (two), bacterial infection (one, *Klebsiella pneumoniae*), fungal infection (one, *Candida albicans*), febrile neutropenia (eight), opportunistic infection (one, cytomegalovirus retinitis). One patient required platelet concentrate transfusion and four patients required at least one red blood cell concentrate transfusion. Dose reduction was not necessary for any patients.

A CR was achieved in five out of six patients. Interestingly, the patient in late relapse, who had previously been treated by CHOP chemotherapy, attained a CR with our modified CHOP plus rituximab regimen. Two patients died, one from NHL progression (non-responder patient) and one from *Pneumocystis carinii* infection 6 months after the end of treatment. The median follow-up of our study is too short (median 13 months, range 9–16) to draw conclusions from the overall or event-free survival. Nonetheless, our findings suggest that the combination of rituximab with intensive chemotherapy is safe, feasible, and may allow high CR rates in patients with AIDS-related NHL.

Jérôme Rey[a,b], Aude Charbonnier[a], Jean-Marc Schiano de Colella[a], Anne-Marie Stoppa[a], Isabelle Poizot-Martin[c], Jean-Albert Gastaut[a,c] and Régis T. Costello[a,b],
[a]Département d'Onco-Hématologie, [b]Laboratoire d'Immunologie des Tumeurs, Institut Paoli-Calmettes, and [c]CISIH Sainte Marguerite, Hôpital Sainte Marguerite, Université de la Méditerranée, Marseille, France.

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Disseminating knowledge about AIDS through the Indian family planning programme: prospects and limitations

There is growing concern that HIV is spreading to low-risk population groups and to women in India. Data from sentinel surveillance of women attending antenatal clinics in 2001 showed a prevalence of up to 1.75% [1]. There is also evidence of spread to rural areas: among a 1998 sample of 1251 women in a rural area accessible to the large city of Pune, Maharashtra, the prevalence was 1.2% [2]. Although generalization to the national level from regional data is not appropriate, and limited information is available about the actual prevalence of HIV in the rural areas of the different states, the large absolute numbers potentially at risk indicate a major challenge to India's health security.

A fundamental condition for protection of the population from HIV infection is the level of knowledge about the disease, which varies considerably between different states in India, between urban and rural areas and between men and women. Overall, 70% of urban and 30% of rural women had heard of AIDS in 1998–1999 [3]. A 2001 survey provided evidence that the urban–rural disparity persists, although overall levels of knowledge had improved [4]. Mass media-based efforts to increase knowledge for health protection are under way. We have attempted to quantify the prospects of using Indian family planning services to deliver information about HIV, by undertaking an analysis of the current status of AIDS knowledge in relation to current or intended use of family planning methods.

The 1998–1999 National Family Health Survey (NFHS-2) was utilized in the present study [3]. The survey (n = 90 303) included questions on AIDS knowledge, fertility and family planning use and intentions. The three aspects of AIDS knowledge to which yes/no responses were sought in the survey were awareness of AIDS, knowledge of whether AIDS can be avoided, and knowledge of whether the condom provides protection from AIDS.

Table 1 shows that, as a result of previous sterilization or subfertility, the national family planning programme would not have the capacity to address many women currently lacking knowledge of AIDS in rural India. Some 38% of the rural sample both lacked any knowledge of AIDS and did not require family planning services; 52% were both unaware that condom use can prevent infection and did not require family planning services. In absolute numbers, based on the estimate of 177 million eligible women in the reproductive age group for 2001 provided by the Government of India Department of Family Welfare [5] of whom we estimate 131 million reside in rural areas, these percentages would translate to 49 and 68 million women, respectively. Those who have been sterilized or experienced subfertility may be at greater risk of HIV infection through unprotected sex both within and outside marriage. The age at sterilization is currently declining, with a median of 25.7 years in the present survey, potentially increasing women's exposure to unprotected sex.

Table 1. Percentage of family planning use and knowledge of AIDS among women in the reproductive age group, rural and urban India, 1998–1999.

