Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome?

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Background: A pruritic papular eruption (PPE) is a common skin manifestation observed in 12–46% of persons with HIV infection living in tropical countries.

Objective: To determine whether PPE responds to HAART and whether monitoring PPE severity could be used as a clinical marker to predict virological outcome in resource-limited settings where viral load testing is not available.

Methods: The study enrolled 53 patients with PPE for at least 1 month before starting a first-line HAART regimen as part of a prospective study. CD4 cell count and viral load were measured at enrolment and every 3 months. A scoring system was developed to evaluate the PPE severity by asking two questions. Over the last month how itchy has your skin been? Over the last month how has itching interfered with your sleep?

Results: Median CD4 cell count was 15 cells/μl and median viral load 268 663 copies/ml. All patients initiated a regimen containing a nonnucleoside reverse transcriptase inhibitor. Mean PPE score declined from 3.9 at enrolment to 0.1 at 24 months. In 37 (86%) of the 43 patients with at least 6 months of follow-up data, the PPE disappeared and never returned. Patients with viral load >400 copies/ml at months 9 and/or 12 had significantly higher PPE scores at months 9 to 12 than the patients with <400 copies/ml.

Conclusions: In most patients, PPE disappears during HAART and PPE severity scores were higher in patients whose first-line HAART failed to control plasma viral load.

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Introduction

A pruritic papular eruption (PPE) is a skin manifestation that has mainly been observed in persons with HIV infection living in tropical countries (occurring in 12–46%) [1–8], but a similar condition has also been reported in patients with HIV infection from nontropical countries [9]. In adult African patients, the presence of PPE is highly predictive of HIV infection [5]. PPE was reported in one study to be associated with low CD4 cell counts [10], but it can occur in early disease [5]. It is considered to be a World Health Organization (WHO) clinical stage 2 condition [11].

PPE presents as erythematous urticarial papules. The initial skin lesions are small, firm and intensely pruritic, which provoke scratching. Scratched papules become hyperpigmented macules or nodules. Lesions are found mainly on the extremities but the face and the trunk can also be involved [10]. Histopathological examination reveals hyperkeratosis, acanthosis, focal dyskeratotic and necrotic cells in the epidermis, and dermal fibrosis. Interstitial and perivascular infiltrates include lymphocytes, plasma cells, eosinophils and mast cells [5,6,11]. A skin biopsy study performed in Uganda has shown histological findings suggestive of arthropod bites [5]. Since PPE may be associated with peripheral and local

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eosinophilia and an increase in IgE, it has been hypothesized that PPE may be an altered and exaggerated immunological response to arthropod antigens [12,13].

Several empirical treatments have been proposed even if there have been no randomized, controlled trials to validate them. PPE has been reported to respond to antihistaminic drugs, systemic steroids, itraconazole, metonidazole, ivermectin, long-term application of permethrin, isotretinoin, ultraviolet B phototherapy, oxpentifylline (pentoxifylline), thalidomide and tacrolimus [7,14–22]. However, these treatments provide only minimal symptomatic relief.

The introduction of HAART has led to a striking reduction in AIDS-related opportunistic infections and complications [23]. This study examined whether, as PPE is an HIV-related condition, an effective HAART regimen could ameliorate this skin condition and whether it would reappear in a failing HAART regimen. If these were correct, then a PPE could be used as an additional clinical parameter to monitor the effectiveness of HAART in limited resource settings where CD4 cell count and viral load measurement are often not available.

Methods

Patients

The study was performed at the Infectious Diseases Clinic in Mulago National Referral Hospital, in Kampala, Uganda and formed a substudy within a prospective, observational, clinic-based cohort of 600 HIV-infected adults starting HAART. Among this cohort, a number of patients were identified who presented with a pruritic skin rash for longer than 1 month before the start of HAART and had evidence of papular lesions at physical examination. All patients gave written informed consent.

Clinic visits and follow up measurement

At enrolment, subjects were interviewed to provide information on demographics and key symptoms. Concerning the PPE, questions were asked about the duration and severity of PPE, the past use of topical or systemic drugs to treat PPE and known allergies to drugs. Every month for the first year, and every 3 months thereafter, a physical examination was performed.

