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Cutaneous response to recombinant interleukin 2 in human immunodeficiency virus 1-seropositive individuals

(human immunodeficiency virus 1 infection/cutaneous anergy/γ interferon)

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ABSTRACT **We report that 11 human immunodeficiency virus 1 (HIV-1)-seropositive patients, including three AIDS patients, were able to generate a cellular immune response to the intradermal injection of low doses (2–10 μg) of recombinant interleukin 2 (rIL-2). A dose-dependent zone of induration appeared at the site of injection, peaked at 24 hr, and was accompanied by the local accumulation of T cells, monocytes, and Langerhans cells. Despite the reductions in the $CD4^+$ T-cell counts in the peripheral blood of most patients, $CD4^+$ T cells could still be mobilized with rIL-2 injections into the skin. The total number of immigrant cells was equivalent to those in HIV-1-seronegative patients, although the $CD4^+/CD8^+$ ratio of the dermal population was reduced. In response to rIL-2, major histocompatibility complex (MHC) class II antigen was expressed on the surface of keratinocytes, Langerhans cells, lymphocytes, and macrophages. In addition, the γ interferon (IFN-γ)-induced protein IP-10 rapidly appeared in dermal inflammatory cells and keratinocytes. A majority of HIV-1-seropositive patients demonstrated low or absent responses to common skin-test antigens. Those with positive zones of induration were often defective in the cellular expression of the IFN-γ-induced MHC class II antigen. The simultaneous administration of rIL-2 and soluble antigen at widely separated cutaneous sites led to an enhancement of skin-test antigen reactivity in seropositive patients. The results suggest that local administration of rIL-2 to seropositive patients may act systemically, stimulating cellular immunity to recall antigens, and thus may be of potential benefit in the defense against opportunistic pathogens encountered in HIV-1 infection.**

Acquired immunodeficiency syndrome (AIDS), an endstage manifestation of human immunodeficiency virus 1 (HIV-1) infection, is characterized by the progressive loss of $CD4^+$ T cells (1) and the subsequent defective secretion of lymphokines, including interleukin 2 (IL-2) (2) and γ interferon (IFN-γ) (3). This results in impaired mononuclear phagocyte activation and predisposes the patients to a variety of intracellular infections. Asymptomatic HIV-1-seropositive individuals with mild $CD4^+$ T-cell deficiencies commonly exhibit cutaneous anergy to skin-test antigens (4) and fail to generate a lymphocyte proliferative response upon stimulation with recall antigens *in vitro* (5). The mechanisms contributing to these events are poorly understood.

We have shown (6) that the intradermal administration of low-dose human recombinant IL-2 (rIL-2) can lead to a delayed-type hypersensitivity (DTH) response that is quantitatively and qualitatively similar to that generated by soluble antigens such as purified protein derivative (PPD) of tuberculin. The cutaneous reaction is accompanied by enhanced proliferation of circulating T cells, the generation of cytotoxic T cells, and the disposal of *Mycobacterium leprae* (7). We reasoned that rIL-2 may also enhance the cutaneous reactivity of poorly responsive individuals with HIV-1 infection. We now report a comparative study of the effects of local rIL-2 administration in a group of HIV-1-seropositive and -seronegative individuals. We demonstrate that rIL-2 can induce a delayed, cell-mediated immune response in the skin of asymptomatic seropositives and those with AIDS. In addition, rIL-2 can enhance the cutaneous reactivity of seropositive individuals to common skin-test antigens.