	Rural			Urban		
	No AIDS awareness	No knowledge that AIDS can be avoided[a]	No knowledge that condom can prevent AIDS	No AIDS awareness	No knowledge that AIDS can be avoided[a]	No knowledge that condom can prevent AIDS
FP service not required	37.94	43.91	52.53	16.35	26.45	43.07
May require FP services	30.20	34.32	39.61	11.54	18.87	30.59
Currently use IUD	1.55	1.91	2.41	0.93	2.04	4.04
Currently use condom	0.58	0.80	1.15	0.89	1.98	3.89
Sub-total	70.27	80.94	95.70	29.71	49.34	81.59
	Have AIDS awareness	Have knowledge that AIDS can be avoided	Have knowledge that condom can prevent AIDS	Have AIDS awareness	Have knowledge that AIDS can be avoided	Have knowledge that condom can prevent AIDS
FP service not required	16.00	10.04	1.71	33.15	23.04	6.41
May require FP services	11.64	7.52	1.91	26.39	19.07	7.37
Currently use IUD	1.16	0.80	0.32	4.87	3.77	1.76
Currently use condom	0.93	0.70	0.36	5.88	4.78	2.87
Sub-total	29.73	19.06	4.3	70.29	50.66	18.41
Total	100.00	100.00	100.00	100.00	100.00	100.00
	N = 66 602	N = 66 592	N = 66 227	N = 23 633	N = 23 626	N = 23 630

FP, Family planning; IUD, intrauterine device.
Differences in the total number of cases within rural and urban areas are the result of missing values.
[a]Includes 'do not know' response.

On the positive side, the analysis shows that up to 30% of rural women currently lack any knowledge of AIDS but may also use family planning services in the future. In absolute numbers this represents approximately 39 million women. Many women have heard of AIDS but are unaware of condom use as a specific measure for protection against HIV infection. Including them, an estimated 52 million rural women both lack the knowledge that condom use can prevent infection and are potential users of family planning services. In urban areas, despite a better knowledge of AIDS, 82% of respondents were unaware that condom use can prevent infection. Overall, however, the current use of temporary contraceptive methods is very low both among those with and those lacking AIDS-related knowledge. Although research-based male [6] and female condom promotion strategies are required, for women who have been sterilized alternatives such as vaginal microbicides promoted through social marketing may offer protection should they prove to be clinically effective.

This survey did not access unmarried but sexually active women, clearly an important group with regard to the transmission of a sexually transmissible disease. Furthermore, it may be argued that in the Indian context of sexual relations, men's sexual behaviour rather than that of married women is of more pressing concern, given the limited capacity of married women to negotiate sexual relations. On the other hand, we believe that the lack of provision of basic knowledge about the disease and its mode of transmission should be considered a denial of the human right to life, liberty and security of person, even if the possession of such knowledge is not sufficient in itself to afford protection.

Saseendran Pallikadavath and R. William Stones, *'Opportunities and Choices' Programme, University of Southampton, Southampton, UK.*

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Women have a greater immunological response to effective virological HIV-1 therapy

In HIV-1 infection, the HIV-1-RNA viral load and CD4 T-cell counts are used as prognostic indicators, which serve as the bases for recommending antiviral therapy [1]. In addition, in individuals whose HIV-1 viral load significantly decreases on combination antiviral therapy, CD4 T-cell peripheral blood counts usually increase [2]. These observations have been made in clinical studies that primarily enrolled adult males [3]. A few studies have recently shown that average viral loads at given CD4 T-cell counts were lower in women than in men [4,5]. We are not aware of any studies that specifically evaluate the sex difference in the immunological responses of patients who have a sustained virological response to therapy. To address this issue, we compared the immunological responses of men with those of women in patients who had achieved sustained virological suppression (< 400 copies HIV-1-RNA/ml) at 24 weeks.

We retrospectively collected data on all patients of an inner city clinic. A patient was considered eligible if: (i) he or she had a pre-therapy viral load greater than 400 copies/ml on more than two consecutive measurements; (ii) his or her viral load decreased to less than 400 copies/ml and remained undetectable at 24 weeks after the initiation of therapy; and (iii) he or she had CD4 T-cell counts performed within 2 weeks before initiating therapy and then 24 weeks after initiating therapy. Exclusion criteria included a failure to sustain virological suppression, an antiretroviral regimen change during the study period secondary to documented resistance, and incomplete laboratory values. HIV-1 viral loads (using reverse transcriptase–polymerase chain reaction methodology) and CD4 T-cell counts were routinely performed by LabCorp (CD4 T cells: Raritan, NJ, USA; and HIV plasma RNA viral loads: Research Triangle Park, NC, USA). Statistics were calculated using SAS version 8.0 (SAS Systems Inc., Cary, NC, USA).

We reviewed 450 charts and excluded 337 individuals, on the basis of the criteria listed above. Data from 53 women and 60 men were analysed (Table 1). Demo-

Table 1. Sex differences in CD4 cell response.

