

## Incidence and Prognostic Significance of Skin Disease in Patients with HIV/AIDS: A 5-year Observational Study

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**Mucocutaneous diseases are common in HIV-infected patients. The aim of the present study was to determine the observed frequency of skin diseases and their prognostic significance for the progression of HIV infection. In a cohort of 150 HIV-infected patients diagnosed from 1986 to 1987 the number of mucocutaneous diseases, the CD4+ cell count, time to development of AIDS and survival time were registered for a period of 5 years. Eight patients were lost for follow-up. In the remaining 142 patients the number of mucocutaneous findings increased markedly during the observation period. The most frequent registered diseases and these with the highest increase were oral candidiasis, hairy leukoplakia, seborrhoeic dermatitis and herpes simplex. On average, 5.2 different diagnoses were registered per patient at the end of the follow-up period. The study showed that the total number of mucocutaneous diseases and the CD4+ cell count were significantly correlated to survival time and time to development of AIDS. The number of mucocutaneous diseases, like the CD4+ count, is an indicator of the immune system and the prognosis of HIV infection. Key words: HIV infection; mucocutaneous diseases; survival time; CD4+ cell count.**

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Cellular immunity is known to play an important role in skin diseases, not only as a defence mechanism against viral and fungal infections, but also in various inflammatory diseases (1–3). Infection with HIV causes a gradual decline in the T-helper cell count (CD4+), the more depleted, the more prone the patient will be to contract infections and develop inflammatory skin diseases (4–10).

A former Danish study covering an observation period of 6 months revealed hairy leukoplakia, seborrhoeic dermatitis, oral candidiasis, pruritic papular eruption and viral infections as the most frequent mucocutaneous diseases in the early stage of HIV infection (11).

In the present study we followed HIV-infected patients for a 5-year period in order to study the relation between mucocutaneous disease, CD4+ count, time to development of AIDS as defined in 1987 by CDC (12) and survival time.

### MATERIALS AND METHODS

From December 1986 through May 1987 150 HIV-infected patients were referred to our department for clinical observation and included

consecutively in the study. The majority of patients was referred from our open clinic for sexually transmitted diseases (STD) in central Copenhagen, a few from practitioners and the two departments of infectious diseases in Copenhagen.

The patients were examined and questioned by senior dermatologists. A questionnaire was filled out by the doctor at each visit. During the following 5 years the patients were seen at regular intervals (range 1 month to 1 year, median 4 months) and in case of new skin symptoms. At the visits a questionnaire about present and past symptoms was filled out. In case of mucocutaneous changes, relevant diagnostic tests were undertaken if considered necessary to ensure a diagnosis (fungal, bacterial and viral tests, skin biopsy and blood analysis). The clinical findings, CD4+ counts and treatments, antiviral (Zidovudine) and antibiotics in case of bacterial and fungal infections were recorded, as were the dates of AIDS diagnosis and death.

After 5 years, 8 patients had been lost to follow-up, leaving a total of 142 patients for the present study.

The age of the patients at enrolment ranged from 19 to 59 years, mean 34 years. A total of 136 were men, of these, 108 were homosexual, 17 bisexual and 11 heterosexual, 10 of whom were intravenous drug abusers and 1 was from central Africa.

### Statistical methods

Kaplan-Meier estimates for survival analysis and exact log rank test for comparison between groups were used for statistical evaluation (13).

### RESULTS

Originally 7 (4.7%) of the group had AIDS and 12 (8%) had a CD4+ count below  $200 \times 10^6/l$ . After 5 years 46 (32%) had developed AIDS according to the CDC criteria (12) and 65 (46%) patients had a CD4+ count below  $200 \times 10^6/l$ .

The number of skin diseases at the first visit and during the observation period is shown in Table I and Fig. 1. Each patient may be presented by different diagnoses.

At the first visit relatively few patients had mucocutaneous diseases, such as mild to moderate seborrhoeic dermatitis, recurrent herpes simplex infection, oral candidiasis and herpes zoster. Three were diagnosed with acute HIV exanthema at entry.