METHODS

After receiving approval from the Rockefeller University Hospital Institutional Review Board, 21 HIV-1-seropositive individuals who are participants in a longitudinal study (8) and 11 HIV-1-seronegative individuals agreed to receive intradermal injections of rIL-2 and/or skin-test antigens. All procedures were carefully explained, and signed consent forms were obtained before the study was initiated. The clinical profile of each participant is listed in Table 1. All seropositive individuals had been skin-tested by us more than 1 year ago and had peripheral blood $CD4^+/CD8^+$ T-cell ratios < 1.0. There was no significant difference in the mean $CD4^+$ T-cell count among those who received rIL-2 and antigen (465 ± 140 cells per μl) and those who received antigen alone (346 ± 179 cells per μl).

rIL-2 Administration. rIL-2 (Proleukin, Cetus; 18×10^6 international units per mg) was reconstituted in 1.2 ml of sterile water and diluted in sterile 5% dextrose to achieve a final concentration of 1, 2, 5, or 10 μg per 100 μl. Using a tuberculin syringe with a 27-gauge needle, we injected each individual intradermally on the right side of the back in an area of normal-appearing skin with 1, 2, and 5 μg (in descending order). In selected individuals, we chose to inject the diluent or 10 μg alone.

Skin-Test Antigen Administration. On the left side of the back in descending order, we injected intradermally 5 tuberculin units of PPD (Connaught Laboratories), intermediate strength *Candida* antigen (Hollister-Stier, Elkart, IN), and intermediate strength *Trichophyton* antigen (Hollister-Stier, IN) in 100-μl volumes. In some individuals both skin-test antigens and rIL-2 were administered at the same time. These individuals were injected with rIL-2 on the right side of the back and antigens on the left side of the back.

Measurement of Response. The diameter of erythema and induration at the site of injection was measured daily with a micrometer. Responses were recorded as negative when there was no erythema or induration. Participants were questioned about local or systemic side effects.

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Abbreviations: HIV-1, human immunodeficiency virus 1; IL-2, interleukin 2; IFN-γ, γ interferon; MHC, major histocompatibility complex; LC, Langerhans cells; PPD, purified protein derivative.

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Table 1. Clinical profile of HIV-1-seropositive and -seronegative individuals under study

Patient	HIV antibody in serum	Clinical status	Antiviral therapy	$CD4^+/CD8^+$* (ratio)
1	+	ASX	—	352/1056 (0.3)
2	+	ASX	—	456/988 (0.5)
3	+	ARC	AZT, ACV	189/639 (0.3)
4	+	ASX	—	399/1600 (0.3)
5	+	ASX	—	627/994 (0.6)
6	+	AIDS	—	533/1165 (0.5)
7	+	ASX	—	606/707 (0.9)
8	+	ARC	—	380/450 (0.8)
9	+	ASX	—	675/1535 (0.4)
10	+	ASX	—	441/885 (0.5)
11	+	ASX	—	355/1933 (0.2)
12	+	AIDS	AZT	312/1306 (0.2)
13	+	ASX	AZT	633/1336 (0.5)
14	+	ASX	—	395/687 (0.6)
15	+	ASX	AZT, ACV	556/996 (0.6)
16	+	ARC	AZT, ACV	76/1215 (0.1)
17	+	AIDS	AZT, ACV	36/472 (0.1)
18	+	ASX	AZT, ACV	283/742 (0.4)
19	+	ASX	AZT	479/1059 (0.5)
20	+	ARC	—	338/857 (0.4)
21	+	AIDS	—	70/297 (0.2)
22	−	ASX	—	ND
23	−	ASX	—	1480/640 (2.3)
24	−	ASX	—	740/440 (1.6)
25	−	ASX	—	650/540 (1.2)
26	−	ASX	—	1573/470 (3.3)
27	−	ASX	—	872/340 (2.5)
28	−	ASX	—	726/1022 (0.7)
29	−	ASX	—	ND
30	−	ASX	—	970/330 (3.0)
31	−	ASX	—	ND
32	−	ASX	—	ND

ASX, asymptomatic; ARC, AIDS-related complex; AZT, azidothymidine; ACV, acyclovir; ND, not determined.
*Cells per microliter of blood.