Sex	Age (mean)	Viral load[a] (mean)	Initial CD4 cell count[b] (mean)	Final CD4[c] (mean)	ΔCD4[c] (mean)
Female (N = 53)	42	5.19	268	438	170
Male (N = 60)	41	5.14	247	349	100

ΔCD4, CD4 T-cell count change.
[a]HIV-1 viral load $\log_{10}$ copies/ml of plasma before therapy.
[b]CD4 T-cell count measured just before the initiation of therapy.
[c] CD4 T-cell count measured at 24 weeks after the initiation of therapy.

graphically, 49% of patients were African American, 30% were Hispanic, and 21% were Caucasian. The majority of women, 70%, acquired HIV through heterosexual contact; 32% of male patients had sex with men as their risk factor; 0.5% acquired HIV through infected blood products. All others were former intravenous drug users. Thirty per cent of both groups were naive to anti-HIV therapy.

The initial CD4 T-cell count and viral load averages were similar in both groups (Table 1). However, the mean of the CD4 T-cell count change (ΔCD4+), was much higher in women than in men (women, 170 cells/μl versus men, 100 cells/μl). The difference in ΔCD4+ was statistically significant ($P = 0.0074$ as determined by the Wilcoxon rank sum test). Multivariable analyses were carried out using regression, and included the patient's age and entry viral load. These analyses failed to show any contribution by these variables. In addition, the initial viral load, the initial CD4 T-cell count, and the final CD4 T-cell count were not statistically different between the two sexes, by rank sum test.

All patients received combination antiviral therapy. Thirty per cent of both groups were treated with a non-nucleoside reverse transcriptase inhibitor and two nucleoside reverse transcriptase inhibitors; 5% were treated with three nucleoside reverse transcriptase inhibitors. Protease inhibitors were used in 61% of men and women.

Studies on the differences in sex response in other disease states have been carried out on animals and humans [6]. However, no report known to us has suggested that there is a sex difference in response to therapy of an infectious disease. Our data reveal that, among virological responders, women have a greater immunological response.

The reasons for this difference are not clear. As shown, no other obvious variable could explain the observed immunological response difference. Age, initial CD4 T-cell count, and initial viral load were similar in the two groups. The therapies used were similar. Therefore, sex is the only variable in this study that correlates with the immunological response difference. The average CD4 T-cell increase in men is 100 cell/μl. Perhaps the immunological response difference seen in this study is secondary to an unexplained factor that reduced the immunological response in men. However, in previous studies that measured CD4 T-cell count changes over time, an average increase of approximately 100 cells/μl was also seen at 24 weeks after initiating therapy [7]. Therefore, it is unlikely that the difference observed in our study is secondary to a reduced immunological response in the group of male patients. This study is the first to analyse the immunological response difference between women and men in patients who respond virologically. The larger increase in CD4 T-cells seen in women suggests that significant pathological differences may exist between the two sexes. Our findings warrant further investigation of the immunological differences between the two sexes.

Diana G. Finkel[a], Genevieve John[a], Bart Holland[b], Jihad Slim[a] and Stephen M. Smith[a,b], *[a]Saint Michael's Medical Center, Newark, NJ, USA; and [b]The New Jersey Medical School – UMDNJ, Newark, NJ, USA.*

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Response to 'High-risk sexual behaviour increases among London gay men between 1998 and 2001: what is the role of HIV optimism?'

With interest we read the paper on HIV optimism and sexual behaviour among gay men by Elford *et al.* [1] in a previous issue of *AIDS*. As all studies concerning the association between HIV optimism and high-risk sexual behaviour are currently based on cross-sectional data at one timepoint [2–5], their study, using cross-sectional data at four timepoints, contributes to an understanding of the changes over time. The authors concluded that it is unlikely that HIV optimism can explain the increase in high-risk sexual behaviour in London gyms. Although this might be true, the study is hampered by some methodological issues that might compromise their findings and raise concerns about the validity of such a conclusion.

