Dyschromonychia: clinical significance in a South African population

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Abstract

Background: The purpose of this study was to determine disease associations with dyschromonychia (DCO) in an out- and inpatient population attending Kalafong Hospital.

Methods: This prospective and observational study included in- and out-patients attending the Immunology Clinic at Kalafong Hospital, Pretoria, Gauteng. The study was divided into three phases, the first of which was to evaluate the kappa values and prevalence of DCO. The second was to determine the disease associations of in-patients, and the third phase consisted of nail evaluation in an out-patient HIV-positive population.

Results: The kappa value was 0.72, as obtained by three investigators. DCO was found to have a 66% sensitivity, 92% specificity, 66% positive predictive value, 92% negative predictive value, a positive likelihood ratio of 8.2 and a negative likelihood ratio of 0.4 for HIV (inpatients). Patients with DCO were found to have a significantly higher rate of infections (predominantly involving the lung), significantly lower lymphocyte counts and CD4 cell counts, and significantly lower CD4:CD8 ratios and albumin levels ($p = 0.0001$). The best discriminatory CD4 for DCO was 216.6 x 10^6/l (sensitivity = 89%; specificity = 63%), while a CD4 value of 134.3 x 10^6/l yielded a sensitivity of 75% and a specificity of 73%.

Conclusions: This study demonstrates a close association between HIV and DCO, especially in the case of lower CD4 cell counts. The absence of DCO is a poor predictor for the presence of HIV, although its presence has a high sensitivity for HIV seropositivity. The clinical finding of DCO is a simple, quick and efficient sign for the evaluation of the immune status of our population with reasonable sensitivity and specificity for low CD4 cell counts.

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Introduction

Dyschromonychia (DCO) is a change in nail and nail-bed colour other than normal and is a term generally applied to patients with increased nail pigmentation. It is our and other clinicians' experience that more patients are noted with DCO, especially in association with advanced human immunodeficiency virus infection (HIV). In 1987, Furth and Kazakis were the first to report two patients with a particular pattern of DCO.[1] Both patients were HIV positive, African-American, and were on azidothymidine (AZT) therapy. The first of the two patients was referred to an emergency department for "cyanosis"; however, arterial blood gas pressures were normal. The doctors concluded that the DCO was the result of AZT therapy. An additional five black patients with HIV/AIDS and DCO, for which there appears to be no cause other than HIV, have been reported in the literature.[2-5]

Besides the aforementioned reports (with the exception of one article that will be discussed later), there are no other known reports of DCO in HIV patients. We found this to be peculiar in the light of the frequency with which it is observed in clinical practice. The aim of this study was to determine the disease associations in an out- and in-patient population attending a state hospital.

Materials and methods

This was a prospective observational study including an in- and out-patient population to evaluate DCO in a predominantly HIV-positive setting. Following ethical clearance from the University of Pretoria, patients were included in the study after their consent had been obtained. The out-patient population consisted of patients attending the Immunology Clinic at Kalafong Hospital, Pretoria, Gauteng. The in-patients were ward patients of the same hospital. The term DCO was used to denote the presence of nail and/or nail-bed dyschromia. This study makes no distinction between the latter two findings and therefore both conditions are included under DCO.

The study hypothesis was that DCO is a predictor of advanced HIV disease. Dyschromonychia was

clinically defined as the total absence of the nail lunula (all nails), with the presence of a bluish-grey discoloration of the nail or nail bed, extending from the base of the nail (on any nail). All nails, on the fingers and toes, were evaluated. Patients were included if HIV serology and a CD4 cell count had been performed. The only exclusion criterion was the inability to evaluate the patient's nails (nail polish or nail dystrophy).

The study was divided into three phases. The first was the evaluation, by three doctors, of the kappa values and prevalence of DCO in an out-patient population. Two doctors were specialist physicians and the third was an HIV specialist. One hundred consecutive clinic patients were evaluated.

The second phase of the study determined in which patients DCO was present. The study population consisted of 183 in-patients admitted to medical wards at Kalafong Hospital. Following patient consent, their nails were examined for the presence of DCO by one doctor. Correlations were made for disease associations. Previous and present diseases, medication and biochemical findings were documented on a patient information sheet.