Skin Biopsy and Analysis. Punch biopsies (3 mm) were taken from the indurated sites primarily on day 2 and/or day 5 after injection. The specimens were processed by paraformaldehyde–lysine–periodate fixation (9) and stored in 25% sucrose/5% (vol/vol) glycerol until sectioned in a cryostat at −20°C. Immunocytochemistry was performed as described (6). Mouse monoclonal antibodies (mAbs) were used to distinguish specific mononuclear cell types: Leu-2a, Leu-3a, and Leu-4 (anti-CD8, anti-CD4, and anti-CD3 T cells, respectively) and Leu-M5 (anti-CD11c monocyte/macrophage) from Becton Dickinson; OKT6 [anti-CD1 Langerhans cells (LC)] from Ortho Diagnostics; and 9.3F10 [mAb against major histocompatibility complex (MHC) class II antigen] from our laboratory. Biotinylated horse anti-mouse immunoglobulin (Vector Laboratories) was used as the secondary antibody reagent. Rabbit antibody against IP-10 induced by IFN-γ (obtained from J. Ravetch, Memorial Sloan–Kettering Cancer Center, NY) followed by biotinylated goat anti-rabbit IgG antibodies were used to identify the IFN-γ-inducible protein, IP-10 (10). The sections were evaluated by light microscopy, and enumeration of positive-staining cells was performed at ×40 magnification. Photomicrographs were taken with a Nikon Microphot.

Peripheral Blood $CD4^+/CD8$ T-Cell Subset Analysis. Venipuncture was performed prior to the administration of rIL-2 and/or skin test antigens and, in selected patients, after 1, 2, and 4 weeks of injection for routine complete blood cell counts and $CD4^+/CD8^+$ T-subset cell analysis.

Statistical Analysis. A paired comparison and Student's *t* test were used to determine significance ($P < 0.01$).

RESULTS

Clinical Response to Intradermal rIL-2. The administration of rIL-2 by the intradermal route led to the migration of circulating cells into the injection site and resulted in a zone of erythema and induration, similar to our previous findings in lepromatous leprosy patients (6). A typical skin response after the injection of 1, 2, and 5 μg of rIL-2 is shown in Fig. 1. The gross cutaneous changes exhibited by HIV-1-seropositive patients (Table 1, patients 1–10 and 17) were equivalent to those exhibited by seronegative controls (Table 1, patients 22–28). No local reactions occurred at the site of excipient injection.

Kinetics and dose–response analyses of rIL-2 injection seen in HIV-1-seropositive and -seronegative patients are shown in Fig. 2. A dose–response correlation following 1-, 2-, and 5-μg injections of rIL-2 was observed. Induration at the injection site was maximal 24 hr after injection and persisted for at least 7 days. Neither parameter of the intradermal response was significantly different in the two groups. Reactions 24 hr after injection were occasionally accompanied by local warmth and pruritus but did not lead to systemic complaints. Peripheral blood $CD4^+$ T cells and the $CD4^+/CD8^+$ T-cell ratios of injected seropositive patients were not significantly different among those tested 1, 2, and 4 weeks after injection.

Immunohistological Response to rIL-2. Punch biopsies from the center of reactional sites resulting from the intradermal injection of 2 μg and 5 μg of rIL-2 were obtained 2 days and 5 days postinjection, respectively. In both HIV-1-seropositive and -seronegative patients, the mononuclear leukocyte inflammatory infiltrate recruited into the injected site occupied ≈10–35% of the dermis. Immunostaining indicated that there was a similar distribution of T cells, monocytes/macrophages, and LC in the dermal infiltrate. T cells were distributed closely in the perivascular regions and diffusely near the epidermis (Fig. 3 *A* and *B*). Appreciable numbers of both $CD4^+$ and $CD8^+$ T cells were found in the skin of both seronegative and seropositive individuals, but the $CD4^+/CD8^+$ T-cell ratios of the dermal infiltrate were quite different. Seropositive patients had mean ratios of <1.0, whereas seronegative patients had mean ratios of 2.0 (Table 2). These ratios were a reflection of the $CD4^+/CD8^+$ T-cell ratios of the

