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Prevalence and factors associated with dry skin in HIV infection: the FRAM study

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Abstract

Objective—Complaints of dry skin in HIV-infected individuals were reported after the advent of HAART. The objective of the study was to evaluate the prevalence of dry skin and associated factors in HIV-infected and control subjects.

Design—Cross-sectional.

Methods—A total of 1026 HIV-infected subjects and 274 controls [from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a population-based study of cardiovascular risk assessment] in the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM) had skin assessed by self-report and examination. Multivariable logistic regression identified factors associated with dry skin.

Results—Self-reported dry skin was more prevalent in HIV-infected subjects than controls. In multivariable analysis, HIV infection was associated with self-reported dry skin. In HIV-infected men, current indinavir use, CD4 cell count less than 200 cells/ μ l and recent opportunistic infections were associated with dry skin. Indinavir use had an elevated risk in men with CD4 cell counts of 200 cells/ μ l or greater but not with CD4 cell counts less than 200 cells/ μ l. In HIV-infected women, a CD4 cell count less than 200 cells/ μ l was associated with dry skin; indinavir use did not reach statistical significance but, as in men, indinavir use had an elevated risk in those with higher CD4 cell counts than in those with CD4 cell counts less than 200 cells/ μ l.

Conclusion—Dry skin is more common in HIV-infected individuals than controls. In HIV-infected individuals, low CD4 cell counts and indinavir use in those with higher CD4 cell counts are associated with dry skin.

Keywords

complication; dermatology; opportunistic infection; protease inhibitors; retinoid

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Conflicts of interest: None.

Introduction

HIV infection is associated with a number of common dermatological disorders [1,2]. As many as 30% of HIV-infected individuals reported dry skin or ichthyosis in the pre-HAART era [3], whereas more recent HAART-era studies have reported the prevalence of dry skin to range from 19 to 28% [4–6]. Although some researchers have reported a decline in infectious dermatological conditions in the HAART era, probably as a result of a low incidence of opportunistic infections (OI) [6], complaints of dry skin and other non-infectious conditions persist.

We evaluated the prevalence of dry skin in the Fat Redistribution and Metabolic Change in HIV infection (FRAM) cohort, a representative sample of HIV-infected subjects and controls in the United States using both self-assessed and examiner-rated measures of skin dryness. To our knowledge, this is the first paper to compare the prevalence of dry skin in a large national study among HIV-infected US adults with a control population. In addition, we examined predictors of self-assessed dry skin among HIV-infected participants.

Methods

Study population

The FRAM Study enrolled 1183 HIV-infected and 297 controls between 2000 and 2002. FRAM was designed to evaluate the prevalence and correlates of changes in fat distribution, insulin resistance, and dyslipidemia in a representative sample of HIV-infected subjects and HIV-seronegative controls in the United States. The methods have been described in detail previously [7]. HIV-infected subjects were recruited from 16 HIV or infectious disease clinics or cohorts from June 2000 to September 2002. Control subjects were recruited from two centers from the Coronary Artery Risk Development in Young Adults (CARDIA) study [8]. CARDIA participants were originally recruited in 1985–1986 as a population-based sample of healthy 18–30-year-old Caucasian and African-American women and men to study cardiovascular risk factors longitudinally. The protocol was approved by institutional review boards at all sites.

Dry skin assessment

Dry skin was assessed in 1172 HIV-infected and 297 control men and women. Self-reported questionnaires were administered to assess for changes in skin over the past 5 years (the time since the introduction of HAART) with bidirectional scales including dry, no change and moist. Clinicians also performed an overall assessment of skin (current) using a similar bidirectional scale (dry, normal, moist). Results were dichotomized for analysis as dry compared with unchanged or normal. Subjects with moist skin were uncommon ($n=30$ or 2% of self-report; and $n=133$ or 9% of examinations) and were excluded (27% of those excluded were controls and 73% were HIV infected), leaving a total of 1026 HIV infected and 274 controls in the analysis. Those excluded as a result of self-reported moist skin were similar in most demographic and clinical characteristics, except they were somewhat more likely to be African-American (57 versus 41%, $P=0.048$), to be physically inactive (63 versus 41%, $P=0.011$), and to have current CD4 cell counts below 200 cells/ μ l (42 versus 23%, $P=0.047$).