During the next 5 years the rank of frequency of skin diseases was only slightly changed. There was an increase in the occurrence of all skin diseases. In all, 49.2% developed seborrhoeic dermatitis, 51.4% oral candidiasis (atrophic and hypertrophic type) (we did not observe pseudomembranous cases, probably because patients were frequently treated with systemic and local antifungals) and 43% oral hairy leukoplakia (Table I). Sporadic cases of acute necrotizing gingivitis,

Table I. Frequency of mucocutaneous diseases in 142 patients with HIV/AIDS at the entry of the study and during a follow-up period of 5 years

Diagnosis	First visit			Follow-up		
	n	%	(95% confidence limits)	n	%	(95% confidence limits)
Mild seborrhoeic dermatitis <sup>a</sup>	7	4.9	(2–10)	59	41.5	(33–50)
Severe seborrhoeic dermatitis <sup>b</sup>	0	0.0	(0–3)	11	7.7	(4–13)
Oral candidiasis	3	2.1	(0–6)	70	51.4	(43–60)
Hairy leukoplakia	0	0.0	(0–3)	61	43.0	(35–52)
Herpes simplex	7	4.9	(2–10)	47	33.1	(25–42)
Dermatomycosis	2	1.4	(0–5)	47	33.1	(25–42)
Pruritic papular eruption	2	1.4	(0–5)	44	30.3	(24–39)
Herpes zoster	4	2.8	(1–7)	36	25.4	(18–33)
Onychomycosis	1	0.7	(0–4)	31	21.8	(15–30)
Drug eruption	1	0.7	(0–4)	23	16.2	(11–23)
Kaposi's sarcoma	0	0.0	(0–3)	12	8.5	(4–14)
Psoriasis	6	4.2	(2–9)	7	4.9	(2–10)
Molluscum contagiosum	1	0.7	(0–4)	8	5.6	(2–11)
Acute HIV exanthema	3	2.1	(0–6)			

<sup>a</sup>Localized slight scaling and redness of the face and scalp.

<sup>b</sup>Marked scaling and redness of face, scalp and trunk.

aphthous stomatitis, xerosis, condylomas and common warts were not included in Table I.

A total of 134 patients (94.4%) developed 1–13 of various skin diseases. Eight patients (5.6%) did not show signs of any mucocutaneous diseases. Three patients had 12 or 13 various skin disorders recorded. A total of 735 skin diagnoses were recorded, on average 5.2 per patient (Fig. 1).

The survival from entry to the study to death of AIDS in patients with an initial CD4+ count below or above  $200 \times 10^6$  is shown in Fig. 2. As expected, survival was significantly longer in patients with an initial high CD4+ count ( $p=0.0001$ ). The median survival time was 2324 days (6.4 years) in patients with a high CD4+ count vs. 911 days (2.5 years) in patients with a low CD4+ count.

In Fig. 3 the time to AIDS and in Fig. 4 the survival of patients with 0–2 and 3 or more diseases at the entry of the study is shown. In both cases the time was significantly longer in patients with few skin diseases compared with those with 3 or more skin diseases ( $p=0.0002$  and  $0.0001$ , respectively). The median survival time was 2384 days (6.5 years) in patients with few skin diseases vs. 1267 days (3.5 years) in patients with more than 2 skin diseases.

Most patients (94%) at some time received Zidovudine and antibacterial prophylactic treatment for AIDS. Thirty-two patients (23%) died, 28 of AIDS, 2 of unknown causes and 2

committed suicide. The 4 patients are not included in the survival estimates.

## DISCUSSION

During the observation period the number of cutaneous findings increased markedly (Table I). The diagnoses are similar to those reported by others from the Western

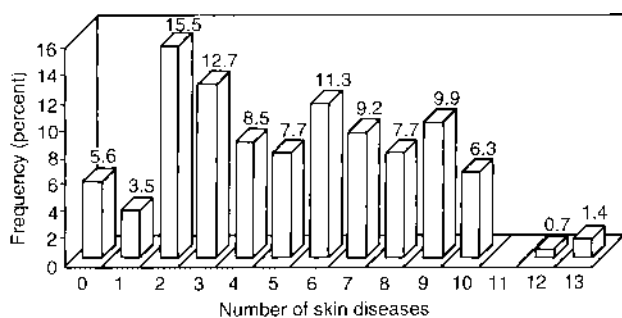


Fig. 1. The observed frequency of skin diseases among 142 HIV-infected patients followed for 5 years.