The third phase of the study consisted of nail evaluation in an out-patient HIV-positive population by doctors who had not been taught to evaluate DCO. A total of 137 outpatients were randomly selected and evaluated by seven different doctors. Pictures of normal and DCO nails were left on each doctor's table for comparison. The doctors were asked to determine the presence or absence of DCO. The patient history, the results of a clinical examination, medication use and blood investigations (urea, creatinine, calcium, liver function tests, cholesterol, C-reactive protein, full blood count, erythrocyte sedimentation rate, CD4, CD8, cell ratios and syphilis serology) were noted on a data collection sheet.

The data were computed and statistically analysed using Statistica 6.0. The probability value was set at 0.05, and the Student's t-test was used to determine significant biochemical, haematological or clinical differences between patients with and without DCO. The Bonferoni equation was applied where indicated. The $ChiX^2$

Table I: Demographics of the study population

Observation	Number (percentage)
Total number	420
Phase 1 (Out-patients)	
Total number	100
Female	76
Male	24
Race	All black patients
HIV status	All positive
(age not determined)	
Phase 2 (In-patients)	
Total number	183
Female	106 (58.15%)
Age (years)	38.86 ± 9.00
Range	15 - 61
Race	105 black; 1 white
HIV status	81.13% positive
Male	77 (41.85%)
Age (years)	39.35 ± 11.85
Range	18 - 74
Race	76 black; 1 white
HIV status	77.92% positive
Phase 3 (Out-patients)	
Total number	137
Female	97 (70.80%)
Age (years)	34.97 ± 8.77
Range	22 - 65
Race	97 black
HIV status	All positive
Male	40 (29.20%)
Age (years)	40.23 ± 8.84
Range	24 - 61
Race	36 black; 2 white; 2 Asian
HIV status	All positive

Figure 1: Examples of dyschromonychia (predominantly nail bed and compressible). Note the loss of lunula with the blue-grey hue extending from the base of the nail, generally involving less than half of the nail

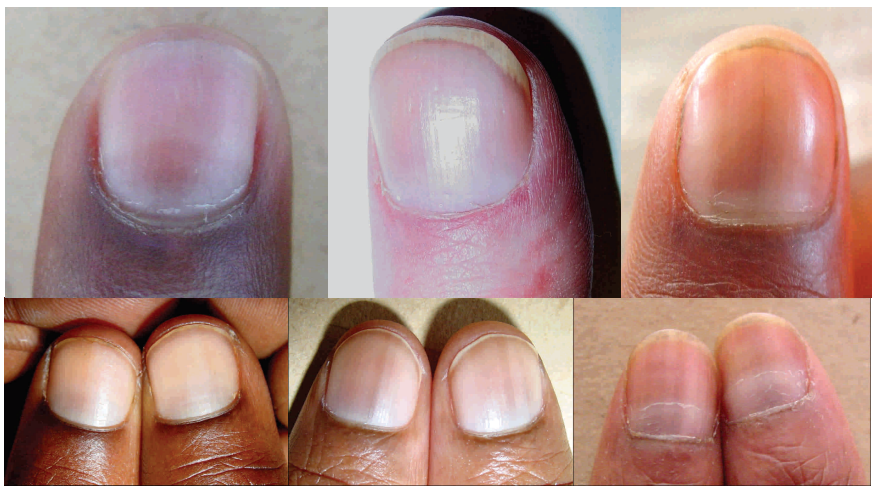


Figure 2: Examples of dyschromonychia (non-compressible). Generally involves more than half the nail.