Other measurements

Age, sex, race, medical history, and risk factors for HIV were determined by self-report, and alcohol, tobacco, and illicit drug use were assessed by standardized questionnaire. A single laboratory measured blood CD4 lymphocyte count and percentage, and plasma HIV RNA in HIV-infected participants (Covance, Indianapolis, Indiana, USA). Trained research

associates performed standardized medical chart abstraction of medications and medical history at HIV sites.

Statistical analysis

Analyses that compared HIV-infected subjects with controls excluded HIV-infected individuals with recent OI, and were restricted to those between the ages of 33 and 45 years ($N = 551$), because the control population did not include subjects outside this age range. Characteristics of HIV-infected participants and controls were compared and tested for statistical significance using the Mann–Whitney U-test for continuous variables, and Fisher's exact test for categorical variables.

Multivariable logistic regression analysis was used to investigate whether there was an independent association of HIV infection compared with controls in self-reported dry skin. Dry skin by examination was not further investigated in multivariable analysis because it was felt that factors such as the use of skin moisturizers and cosmetics could confound the rating, leading to a less reliable assessment of dry skin. We observed a statistically significant HIV by sex interaction ($P = 0.008$), so analysis was stratified by sex. Potential predictors in the combined HIV and control analysis included demographic information (sex, age, ethnicity), level of physical activity (quartiled), current smoking status, illicit drug use (current or ever use of marijuana, speed, crack, cocaine, combination use of crack and cocaine), less than adequate food intake, body mass index (BMI), homeless status (ever versus never), total number of alcohol drinks per week in the past year, menopause status (for women), and season (winter, spring, summer, or autumn).

Multivariable logistic regression models were built using stepwise regression, with $P = 0.05$ for entry and retention and with age (modeled per decade), ethnicity, and HIV status forced to be included in every model. We performed this by evaluating possible models one by one, rather than with an automated stepwise procedure, in order to avoid the exclusion of observations that had missing data only on unselected candidate variables. To account for possible differences between geographical sites, likelihood ratio testing was used to determine whether a random site effect should be added to the model. For each model, tests were conducted for goodness of fit using the Hosmer–Lemeshow test.

A second multivariable regression analysis was performed only among HIV-infected subjects to determine the factors independently predictive of dry skin among HIV-infected individuals. In addition to the predictors listed above, these models included HIV-RNA level (detectable versus undetectable) and CD4 cell count (<200 versus ≥ 200 cells/ μl) at the time of the study visit. Also tested for inclusion in the model were hepatitis C status (hepatitis C virus RNA >615), recent OI status, AIDS by CD4 cell count or OI, HIV duration, days since last OI, and HIV risk factors. In multivariable models controlling for the above factors, we evaluated the current use of each individual antiretroviral drug and antiretroviral class: nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitor (PI), and HAART as previously defined [9]. The current use of each antiretroviral drug, antiretroviral class, and HAART was added to the adjusted model in a forward stepwise manner.

All analyses were conducted using the SAS system, version 9.1 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

The demographics and clinical characteristics of the FRAM participants have been described in detail previously [7]. The demographics of the slightly smaller subset that had dry skin ratings by self-report or examination are shown in Table 1.

Dry skin in HIV-infected participants versus controls

The prevalence of self-reported dry skin was higher in HIV-infected subjects compared with controls in both men (42.1 versus 9.9%, $P < 0.0001$) and women (51.5 versus 31.6%, $P = 0.001$, Fig. 1), with similar results seen for dry skin by examination. The overall prevalence of dry skin was greater in women than in men. No statistically significant associations were found between ethnicity and dry skin. Stratification by ethnicity revealed the same patterns in African-Americans and Caucasians (data not shown).

Being HIV infected was associated with higher odds of reporting dry skin (Table 2). In multivariable analysis, being HIV infected remained associated with higher odds of self-reported dry skin, with larger differences seen in men [odds ratio (OR) 5.7, 95% confidence interval (CI) 3.1–10.4, $P < 0.0001$] than in women (OR 2.2, 95% CI 1.32–3.6, $P = 0.002$) probably caused by the higher prevalence of reported dry skin in control women.

Factors associated with dry skin in HIV infection

As a result of the greater prevalence of dry skin in women and because the HIV effect was larger in men than in women ($P = 0.008$, test for HIV by sex interaction), we elected to stratify the multivariable analysis of factors associated with dry skin in HIV infection by sex.