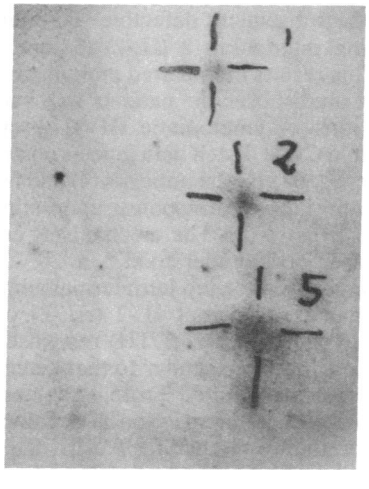

FIG. 1. Response to intradermal injection of rIL-2. Photograph of an individual 24 hr after injection of 1, 2, and 5 μg of rIL-2 down the right side of the back. Induration is noted in a dose-dependent fashion at the three rIL-2 infection sites.

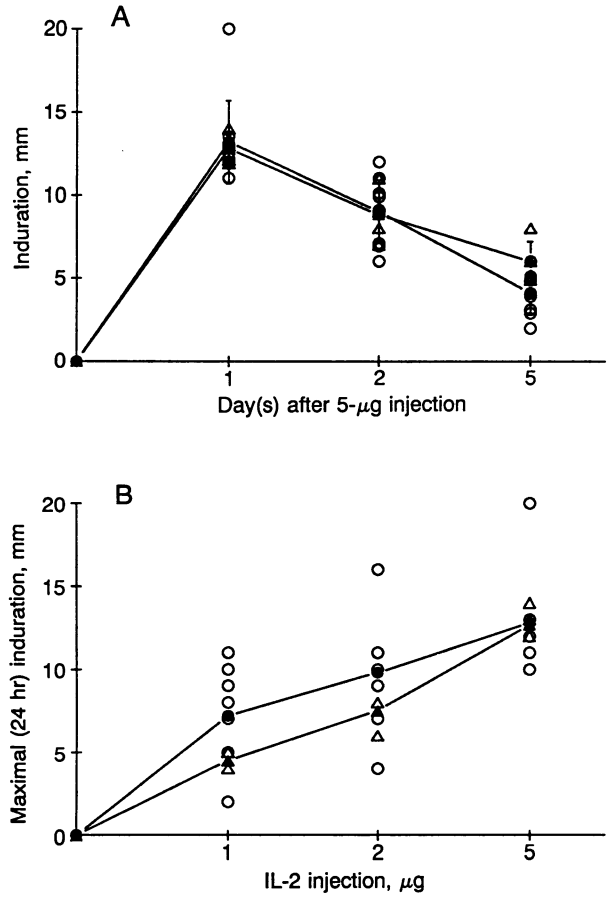

FIG. 2. Response to rIL-2, measured as the diameter of induration at the injection site, in HIV-1-seropositive (○) and -seronegative (△) individuals; ● and ▲ represent mean values. (*A*) Response was maximal at 24 hr after injection. (*B*) Induration became maximal 24 hr after injection, and the degree of induration was dose-dependent. There was no significant difference in response among the two groups tested.