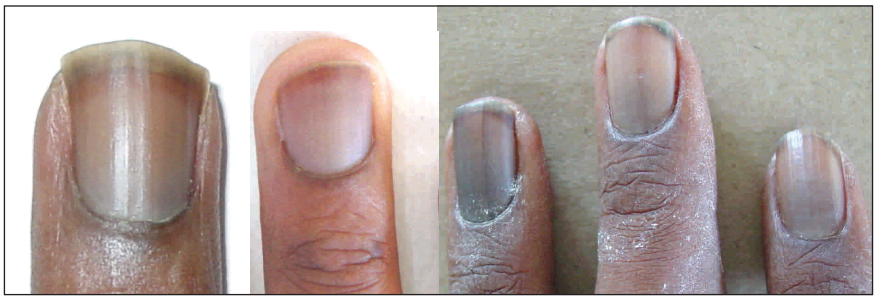


Figure 3: The nail in which dyschromonychia was most prominent (n = 128 patients)

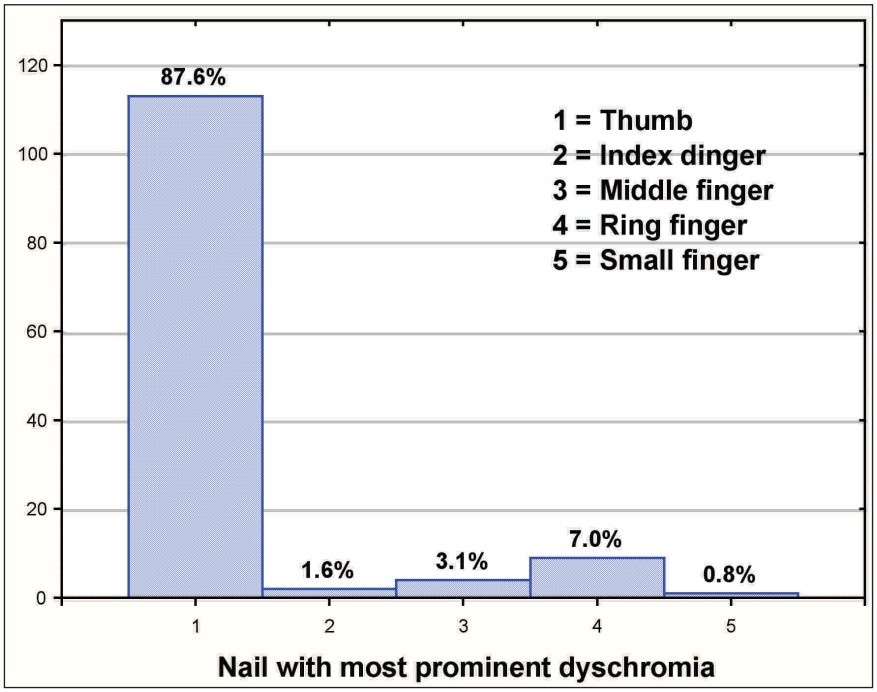
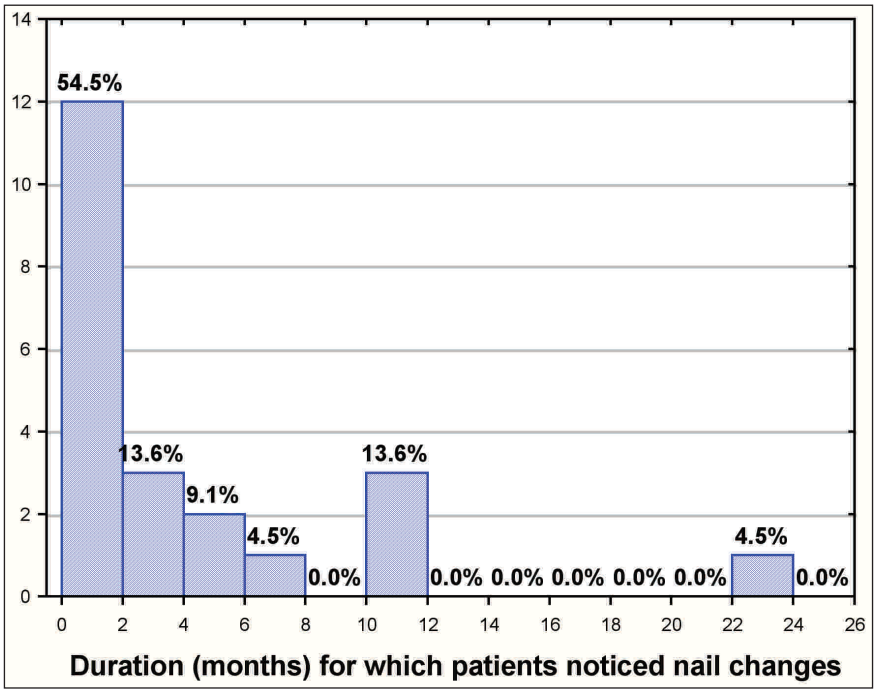


Figure 4: Duration for which dyschromonychia was noted by patients (n = 22 patients)



test was used to determine the significant difference between disease profiles and HIV prevalence.