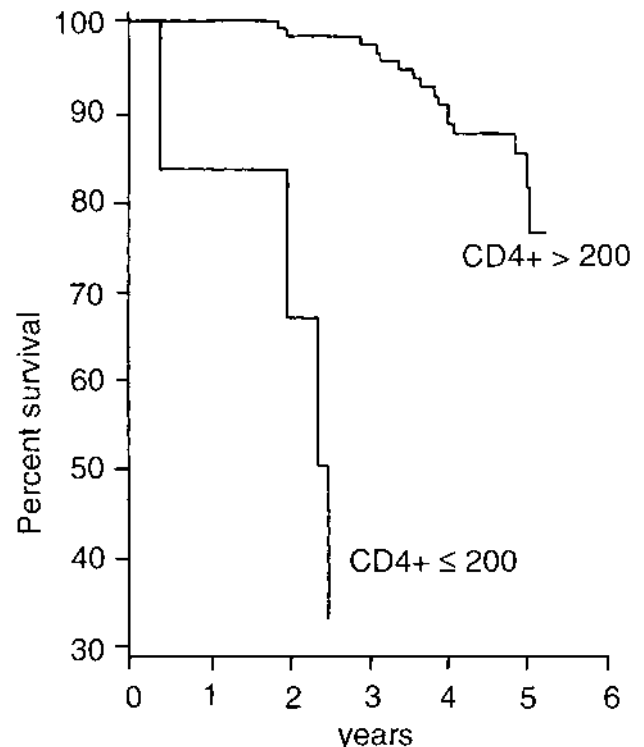


Fig. 2. Kaplan-Meier estimate for survival of HIV-infected patients with a CD4+ count above  $200 \times 10^6/l$  ( $n=121$ ) and below  $200 \times 10^6/l$  ( $n=7$ ) at the entry of the study ( $p=0.0001$  by exact log rank test).

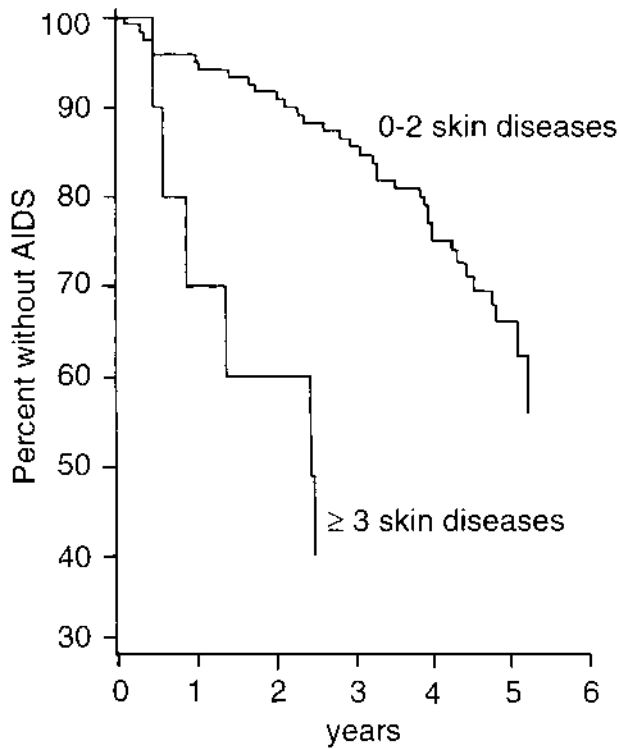


Fig. 3. Kaplan-Meier estimate of time to development of AIDS in patients with 0-2 ( $n=123$ ) and 3 or more skin diseases ( $n=11$ ) at the start of the study ( $p=0.0026$  by exact log rank test).

hemisphere (2, 6, 7, 14-24). The highest increase in frequency were oral candidiasis, followed by hairy leukoplakia, mild seborrhoeic dermatitis and herpes simplex (25).