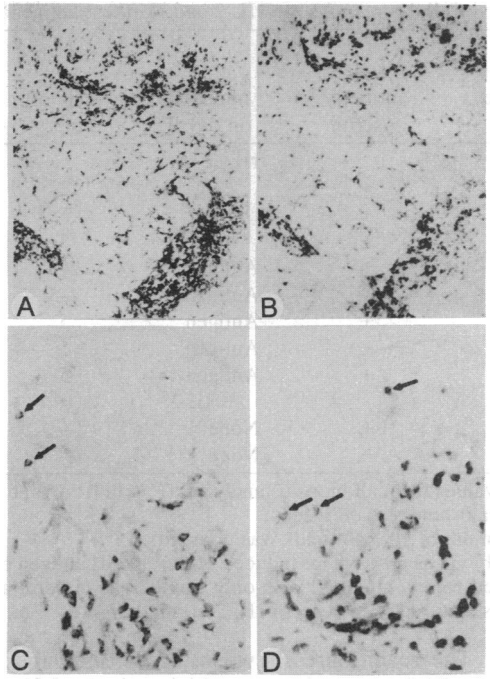

FIG. 3. Photomicrographs depicting immunoperoxidase staining of skin biopsies from HIV-1-seropositive patient 7 taken 2 days after a 2-μg rIL-2 injection. (*A*) Dermal distribution of $CD3^+$ T cells staining with Leu-4. (*B*) $CD8^+$ T cells staining with Leu-2a in the dermis and epidermis. (*C*) $CD4^+$ T cells staining with Leu-3a in the dermis and epidermis (arrows). (*D*) $CD8^+$ T cells staining with Leu-2a in the dermis and epidermis (arrows). (*A* and *B*, ×100; *C* and *D*, ×250.)

peripheral blood compartment. With the passage of time, 2–5 days postinjection, the $CD4^+/CD8^+$ T-cell ratios of seropositive patients decreased progressively (Table 2). It is uncertain whether this represented the preferential loss of $CD4^+$ T cells and/or the continued recruitment of the $CD8^+$ T-cell subset. However, it is clear that seropositive patients with or without AIDS were able to mobilize significant numbers of $CD4^+$ T cells into the skin in response to rIL-2.

The number of LC per ×40 field was not significantly different in the uninjected skin of HIV-1-seropositive and -seronegative individuals (Table 2). After rIL-2 injection, the number of $CD1^+$ LC was slightly higher in the thickened epidermis and in the upper dermis (Fig. 4), but similar numbers were present in both groups. In both cases ≈30–50% of the LC strongly expressed MHC class II antigen. The injection of rIL-2 modified the phenotype of keratinocytes overlying the injection sites. In both seropositive and seronegative individuals, both MHC class II antigen and IP-10 were expressed on the keratinocytes (Fig. 4 and Table 2). Both effects are known to result from the presence of IFN-γ, and it is likely that rIL-2 initiates the local production of IFN-γ in both patient groups.

Clinical and Immunohistological Response to Skin-Test Antigens. HIV-1-seropositive and -seronegative individuals were skin-tested with three common antigens. The seropositive group showed the following positive responses (any measurable induration): 85% to *Candida* antigen, 20% to *Trichophyton* antigen, and 5% to tuberculin PPD. The seronegative group demonstrated an overall greater positive response rate, with 100% to *Candida*, 50% to *Trichophyton*, and 33% to tuberculin PPD. The time course of local induration was maximal at 48–72 hr and was similar in both groups. However, there were significantly larger zones of induration in the seronegative group than in the seropositive group ($P < 0.001$).

Biopsies taken 2 and 5 days after antigen injection demonstrated a mononuclear cell infiltrate, the extent of which was in proportion to the zones of induration and occupied from 15–50% of the dermis. The infiltrate contained T cells, monocytes/macrophages, and LC, the number and distribution of which were similar to those induced with rIL-2. The $CD4^+/CD8^+$ T-cell ratios of dermal T cells were again much higher in seronegative individuals (Table 2).

Unlike the response to rIL-2, epidermal keratinocytes from the majority of HIV-1-seropositive patients failed to demonstrate surface membrane MHC class II antigens upon immunostaining. In contrast, all of the seronegative patients expressed MHC class II staining 5 days after antigen injection. No differences were noted in the percentage of $CD1^+$ LC, which expressed MHC class II antigen in seropositive or seronegative patients. Whereas the expression of MHC class II antigen on keratinocytes was subnormal in seropositive patients, IP-10 was present in all biopsies examined (Fig. 4).