Results

Patient demographics are shown in Table I and examples of DCO are shown in Figures 1 and 2. The kappa value was determined to be 0.72 for the DCO evaluation. The prevalence of DCO in patients in the Immunology Clinic was 19.00% and in the ward patients it was 51.61%. The nails involved most commonly were those of the thumb and the ring finger (Figure 3). In 7.25% of cases, all fingernails were equally affected. The toenails were more difficult to evaluate, with only 33.59% found to be positive, together with concomitant fingernail DCO. There were no patients with exclusive toenail DCO. Most patients were unaware of the nail changes (80%), and only 20% of the patients had observed a change in nail colour. The mean duration of DCO was 4.7 ± 5.7 months (min = 1 month, max = 24 months) (Figure 4).

Inpatients with DCO had significantly higher rates of infections, predominantly involving the lung (Table II), as well as a significantly higher prevalence of HIV infection (97.00% vs. 59.04%), significantly lower lymphocyte, CD4, and albumin levels, as well as a significantly lower CD4:CD8 ratio (p 0.0001). Of all the biochemical and haematological variables examined (see Materials and Methods), only the aforementioned were found to be significantly different (Bonferoni equation: $p < 0.0019$). Previous medication used by the patients with and without DCO did not differ, with the exception of trimethroprim, which was used as a prophylaxis in known HIV-positive patients.

Dyschromonychia was found to have 66% sensitivity, 92% specificity, 66% positive predictive value, 92% negative predictive value (prevalence

Table II: Variables investigated in the in-patients with and without dyschromonychia (DCO)

Variable	DCO absent (n = 83)	DCO present (n = 100)	P value
Disease group			
Infective	48 (57.83%)	96 (96.00%)	<0.0001
Inflammatory/CTD	7 (8.43%)	0	
Malignancy	6 (7.23%)	1 (1.00%)	
Renal	2 (2.41%)	1 (1.00%)	
Miscellaneous	20 (24.10%)	2 (2.00%)	
Organ involved			
Lung	41 (49.40%)	83 (83.00%)	<0.0001
Other than lung	42 (50.60%)	17 (17.00%)	
HIV status			
Positive	49 (59.04%)	97 (97.00%)	<0.0001
Negative	34 (30.96%)	3 (3.00%)	
Blood analyses			
Lymphocyte count (x10^6/l)	1824 ± 1229	1079 ± 674	<0.0001
CD4 count (x10^6/l)	505 ± 508	124 ± 223	<0.0001
CD4 percentage	25.82 ± 17.27%	9.42 ± 10.13%	<0.0001
CD8 count (x10^6/l)	762 ± 556	602 ± 422	<0.0001
CD8 percentage	43.38 ± 17.99%	54.91 ± 16.06%	NS
CD4:CD8 ratio	0.92 ± 0.30	0.21 ± 0.30	<0.0001
Albumin (g/l)	26.9 ± 7.9	20.6 ± 5.8	<0.0001