As expected, we did not see exotic diseases such as histoplasmosis, cryptococcosis or infection with *Penicillium marneffeii*, as in Thailand and Brazil (4, 15, 21, 26, 27). No case of bacillary angiomatosis (27) was seen.

Psoriasis, which is one of the inflammatory diseases associated with HIV infection, occurred at a higher rate than in the general population, the cumulated incidence over 5 years was 9.2%. This has been reported by others (4, 16, 17).

The CD4+ cell count is a predictor of survival time (19). Our study showed a median survival time of 2.5 years when the CD4+ count at the entry of the study was below  $200 \times 10^6$  cells/l; significantly less than the 6.4 years for patients with a higher count. In the same way, the number of skin diseases at entry to the study indicated a shorter survival time in the case of 3 or more skin diseases, 3.5 years vs. 6.5 years in patients with few skin diseases. Figs. 2 and 4 run an almost parallel course. The survival estimate of Fig. 4 probably reflects the patients' immune system, i.e. their CD4+ count, but we lack evidence for this notion.

The fact that 91% of the patients had 2 or more skin disorders, the average number being 5.2, makes it problematic to try to calculate prognosis associated with a single dermatosis. Interference between various skin diseases cannot be excluded. We believe that the total number of skin diseases in the present study gives a valid estimate of the prognosis of the patients. The findings are consistent with the fact that immune function plays an important role for the development of skin diseases, especially those due to infections (2-5, 10).

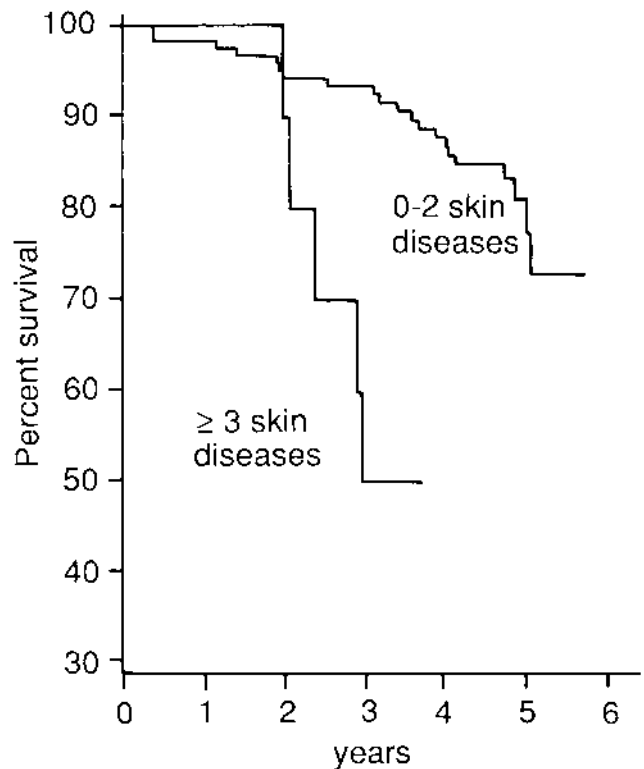


Fig. 4. Kaplan-Meier estimate of survival of HIV-infected patients with 0-2 ( $n=125$ ) and with 3 or more skin diseases ( $n=11$ ) at the start of the study ( $p=0.0001$  by exact log rank test).

There was an increase in skin diseases during the study, and during the last 2 years, when 94% of our patients were having antiretroviral therapy. Whether this might have influenced the occurrence of skin diseases is not known.

This study was performed before the advent of protease inhibitors, which tend to increase the CD4+ cell count and reduce the HIV RNA viral load. A case of resolution of Kaposi's sarcoma in an AIDS patient after protease inhibitor therapy has been reported (28), suggesting that the host immune defence was improved by this therapy. We have observed improvement of the skin condition in patients receiving protease inhibitors. Overall, dermatological signs have become less frequent with the introduction of new therapeutic agents. Further studies monitoring skin conditions, immune functions and the RNA viral load should be undertaken.

The results of the present study, which should not be generalized, especially not to other geographic areas, stress the importance of a continuous dermatological surveillance of patients infected with HIV (29).

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