PPE outcome was evaluated using the following information: the current use of topical or systemic drugs for PPE, PPE severity, and the timing of the disappearance of PPE. Patients were asked to describe the grade of itchiness during the day and night using one of four options: very much, a lot, a little, or not at all. These were assigned numeric values 3, 2, 1 and 0, respectively: A total score was calculated by adding the day and night score. PPE was defined as severe if the total score was 5 or 6, moderate if the total score was 3 or 4 and mild if the total score was 1 or 2.

PPE immune reconstitution syndrome (IRIS) was defined as an initial worsening of PPE after HAART initiation followed by a complete resolution by month 6 in a patient with an undetectable viral load at month 6. Current and past opportunistic infections and WHO clinical stage were also noted. All data were collected on standardized data collection forms.

Laboratory evaluation

At enrolment and then every 6 months, the following laboratory tests were performed: complete blood cell count (Beckman Coulter ACT diff 2, Fullerton, California, USA), CD4 cell count by FACS (Becton Dickinson, Mountain View, California, USA) and quantitative HIV RNA viral load (Amplicor HIV-1 Monitor version 1.5, Roche Diagnostic, GmbH Molecular Systems, Pleasanton, California, USA).

Virological failure was defined as viral load >400 copies on at least two occasions while taking HAART.

Data collection and statistics

Data were collected using Microsoft Office Access package and analysed using the statistical package SAS 9.01 (SAS Institute, Cary, North Carolina, USA).

Data were summarized using means, medians and proportions at baseline and after 6, 12, 18 and 24 months on treatment. Mean severity scores and proportion of patients with any symptoms were calculated at each clinic visit and displayed graphically. The relationship between the viral load and the presence/absence/severity of PPE was analysed. For this analysis, patients who switched to second-line therapy because of treatment failure were excluded from the analysis after the treatment switch. Mean severity scores were compared between patients with and without virological failure using the Wilcoxon rank sum test.

Results

Between June 2004 and February 2005, 53 patients with PPE for more than 1 month and starting HAART were enrolled in the study. Characteristics of patients at enrolment are shown in Table 1. Thirty nine (74%) patients were females. Median age at enrolment was 32 years (range, 20–58). Most patients were in an advanced stage of disease: 49 (92%) were in WHO stage 3 or 4. Median CD4 cell count was 15 cells/μl (range, 1–347) and median viral load was 268 663 copies/ml (range, 16 984–750 000). Two patients with a history of allergy to co-trimoxazole received dapsone as prophylaxis for opportunistic infections.

Table 1. Characteristics of patients at enrollment.

Characteristics	
Mean age [years (range)]	34.1 (20–58)
Sex	
Female	39 (73.6%)
Male	14 (26.4%)
WHO stage [No. (%)]	
1	0
2	4 (7.5%)
3	25 (47.2%)
4	24 (45.3%)
Median weight [kg (range)]	53 (33–78)
Prophylaxis	
Co-trimoxazole	48 (90.6%)
Dapsone	5 (9.4%)
Median CD4 cell count [cell/μl (range)]	52 (1–347)
Median HIV RNA [copies/ml (range)]	268 663 (16 984–750 000)
Median severity of the rash [scale value (range)]	4 (1–6)
Symptoms of rash [No. (%)]	
Mild	19 (35.8%)
Moderate	21 (39.6%)
Severe	13 (24.6%)
Median duration of rash [months (range)]	8 (1–60)
Duration of rash [No. (%)]	
1–6 months	22 (41.5%)
>6 months	22 (58.5%)
Known allergies [No. (%)]	2 (3.7%)
Past use of drugs for PPE [No. (%)]	
Topical	53 (100%)
Systemic	37 (69.8%)

WHO, World Health Organization; PE, pruritic papular eruption.

The mean PPE severity score at enrolment was 3.9; 19 (36%) patients had severe PPE, 20 (38%) moderate PPE and 14 (26%) mild PPE. The median duration of the rash at the time of the enrolment was 8 months (range, 1–60). The majority (58%) of the patients had PPE for more than 6 months.

All patients had received symptomatic PPE treatment before enrolment; all had used different types of oral antihistamine and 37 (70%) had also used topical steroids. No significant relationship between baseline viral load or CD4 cell count and severity or duration of PPE was detected (data not shown).

All patients started HAART with lamivudine plus stavudine, plus either nevirapine (51 patients) or efavirenz (two patients). Six patients (11%) who died during the first 3 months of HAART and two patients who were transferred to another facility were not included in the follow-up analysis because data on PPE were not available.