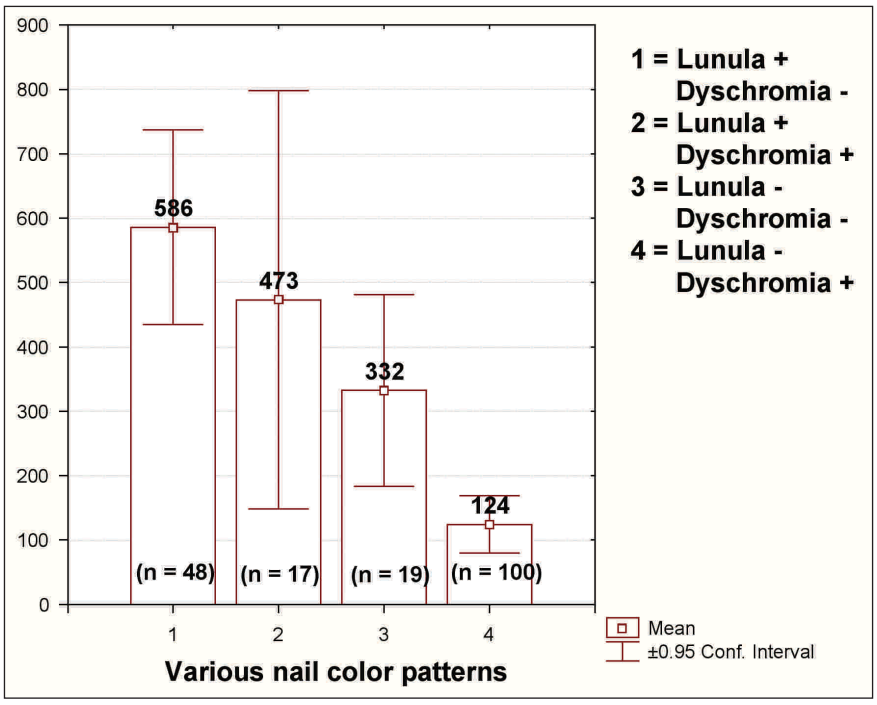
[ChiX^2 test used for disease group, organ involved and HIV status analysis, Student's t-test used for blood analysis determinations, NS = non significant p > 0.0019]

Table III: Lymphocyte cell counts with different nail presentations

Variable	Group 1: Lunula + Dyschromia – (n = 48)	Group 2: Lunula + Dyschromia + (n = 17)	Group 3: Lunula – Dyschromia – (n = 19)	Group 4: Lunula – Dyschromia + (n = 100)
Lymphocyte count (x10^6/l)	1885 ± 1256	2094 ± 1355	1555 ± 1011	1056 ± 652
CD4 count (x10^6/l)	586 ± 515	473 ± 632	332 ± 309	124 ± 223
CD4 percentage	29.8 ± 16.9	18.8 ± 17.2	21.8 ± 16.9	9.5 ± 10.1
CD8 count (x10^6/l)	699 ± 459	1067 ± 727	738 ± 609	584 ± 400
CD8 percentage	40.0 ± 18.7	50.3 ± 15.7	46.6 ± 17.9	54.6 ±16.0
CD4:CD8 ratio	1.14 ± 1.06	0.50 ± 0.53	0.72 ± 0.78	0.22 ± 0.30
Albumin (g/l)	29.2 ± 8.6	25.9 ± 5.4	22.8 ± 5.8	20.5 ± 5.7

[0.0001 for all variables between group 1 and group 4, except CD8 cell count]

Figure 5: Association with various nail presentations and CD4 cell counts



of in-patients tested for HIV in medical wards is 80-90%; unpublished findings, PF Levay), a positive likelihood ratio of 8.2 and a negative likelihood ratio of 0.4 in the HIV in-patient population. The association with HIV was further supported by the various nail patterns and progressive decline in CD4 cell counts (see Table III and Figure 5). The best discriminatory CD4 for DCO was 216.6 x 10^6/l (sensitivity = 89%; specificity = 63%), while a CD4 value of 134.3 x 10^6/l yielded a sensitivity of 75% and a specificity of 73%. Eliminating patients with leukonychia increased the specificity from 63% to 68%.