Enhancement of Skin-Test Responsiveness by rIL-2. Our findings show that through the selective loss of $CD4^+$ T cells, HIV-1 infection results in depression of the cell-mediated immune response to skin-test antigens. As shown in the previous section, rIL-2 can by itself evoke cell-mediated immune response in the skin of HIV-1-infected individuals. Therefore we evaluated the role of rIL-2 in enhancing skin-test reactivity in HIV-1-seropositive patients. For this purpose, rIL-2 was administered simultaneously with skin-test antigens, but in widely separated sites, in seropositive indi-

Table 2. Cellular response to rIL-2 and skin-test antigen determined by immunostaining of skin biopsies from test sites

Biopsies analyzed, no.	HIV antibody in serum	Injection on day 0	Day of biopsy	Dermis $CD4^+/CD8^{+\dagger}$ T-cell ratio*	Epidermis			
					LC, no. per ×40 field†		Keratinocytes‡	
					$CD1^+$	Class II^+	Class II^+	$IP\text{-}10^+$
		rIL-2						
7	+	2 μg	2	0.77 ± 0.19 (a)	20 ± 11	12 ± 2	5/7	7/7
7	+	5 μg	5	0.48 ± 0.11 (b)	22 ± 20	10 ± 6	5+*2*/7	6+*1*/7
3	−	5 μg	5	2.00 ± 0.24 (c)	15 ± 1	5 ± 1	3/3	3/3
7	+	Antigen	2–3	1.25 ± 0.49 (d)	15 ± 6	6 ± 1	1/7	7/7
4	−	Antigen	2–3	2.02 ± 0.30 (e)	12 ± 7	9 ± 4	1+*1*/4	4/4
3	+	Antigen	5	0.85 ± 0.25	16 ± 1	8 ± 1	1/3	3/3
3	−	Antigen	5	6.84 ± 2.30	13 ± 2	9 ± 1	3/3	3/3
7	+	Antigen +rIL-2§	5	0.87 ± 0.27	22 ± 14	7 ± 3	1/7	7/7
4	+	None	—	ND	9 ± 5	4 ± 2	0/4	0/4
4	−	None	—	ND	10 ± 7	5 ± 1	0/4	*1*/4

*Mean values from all biopsies analyzed ($P < 0.01$: a vs. b; b vs. c; d vs. e). ND, not determined, as normal uninjected skin does not contain significant numbers of T cells.

†A minimum of 10 ×40 fields was counted.

‡No. of biopsies positive for induced MHC class II antigen or IP-10 on keratinocytes over the total no. of biopsies evaluated. Italicized numbers indicated patchy staining, with only small areas of keratinocytes staining.

§Patients also received 5 μg of rIL-2 at another site.

viduals. The results are shown in Table 3. In the case of tuberculin PPD, an antigen to which only 1 of 20 patients demonstrated any previous sensitization, rIL-2 was without effect. A similar result was obtained with *Trichophyton* antigen. However, the situation was quite different with *Candida* antigen, to which most patients were minimally or moderately responsive. Here, there was a significant enhancement in skin-test reactivity in the majority of seropositive patients 1–10 ($P < 0.005$). The enhancement of skin-test reactivity was based upon comparisons with prior tests done as long as 1 year previously. Patients not receiving rIL-2 failed to show appreciable increments in skin-test reactivity compared with prior testing (patients 11–20), unless antiviral therapy had been initiated.

rIL-2 at a distant site induced more extensive areas of induration as a result of increased cellular infiltration in response to *Candida* injection. The cellular distribution was similar to that noted with rIL-2 and antigen alone (Table 2).

We conclude that low-dose rIL-2 can accentuate the cell-mediated immune response to skin-test antigens to which the patient had been sensitized.