Table 2 summarizes the evolution of the patients in the study. The mean PPE severity declined from 3.8 at baseline to 0.1 at month 24, and the proportion of the patients with active PPE declined from 100% to 7% (Fig. 1). At baseline, 100% of the patients were using treatment for symptomatic PPE whereas only 4% required treatment at month 24.

In 37 (86%) of the 43 patients with at least 6 months of follow-up data, the PPE disappeared and never came back. In two (4%) patients, the PPE disappeared while the patient was taking the first-line HAART and then reappeared. One of them had a detectable viral load when the PPE reappeared, but viral load data at the time of the reappearance of PPE were unavailable for the other patient. In four (9%) patients, the PPE did not disappear during first-line therapy. Two were taking an effective HAART regimen and had undetectable viral load throughout all the follow-up visits, but the other two were taking a failing HAART regimen.

Patients on a virologically failing regimen at months 9 and/or 12 had significantly higher PPE scores at months 10 to 12 then patients on a successful HAART regimen (Fig. 2).

A total of seven patients experienced virological failure: of these five were switched to second-line therapy and two were still taking the first-line regimen at month 24 and were undergoing adherence counselling sessions. At the time of the regimen switch, three of the five had an active PPE; by month 6 on second-line therapy viral suppression was achieved in all five and the PPE had also disappeared in all five.

No association between baseline PPE severity score or prior duration of PPE and PPE severity score during HAART was noted.

Table 2. Evolution of patients with prurigo over 24 months of HAART.

	Month 6	Month 12	Month 18	Month 24
No. patients	43	43	39	29
Mean weight (kg)	59.4	61.8	61.0	60.8
Mean CD4 cell count (cells/μl)	198	217	254	324
Patients with viral load < 400 copies/ml (%)[a]	83.7	81.4	89.7	89.7
Mean severity score	0.9	0.5	0.1	0.1
Any pruritic papular eruption (%)	63	23	5	7
Taking any rash medications (%)	53	20	3	4

[a]Patients switched to second-line treatment were not included.

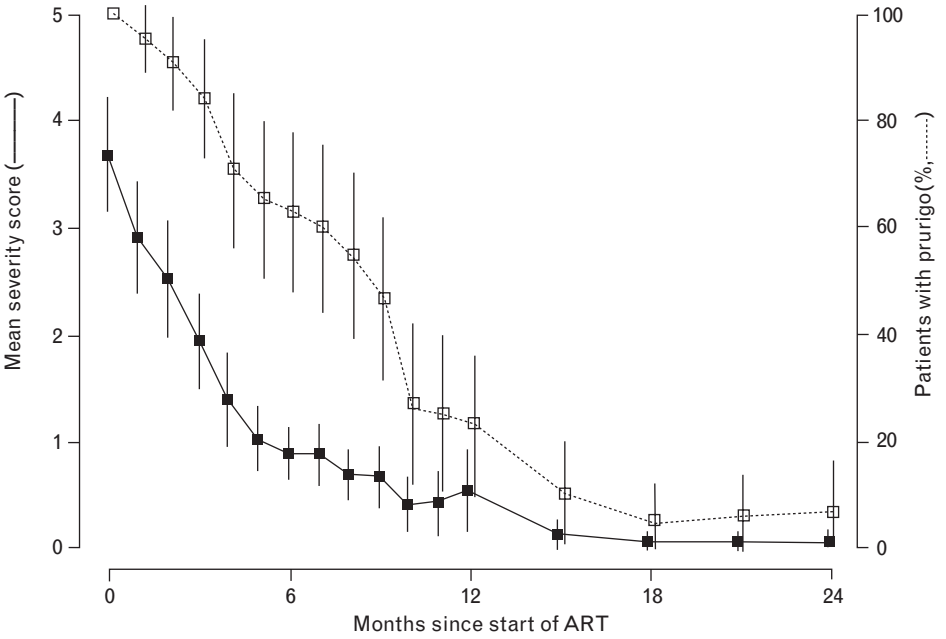

Fig. 1. Changes in the mean severity score of pruritic papular eruption (PPE) (–▪–) and the proportion of patients with PPE over 24 months of antiretroviral treatment (ART) (···▫···).