A low CD4 cell count was associated with increased report of dry skin in both HIV-infected men (<200 versus >200 cells/ μ l, OR 1.58, 95% CI 1.06–2.4, $P = 0.026$) and women (<200 versus ≥ 200 cells/ μ l, OR 2.0, 95% CI 1.11–3.6, $P = 0.021$; Table 3). In HIV-infected men, current indinavir use was associated with increased odds of dry skin (OR 1.96, 95% CI 1.30–3.0, $P = 0.001$). Although the indinavir by CD4 cell count interaction did not reach statistical significance ($P = 0.12$), we found that the association between indinavir use and dry skin was stronger in men with a highest CD4 cell count (OR 2.3, 95% CI 1.45–3.6, $P < 0.001$) compared with those with CD4 cell counts less than 200 cells/ μ l (OR 1.02, 95% CI 0.40–2.6, $P = 0.96$). In women, indinavir use did not reach statistical significance (OR 1.12, 95% CI 0.57–2.2, $P = 0.74$) but, as in men, higher odds of dry skin on indinavir were seen in those with higher CD4 cell counts (OR 1.41, 95% CI 0.64–3.1, $P = 0.39$) than in those with CD4 cell counts less than 200 cells/ μ l (OR 0.52, 95% CI 0.12–2.2, $P = 0.37$). The association of indinavir with dry skin was stronger than any other antiretroviral medication. We examined other PI (as well as PI as a class) and found that their effects trended in the same direction as indinavir, but only indinavir reached statistical significance.

Lacking adequate food intake was also associated with the report of dry skin in HIV-infected men (OR 1.80, 95% CI 1.21–2.7, $P = 0.004$). A similar tendency for inadequate food intake to be associated with dry skin appeared in HIV-infected women (OR 1.40, 95% CI 0.86–2.3, $P = 0.18$). BMI did not appear to be associated with dry skin in either men or women. Another factor associated with dry skin was recent OI in men (within 100 days versus 100+ days ago or never, OR 1.80, 95% CI 1.30–2.5, $P < 0.001$). In women, current crack cocaine use was associated with lower odds of dry skin (OR 0.30, 95% CI 0.10–0.91, $P = 0.034$).

Subjects with acne and atopic diseases may have a higher risk of developing dry skin, and therefore we analysed their prevalence and association with dry skin. Approximately 18% of

the HIV-infected subjects were found to have acne or an atopic disease, of whom 52% of women and 39% of men reported dry skin, a prevalence similar to that seen in the full cohort. In both unadjusted and adjusted models, acne/atopic disease status was found to have little association with dry skin (data not shown).

Discussion

Using the FRAM cohort, we found a higher prevalence of dry skin by both self-report and examination in HIV-infected men and women compared with controls. After multivariable adjustment, we found that low CD4 cell count, indinavir use, recent OI status, and inadequate food intake were associated with higher odds of self-reported dry skin in HIV-infected men. Low CD4 cell count was also associated with dry skin in HIV-infected women, whereas current crack cocaine use was associated with lower odds of dry skin.

Our finding of an association between the current use of indinavir and dry skin is supported by other smaller studies that have described PI-related severe dry skin. A prospective study of 332 HIV-infected patients found PI-related desquamative cheilitis and skin dryness in 15 patients on indinavir (20% of patients receiving indinavir) and one patient on zidovudine [10]. They reported resolution of the dermatological disorders upon discontinuation of the medication. Other indinavir-related dermatological problems have been reported [11–17].

A proposed mechanism for the induction of dry skin by PI such as indinavir is the displacement of vitamin A from cytoplasmic retinoic acid binding protein, enhancing its interaction with the retinoic acid receptor [18]. Other data also support the concept that PI enhance the potency of retinoids [19]. To date, plasma retinol levels have not been found to be higher in individuals taking PI, although retinal dehydrogenase activity was higher in a small group of HIV-infected individuals administered PI, which could increase retinoic acid concentrations [20]. A recent in-vitro investigation found that five HIV PI (zidovudine, zalcitabine, didanosine, zalcitabine, and zalcitabine) inhibited cytochrome P450 3A isoforms to varying degrees [21]. This inhibition may alter or disrupt the normal metabolism of retinoic acid, because cytochrome P450 3A enzymes are known to mediate the synthesis of retinoic acid [22].