DISCUSSION

Patients infected with HIV-1, with depressed levels of $CD4^+$ T cells and low $CD4^+/CD8^+$ T-cell ratios, can still mount a vigorous cell-mediated immune response in the skin after the administration of rIL-2. The response encompasses the generation of a variety of signals leading to the effective homing, transmigration, and accumulation of peripheral blood mononuclear cells into the dermis. The process leads to release of IFN-γ, either through activation of T cells or through stimulation of natural killer cells. This is expressed as the IFN-γ-induced changes in the dermis and epidermis. We suspect that by supplying rIL-2, thereby bypassing the need for large numbers of $CD4^+$ helper T cells, we initiate and maintain the sequellae of the cell-mediated reaction in a

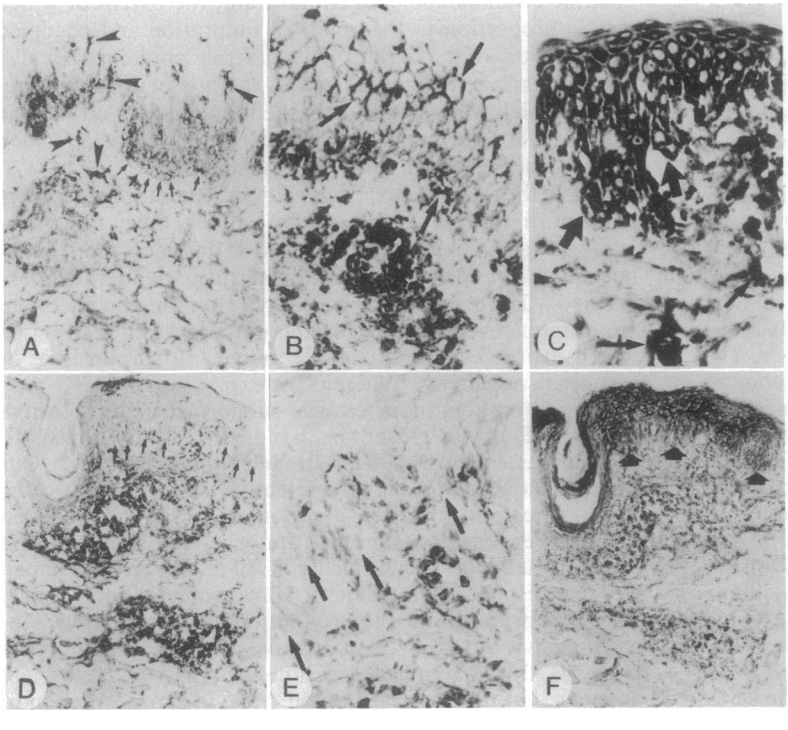

FIG. 4. MHC class II antigen and IFN-γ-induced peptide (IP-10) expression in the dermis (mononuclear cells) and epidermis (keratinocytes and LC) in HIV-1-seropositive patients. (*A*) MHC class II staining of cells in the dermis and epidermis of a skin biopsy taken 2 days after a 2-μg rIL-2 injection. The basal keratinocytes have been induced to express class II antigen on their surface (arrows). LC also stained in both the epidermis and upper dermis (arrowheads). The inflammatory cells of the dermis are also Ia^+. (*B*) High magnification of *A*. Surface staining of the keratinocytes is shown (arrows). (*C*) IP-10 expression in the keratinocytes and dermal inflammatory cells 2 days after a 2-μg rIL-2 injection (large arrows). All keratinocytes and some of the dermal inflammatory cells are highly positive (small arrows). (*D*) Lack of MHC class II expression on the keratinocytes (arrows) of a biopsy taken 5 days after *Candida* antigen injection (13-mm induration at 48 hr). The mononuclear cells of the dermis are positive for MHC class II antigen. (*E*) High magnification of *D*. The keratinocytes of the epidermis are clearly not staining (arrows). (*F*) IP-10 expression in the keratinocytes (arrows) and some of the inflammatory cells of the dermis 5 days after *Candida* antigen injection. (*A*, *D*, and *F*, ×100; *B*, *C*, and *E*, ×250.) Biopsy samples were from seropositive patient 7 (*A–C*) and seropositive patient 4 (*D–F*).