First, the authors report that they have changed the answering categories on the two optimism items from a five-point linear scale ('not at all'; 'a bit'; 'somewhat'; 'quite a lot'; and 'a lot') in the cross-sectional studies in 1998 and 1999, to a four-point scale ('strongly disagree'; 'disagree'; 'agree'; 'strongly agree') in 2000 and 2001 [1]. Consequently, the definition of being 'optimistic' changed. In the first 2 years men were considered optimistic when they answered the two optimism items with 'a bit', 'somewhat', 'quite a lot', or 'a lot', whereas in the last 2 years they were considered optimistic when they answered 'agree' or 'strongly agree'. Results show that the level of optimism decreased remarkably after the year 2000. Although the authors mentioned that the level of optimism is possibly slightly overestimated in the period before the year 2000 because of discontinuity in the measurement of HIV optimism, they argued that it is unlikely that the change has introduced a major source of bias. However, we feel that the discontinuity could generate an important bias, not only in the optimism levels but also in the levels of unprotected anal intercourse among optimistic and non-optimistic men. Consequently, the validity of the univariate and multivariate results as presented in this study is arguable.

Second, men who filled in the questionnaire more than once were excluded in the multivariate analyses but not in the univariate analyses [1], resulting in different sample sizes used throughout the paper. This creates difficulties in the interpretation of the multivariate results. Are the adjusted effects of 'year of survey' and 'optimism 1' among HIV-negative individuals in the multivariate results really higher than the unadjusted effects, or is it a result of bias introduced by using a smaller sample in the multivariate analysis? Reanalysing the univariate results using the same sample size as in the multivariate analyses would facilitate a better understanding of the multivariate effects and the confounding role of the different covariates in the model.

Finally, the behavioural dynamics in homosexual populations are known to be very complicated [6]. Some men change to risky behaviour, some men to more preventative behaviour, whereas other men do not change their behaviours at all. Looking at the population level, as was done in the study by Elford *et al.* [1], cannot reveal the complicated behavioural dynamics at an individual level. At an individual level, treatment-related optimism appears to be a factor that increases high-risk sexual behaviour [7], whereas this effect might not be noticed at the population level. Future studies, examining changes over time at an individual level, might give more insight into the role of HIV optimism in the total increase in high-risk sexual behaviour.

In conclusion, we are not convinced by the report of Elford *et al.* [1] that HIV optimism is unlikely to explain the increase in high-risk sexual behaviour. We would like to emphasize that HIV optimism should still be addressed by prevention efforts, although we do agree that it is important to keep searching for other important factors that help to explain the increase in sexual risk behaviour, enabling the development of more effective prevention strategies.

Ineke G. Stolte and Nicole H.T.M. Dukers, *HIV and STI Research, Cluster Infectious Diseases, Municipal Health Service, Amsterdam, the Netherlands.*

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Authors' response to letter from I.G. Stolte and N.H.T.M. Dukers concerning the paper 'High-risk sexual behaviour increases among London gay men between 1998 and 2001: what is the role of HIV optimism?'

Our paper [1] concluded that HIV optimism was unlikely to explain the recent increase in high-risk sexual behaviour among London gay men. Stolte and Dukers comment that although this may be true, our study was hampered by some methodological issues that might compromise the findings. Our key finding was that among London gay men, no difference was detected between those who were optimistic and those who were not in the rate of increase in high-risk sexual behaviour between 1998 and 2001. This finding challenges the notion that HIV optimism can explain the recent increase in high-risk behaviour among gay men.

Stolte and Dukers express concern that the response categories of the independent variable (HIV optimism) changed in 2000. We made this change to harmonize our scales with those used elsewhere [2]. As a consequence, we may have overestimated the levels of optimism in 1998–1999. Some men who were classified as optimistic in 1998–1999 would have been classified as not being optimistic had we used the 2000–2001 response categories throughout. In our paper, we wrote that it was unlikely that this discontinuity introduced a major bias. In fact, any bias introduced by the change in response categories would seem to strengthen rather than weaken the validity of our results.

Classifying some men as optimistic when in fact they were not would if anything reduce the overall level of high-risk sexual behaviour among 'optimistic men' in 1998–1999. This is because, in cross-sectional analysis, men who were not optimistic were less likely to report high-risk sexual behaviour than other men. The change in response categories may thus have led us to overestimate the actual rate of increase in high-risk sexual behaviour among optimistic men in our study between 1998 and 2001. Such a bias, if it exists, would strengthen rather than weaken our findings.

In univariate analysis based on all men (n = 1776), the odds ratio for HIV optimism 1 and high-risk sexual behaviour among HIV-negative men was 2.87 [95% confidence interval (CI) 2.06, 3.99] (see Table 4 in our paper [1]). In multivariate analysis, based on independent samples (n = 1187) the odds ratio was 3.80 (95% CI 2.41, 6.00) (see Table 5 in our paper [1]). Although the 95% confidence intervals for these odds ratios overlap, Stolte and Dukers ask whether the difference in point estimates derives from bias introduced by using a smaller sample size in the multivariate analysis. Repeating the univariate analysis with independent samples yielded an odds ratio of 3.38 (95% CI 2.22, 5.14), similar to the value from the multivariate analysis (3.80). The differences in the point estimates for the odds ratios in univariate and multivariate analysis seen in the paper clearly occurred by chance and were not the result of bias because of the smaller sample size in multivariate analysis.