Our finding that a low CD4 cell count is associated with higher odds of dry skin is also supported by previous reports before the common use of HAART. One report found that cutaneous findings more than doubled at CD4 cell counts less than 100 cells/ μ l [23]. A second study found higher rates of xerosis and other dermatological problems in those with CD4 cell counts below 200 cells/ μ l [24]. Another study found a mean CD4 cell count of only 179 cells/ μ l among HIV-infected patients with xerosis [4]. Our findings thus support the concept that even in the era of effective HAART, dry skin is associated with a low CD4 cell count.

The association between recent OI and dermatological problems is also supported by findings in the literature. For example, many viral, bacterial, and fungal infections can cause OI in HIV-infected patients and are associated with cutaneous manifestations [16]. The association of recent OI with dry skin, combined with the association with low CD4 cell count, emphasize that advanced HIV disease is associated with dry skin.

We also found a strong association between the report of inadequate food intake and dry skin in HIV-infected men. A similar finding is seen in patients with anorexia nervosa, in whom low BMI is associated with xerosis, which often resolves when balanced nutrition or higher body weight are restored [25]. We found that those with and without adequate food intake had similar BMI (data not shown), and BMI itself showed no apparent association

with dry skin in adjusted or unadjusted models. It is possible that poorer nutrition *per se* may be associated with dry skin.

This study has several limitations. Most importantly, the cross-sectional design limits the ability to determine causality. For example, we cannot determine whether having a recent OI causes dry skin, whether treatment regimens for OI cause cutaneous reactions, or whether the dry skin occurred before or independent of the OI. Individuals with acne or atopic disease may have a higher risk of developing dry skin, possibly biasing the results. The prevalence of dry skin in such subjects was similar to the full cohort, however, so inclusion in our analysis of such subjects should not have biased the results. Furthermore, acne/atopic disease status showed little association with dry skin in adjusted and unadjusted models. Lifestyle variables such as food intake and crack cocaine use could also impact dry skin, although it may have existed already. Another limitation is the use of self-report, which may have problems of perception. Control men reported much less dry skin compared with control women and HIV-infected men and women. It is possible that control men do not notice their skin as much as HIV-infected men. Although past studies have found an association of other PI in addition to indinavir with dry skin, only indinavir reached statistical significance in our analysis. As the other PI showed a weak trend in the same direction as indinavir, we cannot rule out a class effect. Finally, there may have been incomplete or inadequate control for factors that confound the association of HIV infection and dry skin. It is likely that HIV infection, and in particular advanced HIV disease, is the primary predictor of dry skin. To address the concerns of causality, a prospective study evaluating the evolution of dry skin in an HIV-infected population may be helpful.

Some factors associated with dry skin, as identified in HIV-infected men, did not reach statistical significance in women. The results seen in women often trended in the same direction as for men, but were of smaller magnitude.

In summary, dry skin is more common in HIV-infected individuals compared with controls. In HIV-infected men and women, low CD4 cell count is associated with dry skin. In HIV-infected men, indinavir use, recent OI and inadequate food intake were also found to be associated with dry skin. Future research may better elucidate the relationship of these factors to dry skin in the setting of chronic HIV infection.

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Fig. 1. Prevalence of dry skin in HIV-infected and control participants^a

^aAge-restricted analysis. Self-report excludes subjects with moist skin by self-report, Exam excludes subjects with moist skin by examination. HIV-infected (grey bars); control subjects (open bars). CI, Confidence interval.

Table 1

Demographics and clinical characteristics of HIV-positive subjects versus controls

	HIV-positive (age-restricted)	Control	<i>P</i> value	HIV-positive (all)
<i>n</i>	551	274		1026
Sex				
Female	31%	49%	<0.0001	31%
Age (years)				
Median	40.0	40.5	0.025	42.0
IQR	37.0–43.0	37.0–43.0		37.0–48.0
Ethnicity				
Caucasian	50%	51%	0.095	49%
African-American	37%	49%		39%
Hispanic	11%			10%
Other	1%			3%
BMI				
Median	24.5	27.2	<0.0001	24.6
IQR	22.0–27.8	23.8–31.5		22.1–27.8
Inadequate food intake	26%	13%	<0.0001	25%
Ever homeless	8%		NA	8%
Alcohol				
None	28%	19%	0.002	29%
<1/week	32%	27%		30%
1–7/week	28%	37%		27%
>7/week	12%	17%		13%
Current smoker	47%	17%	<0.0001	43%
Physical activity				
1st Quartile	42%	24%	<0.0001	45%
2nd Quartile	20%	25%		21%
3rd Quartile	21%	25%		18%
4th Quartile	18%	26%		16%
Menopausal (% of women)	5%	5%	>0.99	23%
Current crack	4%	1%	0.056	4%
Current CD4 cell count (cells/μl)				
Median	368.0			350.0
IQR	217.0–542.0			215.0–541.0
CD4 cells <200	23%			23%
HIV RNA (1000 copies/ml)				
Median	0.4			0.4
IQR	0.4–14.5			0.4–12.5
Undetectable HIV RNA	50%			51%
AIDS by CD4 cell count/OI	73%			72%
Recent OI	40%			42%