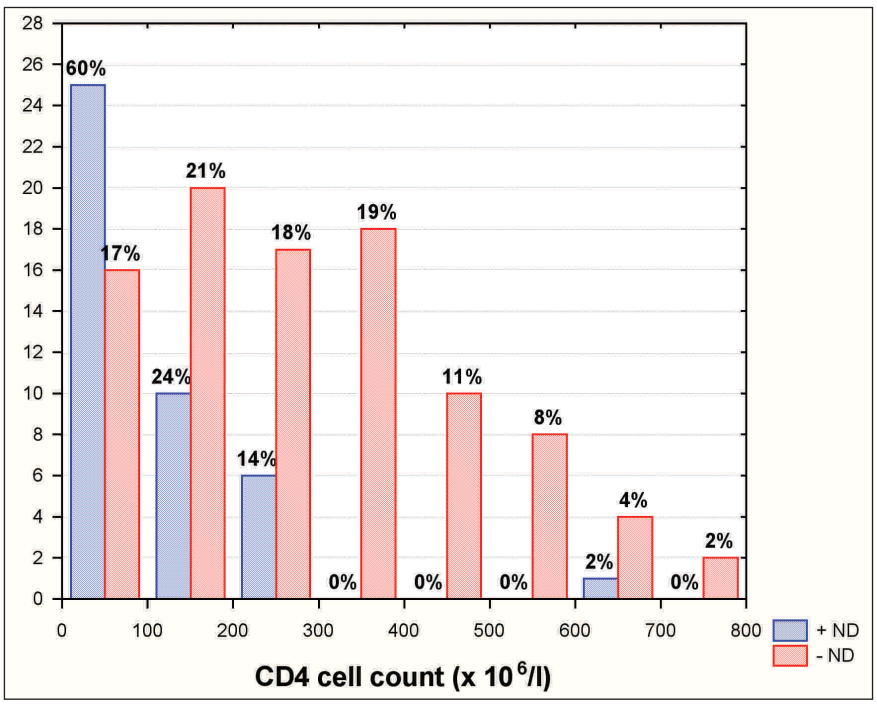
Three patients had DCO but were HIV-negative on blood serology. The first patient was a 53-year-old male with squamous cell cancer of the lung

Table IV: Variables investigated in the out-patients with and without dyschromonychia (DCO)

Variable	DCO Absent (n = 95)	DCO Present (n = 42)	P-Value
Disease group			
Infective	28 (75.68%)	25 (86.21%)	NS
Inflammatory/CTD	4 (10.81%)	2 (6.90%)	
Malignancy	0	0	
Renal	2 (5.41%)	0	
Miscellaneous	3 (8.11%)	2 (6.90%)	
Organ involved			
Lung	16 (43.24%)	18 (62.07%)	=0.0071
Other than lung	21 (56.76%)	11 (37.93%)	
Medication history			
Positive trimethroprim use	25 (26.32%)	28 (66.67%)	<0.0001
Negative trimethroprim use	70 (73.68%)	14 (33.33%)	
Blood analyses			
Lymphocyte count (x10^6/l)	1886 ± 751	1667 ± 1118	NS
CD4 count (x10^6/l)	282 ± 181	110 ± 114	<0.0001
CD4 percentage	14.53 ± 8.43%	6.48 ± 6.23%	<0.0001
CD8 count (x10^6/l)	1059 ± 615	1129 ± 786	NS
CD8 percentage	54.43 ± 14.44%	62.90 ± 13.24%	NS
CD4:CD8 ratio	0.32 ± 0.28	0.12 ± 0.15	<0.0001
Albumin (g/l)	34.10 ± 7.6	26.7 ± 9.0	<0.0001

[ChiX^2 test used for disease group, organ involved and HIV status analysis, Student's t-test used for blood analysis determinations, NS = non significant p > 0.0019]

Figure 5: Association with various nail presentations and CD4 cell counts



who had received chemotherapy (adriamycin-containing regime), which is known to cause DCO. The second was a 33-year-old female patient who had chronic lung disease due to previous pulmonary tuberculosis, complicated by bronchiectasis, clubbing and superimposed chronic pneumonia. The third patient was a 27-year-old male with chronic lung disease complicated by empyema.

All the outpatients examined were HIV positive. Unlike the inpatients, no significantly higher incidence of infective diseases was found in those with or without DCO. However, previous pulmonary disease was found to be significantly higher in patients with DCO. The use of trimethroprim was substantially higher in patients with DCO, although this is most likely due to their lower CD4 cell counts. Biochemical and haematological differences were almost the same as for in-patients: lower CD4 cell counts, CD4:CD8 ratios and albumin levels (Table IV, Figure 6). The presence of DCO was 74% sensitive and 78% specific for a CD4 cell count of 130.

Discussion

In the present HIV/AIDS epidemic, clinicians have generally observed an increased occurrence of DCO. DCO is generally assumed to be a sign of advanced HIV/AIDS, despite there being little substantiated evidence.