Table 3. The effect of rIL-2 on the delayed-type hypersensitivity response to common antigens in HIV-1-seropositive individuals

Patient*	rIL-2 treatment†	Induration,‡ mm		
		Tuberculin PPD	*Candida*§	*Trichophyton*
1	+	0 (0)	11 (11)	6 (3)
2	+	0 (0)	12 (4)	0 (0)
3	+	0 (0)	0 (0)	0 (0)
4	+	0 (0)	10 (0)	0 (0)
5	+	0 (0)	13 (0)	0 (0)
6	+	0 (0)	6 (4)	0 (0)
7	+	0 (0)	11 (3)	0 (0)
8	+	0 (0)	9 (8)	0 (0)
9	+	15 (15)	9 (4)	0 (0)
10	+	0 (0)	10 (5)	0 (0)
11	−	0 (0)	4 (3)	0 (3)
12	−	0 (0)	6 (10)	4 (6)
13¶	−	0 (0)	10 (5)	0 (0)
14	−	0 (0)	5 (3)	6 (5)
15¶	−	0 (0)	11 (8)	0 (0)
16¶	−	0 (0)	3 (0)	0 (0)
17	−	0 (0)	0 (0)	0 (0)
18¶	−	0 (0)	7 (5)	0 (0)
19	−	0 (0)	7 (8)	8 (9)
20	−	0 (0)	0 (0)	0 (0)

*Patient numbers correspond to those in Table 1.
†Injections of 1, 2, and 5 μg.
‡Induration was determined 48 hr after antigen injection. The previous antigen skin test was carried out >1 year before the present test.
§In a paired comparison test, the enhancement of responsiveness in patients 1–10 was significant, with $P < 0.005$. The changes observed in patients 11–20 were not significant.
¶Azidothymidine treatment with or without acyclovir therapy was initiated between the two test periods.

fashion similar to that observed in the immunodeficiency of lepromatous leprosy (6). Our conclusion is supported by the study of Murray *et al.* (12), which provides evidence that the administration of parenteral IL-2 gives rise to large amounts of IFN-γ in AIDS patients.

The intensity of the cutaneous response to a skin-test antigen is not as great in HIV-1-seropositive patients as that to recombinant lymphokine. HIV-1-infected patients with prior sensitivity to common antigens may lose or demonstrate fractional reactivity to antigen causing delayed-type hypersensitivity when injected intradermally. In our study this was expressed both as reduced zones of induration and the inability to express MHC class II determinants on the surface of overlying keratinocytes. The expression of IP-10 but not MHC class II antigens on the surface of the keratinocytes suggests that less IFN-γ is produced locally in the antigen-responsive site of HIV-infected patients. Since IP-10 can be induced by tumor necrosis factor (TNF) as well as IFN-γ (J. V. Ravetch, personal communication), it is possible that TNF is also induced during the local response to antigens in HIV-infected patients. Thus, whereas rIL-2 can stimulate a polyclonal T-cell response with the production of IFN-γ and TNF (13, 14), antigen reactivity recruits only a small percentage of $CD4^+$ T cells, the numbers and activity of which are even further compromised by the disease process.

The ability of rIL-2 to generate an enhanced delayed-type cell-mediated response in the poorly reactive HIV-1-seropositive patients deserves further comment. First, it appears that enhancement is dependent upon prior sensitization of patients to the skin-test antigen and is in keeping with our previous studies in leprosy (11). Second, it is unlikely that sufficient quantities of rIL-2, given at disparate sites, can reach the skin site receiving antigen by a direct vascular or lymphatic route. We suspect that this requires modification of cells passing through the rIL-2 site, their passage back into the circulation and their enhanced homing and reactivity upon entering skin containing an ongoing antigenic challenge. Further studies are required to establish this scenario and to examine the potential of multiple rIL-2 injections and optimal dose range on host cell-mediated reactions. We would hope that this might influence the host's response to secondary intracellular invaders and facilitate defense against opportunistic infections (15). We caution investigators of the potential hazard of inducing HIV-1 replication in cycling T cells with rIL-2 and suggest the combined usage of azidothymidine (AZT) under these conditions.

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