	HIV-positive (age-restricted)	Control	<i>P</i> value	HIV-positive (all)
Current HAART use	80%			77%
Duration (years)				
Median	2.8			2.8
IQR	1.5–4.3			1.4–4.4
Current PI use	57%			55%
Duration (years)				
Median	2.9			2.9
IQR	1.5–4.2			1.3–4.3
Current indinavir use	15%			16%
Duration (years)				
Median	2.8			2.8
IQR	1.5–4.5			1.4–4.4

BMI, Body mass index; IQR, interquartile range; OI, opportunistic infection; PI, protease inhibitor.

Table 2Multivariable analysis^a of self-reported dry skin in HIV-positive subjects versus controls

	Men		Women	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
HIV versus control				
Unadjusted	6.6 (3.7, 11.9)	<0.0001	2.3 (1.43, 3.7)	0.001
Adjusted ^b	5.7 (3.1, 10.4)	<0.0001	2.2 (1.32, 3.6)	0.002

CI, Confidence interval; OR, odds ratio.

^a Age-restricted analysis. Excludes subjects with moist skin by self-report.^b Adjusted model controls for HIV status, demographics, and lifestyle factors.

Because the HIV by sex interaction was statistically significant ($P = 0.008$), and because the factors associated with dry skin appeared to be different in men and women, we elected to fit models stratified by sex.

Table 3Multivariable analysis^a of factors associated with self-reported dry skin in HIV-positive subjects

	Men		Women	
	OR (95% CI)	P value	OR (95% CI)	P value
Factors				
African-American versus Caucasian	0.94 (0.66, 1.36)	0.76	0.98 (0.58, 1.63)	0.92
Hispanic versus Caucasian	1.07 (0.62, 1.82)	0.81	1.16 (0.46, 2.96)	0.75
Other versus Caucasian	1.85 (0.68, 5.04)	0.23	2.07 (0.43, 9.95)	0.36
Age (per decade)	1.05 (0.88, 1.25)	0.61	1.23 (0.92, 1.64)	0.17
HIV-related				
Current CD4 cell count (<200 versus ≥ 200 cells/μl)	1.58 (1.06, 2.36)	0.026	2.00 (1.11, 3.61)	0.021
Current HIV viral load (<400 versus ≥ 400 cells/μl)	0.82 (0.58, 1.16)	0.26	1.50 (0.91, 2.48)	0.110
Recent OI (<100 versus ≥ 100 days)	1.80 (1.30, 2.48)	0.0004	1.47 (0.91, 2.36)	0.113
Current use of indinavir	1.96 (1.30, 2.95)	0.001	<i>1.12 (0.57, 2.23)</i>	<i>0.74</i>
<i>CD4 cell count ≥ cells/μl</i>	<i>2.29 (1.45, 3.61)</i>	<i>0.0003</i>	<i>1.41 (0.64, 3.10)</i>	<i>0.39</i>
<i>CD4 cell count <200 cells/μl</i>	<i>1.02 (0.41, 2.55)</i>	<i>0.96</i>	<i>0.52 (0.12, 2.21)</i>	<i>0.37</i>
Lifestyle				
Food: inadequate versus adequate	1.80 (1.21, 2.69)	0.004	<i>1.40 (0.86, 2.29)</i>	<i>0.18</i>
Current crack	<i>0.79 (0.31, 2.03)</i>	<i>0.63</i>	0.30 (0.10, 0.91)	0.034

CI, Confidence interval; OI, opportunistic infection; OR, odds ratio.

^a Analysis is not age-restricted. Excludes subjects with moist skin by self-report.

Note: italicized factors did not enter into the model above, but are shown controlling for other factors in the model.