This is the first study to investigate the sensitivity and specificity of DCO and associated diseases. Our findings indicate an association with HIV infection. The only other study to investigate DCO examined 75 patients attending the Kilimanjaro Christian Medical Centre.[6] All the patients in this study were HIV positive, indicating a specificity of 100% in the population studied. In the present study, the specificity was found to be 66%, although it is related to the stage of HIV. Sensitivity was not examined in

the aforementioned study, as patients without nail dyschromia were not tested for HIV. The current study found a clear relationship between the stage of HIV based on CD4 cell counts and the presence of DCO. In both the in- and out-patient setting, the presence of DCO was approximately 75% sensitive and specific for CD4 cell counts below approximately 140 x 10^6/l.

Leppard describes DCO as a diffuse, bluish discoloration, rather than linear, pigmented bands, which begins in the lunulae and gradually spreads distally.[6] The findings of this study correspond with those of previous authors. There appears to be a progression in nail findings, ranging from normal nails, dyschromia of the nail bed in the presence of a lunula, alternatively disappearance of the lunula without dyschromia, then loss of the lunula with dyschromia, followed by or associated with nail dyschromia, which has been noted to be a predominately brown discoloration, often extending the full length of the nail. The brown discoloration is non-compressible. As in previous reports, the DCO is a blue-grey discoloration, most prominent on the thumbnail, extending from the nail base towards the nail edge, rarely longer than half the nail, and it disappears on compression. Toenails have been reported to be affected later than fingernails, possible due to their slower growth rate.[5] This study found toenail evaluation to be far inferior to fingernail evaluation, possible due to the population examined, the members of whom are generally poor and who practise poor hygiene. It is therefore the authors' opinion that toenail evaluation for dyschromia is ineffective and should be abandoned in favour of fingernail evaluation.

There are no known reports of DCO in white patients, although we have observed these changes in three white males (none on antiretroviral therapy). One of these patients is presently following-up at the Immunology Clinic, and two have died (one after a fourth episode of cyptococcus meningitis, and the other from tuberculous meningitis and psoriasis). All these patients' CD4 counts were lower than 100 x 10^6/l.

The mechanism responsible for the occurrence of DCO is unknown. This study clearly demonstrates an association with advanced HIV, although it would be rash to consider this a sign peculiar to this disease. HIV is more likely to be the precipitant, leading to immunosuppression and increased infections. The three patients with DCO in the absence of HIV infection noted in this study had chronic lung disease. Since the initiation of this study, another HIV-negative patient has been noted with DCO, with a necrotising pneumonia, finger clubbing, destruction of his left lung, and with a large abscess in the upper lobe of the right lung. It would appear that chronic forms of lung infections are a more likely etiology for DCO than HIV infection itself. The argument of cyanosis as an etiological factor does not stand ground. Most of our patients demonstrated no central cyanosis, and those who did, retained their DCO when given supplemental oxygen (PO2 returned to normal on blood gas).

Study limitations include possible bias due to the high prevalence of HIV in the population studied. The prevalence differed between out- and in-patients, although the sensitivities and specificities for CD4 levels did not, indicating that sensitivities and specificities for the CD4 cell count may be retained in communities with lower HIV prevalence. The population studied was predominately black, with only three white patients included. This reflects the population served by the hospital. Additional causes of DCO (such as silver intoxication) were not excluded, although these causes were unlikely in the light of the prevalence of DCO in our population.

In conclusion, this study demonstrates a close association between HIV and DCO, especially in patients with lower CD4 cell counts. The absence of DCO is a poor predictor for the presence of HIV, although its presence has a high sensitivity. The identification of DCO is a simple, quick, and efficient method for evaluating the immune status of our population with reasonable sensitivity and specificity for a CD4 value of 140 and below. DCO is most likely a feature of chronic infection, possibly chronic lung infections. The pathophysiology of this clinical sign warrants further investigation.

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Conflict of interest

In terms of the broad definition of conflict of interest published under the information for authors in *South African Family Practice*, we declare that we have no financial or personal relationship(s) which may have inappropriately influenced us in writing this paper.

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