Stolte and Dukers comment that examining changes in sexual behaviour at a population level may conceal changes at an individual level. The objective of our analysis, however, was to examine behaviour at a population level because this provides crucial information about changes in risk for the community rather than for individuals. To support the possibility that 'at an individual level, treatment-related optimism appears to be a factor that increases high-risk sexual behaviour' Stolte and Dukers cite their own unpublished research [3]. Their research is based on 78 gay men surveyed on two occasions, once in 1999 and again in 2000. Some men (n = 8) switched from reporting no sexual risk in 1999 to reporting a risk in 2000. The increase in risk reported by these men was associated with a reduction in the perceived threat of HIV/AIDS since highly active antiretroviral therapy was introduced ($P < 0.05$), but interestingly, not with the perceived effectiveness of highly active antiretroviral therapy ($P > 0.05$).

We have now updated our analysis to include an additional 828 London gay men (121 HIV positive, 542 HIV negative, 165 never-tested) surveyed in

Table 1. Year of survey, HIV optimism and sexual risk behaviour 1998–2002; multivariate analysis.

	HIV positive men			HIV negative men		
	Odds ratio[a]	95% CI	*P*	Odds ratio[a]	95% CI	*P*
Nonconcordant UAI with a casual partner						
Year of survey	1.59	1.32, 1.91	< 0.001	1.34	1.19, 1.51	< 0.001
Optimism 1	1.20	0.67, 2.15	0.5	4.06	2.73, 6.04	< 0.001
Optimism 2	2.12	1.17, 3.85	0.01	1.24	0.80, 1.92	0.3
Interaction term[b]	1.32	0.88, 1.99	0.2	1.12	0.88, 1.42	0.4

CI, Confidence interval; UAI, unprotected anal intercourse.
Optimism 1: Reduced severity optimism ('I am less worried about HIV infection now that treatments have improved').
Optimism 2: Reduced susceptibility optimism ('I believe that new HIV drug therapies make people with HIV less infectious').
[a]Odds ratio from multivariate logistic model with year of survey, optimism 1 and optimism 2 (independent variables) and non-concordant UAI with a casual partner (dependent variable) entered simultaneously.
[b]For HIV-positive men, this refers to the interaction between UAI, year of survey and optimism 2, whereas for HIV-negative men it refers to the interaction between UAI, year of survey and optimism 1.

January–February 2002, thereby increasing the total sample size (1998–2002) to 3766 men. Using data for 1998–2002, the univariate and multivariate associations between HIV optimism and high-risk sexual behaviour were similar to those seen in the published paper with one notable difference. For HIV-positive men, in the 1998–2002 analysis, the interaction between optimism and time in the multivariate model was clearly non-significant ($P = 0.2$) (Table 1), whereas in the earlier analysis it had been borderline ($P = 0.07$) [1]. Although this was non-significant at the 5% level, it nonetheless raised the possibility of a type II error. That is to say, for HIV-positive men the rate of increase in high-risk sexual behaviour between 1998 and 2001 could have been greater for those who were optimistic than for those who were not, but our study did not have sufficient power to detect this differential. Including data for 2002 has increased the sample size and power, and substantially reduced the likelihood of a type II error [4]. Consequently, among HIV-positive men no difference was detected between those who were optimistic and those who were not in the rate of increase in high-risk sexual behaviour between 1998 and 2002 ($P = 0.2$) (full set of data for 1998–2002 available from the authors).

There is no evidence of our findings being compromised by methodological issues as suggested by Stolte and Dukers. Indeed, including data collected over 5 rather than 4 years serves only to strengthen and confirm our earlier analysis. It is unlikely that HIV optimism can explain the increase in high-risk sexual behaviour among London gay men between 1998 and 2002. Once again, we would emphasize the importance of focusing future research on those factors that may be associated with the recent increase in high-risk sexual behaviour among gay and bisexual men.

Jonathan Elford[a], Graham Bolding[a] and Lorraine Sherr[b], *[a]City University, London, UK; and [b]Royal Free and University College Medical School, London, UK.*

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