Seven (13%) patients were considered to have developed PPE IRIS and were compared with 11 patients without IRIS (with a PPE that had disappeared and with an undetectable viral load at month 6). There were no significant differences in baseline characteristics except that baseline PPE severity scores were lower in the patients with PPE IRIS. The CD4 cell count increase and viral load decrease by month 6 were similar in both patients with PPE IRIS and those without (data not shown). Based on medical chart review, patients with PPE IRIS did not experience any other IRIS manifestations.

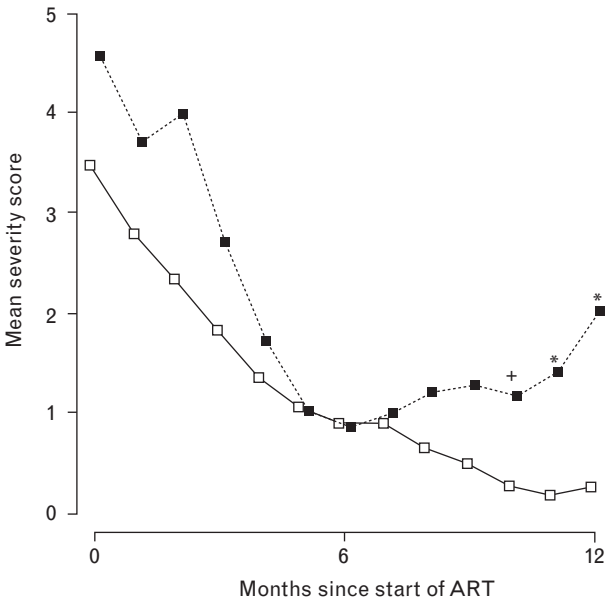

Fig. 2. Changes in the mean severity score of pruritic papular eruption in patients on antiretroviral therapy (ART) whose therapy was failing virologically at 12 months (–▪–) and in those whose regimen was successful (···▫···). *p-value <0.05; $^{+}$p-value >0.050 and <0.100 p-value for difference between treatment success and failures: 0.084 at month 10, 0.019 at month 11, 0.015 at month 12.

Discussion

Our results show that PPE responds to HAART. Indeed, in our study, the prevalence of PPE declined from 100% to 7% in 24 months, and even patients for whom the PPE persisted at 24 months reported a reduction in the severity of the itching.

At month 24, only 4% of the patients were still receiving symptomatic drugs because they had an active PPE. In all the others, HAART alone was able to maintain patients free of symptoms.

In resource-limited settings, there is need for alternative tools to evaluate HAART outcome because of the inability to provide virological monitoring. The re-appearance of PPE after 6 months of HAART has been proposed as a potential clinical parameter to predict virological failure [24].

In our study at month 10 and 12, patients with virological failure had a significantly higher PPE severity score compared with patients with virological suppression. However, this difference was not significant after month 12. The latter can be explained by the small sample size of the study. Indeed, after 12 months, the majority of patients on a failing regimen were switched to an effective

second-line treatment and, therefore, very few patients on a failing treatment regimen remained in the study.

Also, we observed, although in small proportions, discordant response of PPE. Particularly, PPE persisted despite an undetectable viral load in two patients (4%); this suggests that response to PPE should be used together with other clinical and, if available, immunological parameters to monitor virological outcome.

Immunoreconstitution disease has been observed for several HIV-related conditions including skin conditions, but PPE IRIS has never been documented so far [25]. In our study, we identified seven patients with an initial worsening of PPE despite a successful HAART regimen. Whether this worsening was caused by an IRIS phenomenon remains to be proven. At present, the pathophysiology of IRIS remains incompletely understood and certainly we do not have a laboratory test to confirm the diagnosis of IRIS. In future prospective studies of PPE during HAART, it would be useful to follow patients clinically and also to perform consecutive skin biopsies and more in-depth studies of the patient's cellular immunity.

In conclusion, PPE seems to disappear in most patients with HIV infection during an effective HAART. These findings confirm that PPE is an HIV-related condition. Whether (and when) PPE may reappear in treatment failure needs to be determined in a larger study. Occasionally, PPE may temporary increase shortly after starting HAART. Whether this is an IRIS phenomenon needs further investigation. In countries with limited resources, where laboratory tests such as CD4 cell count and viral load are often not available, doctors should consider the evolution of PPE and other HIV-related clinical manifestations as clinical criteria suggesting treatment failure.

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