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Factors associated with pruritic papular eruption of human immunodeficiency virus infection in the antiretroviral therapy era

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Summary

Background—Pruritic papular eruption (PPE) of HIV is common in HIV-infected populations living in the tropics. Its aetiology has been attributed to insect bite reactions and it is reported to improve with antiretroviral therapy (ART). Its presence after at least 6 months of ART has been proposed as one of several markers of treatment failure.

Objectives—To determine factors associated with PPE in HIV-infected persons receiving ART.

Methods—A case–control study nested within a 500-person cohort from a teaching hospital in Mbarara, Uganda. Forty-five cases and 90 controls were enrolled. Cases had received ART for 15 months and had an itchy papular rash for at least 1 month with microscopic correlation by skin biopsy. Each case was individually matched with two controls for age, sex and ART duration.

Results—Twenty-five of 45 cases (56%) had microscopic findings consistent with PPE. At skin examination and biopsy (study enrolment), a similar proportion of PPE cases and matched controls had plasma HIV RNA < 400 copies mL⁻¹ (96% vs. 85%, $P = 0.31$). The odds of having PPE increased fourfold with every log increase in viral load at ART initiation ($P = 0.02$) but not at study enrolment. CD4 counts at ART initiation and study enrolment, and CD4 gains and CD8 T-cell activation measured 6 and 12 months after ART commencement were not associated with PPE. Study participants who reported daily insect bites had greater odds of being cases [odds ratio (OR) 8.3, $P < 0.001$] or PPE cases (OR 8.6, $P = 0.01$).

Conclusions—Pruritic papular eruption in HIV-infected persons receiving ART for 15 months was associated with greater HIV viraemia at ART commencement, independent of CD4 count. Skin biopsies are important to distinguish between PPE and other itchy papular eruptions.

Pruritic papular eruption (PPE) of HIV has been described as a chronic, intensely pruritic papular and symmetrically distributed rash where the greatest numbers of lesions are often found on the extremities, but the rash may be generalized (Fig. 1).^{1,2} It is one of the most common skin conditions in HIV-infected populations living in the tropics, with a reported prevalence of 11–46%.^{1–5} The typical microscopic findings of PPE consist of a wedge-shaped mild-to-moderate perivascular and interstitial infiltrate of lymphocytes and eosinophils, similar to the microscopic findings of arthropod bites or stings (Fig. 2). This, together with eosinophilia and elevated IgE levels, has led to the suggestion that PPE is the result of an exaggerated immunological reaction to arthropod bites or stings.^{3,6}

Pruritic papular eruption has been reported as an early manifestation of HIV infection in Haiti¹ and Kinshasa, Democratic Republic of Congo.² Its high prevalence, reported early presentation and high predictive value for HIV disease have prompted suggestions of its use as a marker for early diagnosis of HIV infection.^{1,2} However, this is disputed by other studies^{7,8} that report other opportunistic infections or skin diseases before the development of PPE. Several observational studies have reported a link between low CD4 counts,^{3,7,9} advanced HIV disease [World Health Organization (WHO) clinical stage 3 and 4]¹⁰ and PPE, thus proposing the use of PPE as a marker for advanced HIV disease.⁷ PPEs are included in stage 2 of the WHO's clinical staging of HIV, a demonstration of its current role in clinical evaluation of HIV disease.¹¹

Anecdotal reports of the resolution of PPE after a few months of antiretroviral therapy (ART) commencement and its recurrence within weeks of ART discontinuation have been described.¹² In an observational study, 27/29 patients with PPE reported resolution of PPE, and two reported a reduction in its severity within 24 months of ART.¹⁰ As a consequence of PPE's response to ART, new-onset, recurrent or worsening PPE has been proposed as part of an algorithmic approach to the clinical evaluation of treatment failure after at least 6 months of ART.^{12,13}

Our primary objective was an exploration of predictors associated with the presence of PPE in HIV-infected persons receiving ART. Predictors studied included HIV viral load, CD4 cell count and percentage of CD38⁺ human leucocyte antigen (HLA)-DR⁺ CD8⁺ T cells, a marker of CD8⁺ T-cell activation and predictor of HIV disease progression.^{14–16} Environmental predictors examined include factors that may influence exposure to insect bites or stings, including time of work, bed net or mosquito net use and housing characteristics. Dermatology-specific predictors such as a history of skin conditions that may manifest as chronic pruritic papules were also explored.

Patients and Methods

Approvals from the Committee on Human Research at the University of California, San Francisco and the Institutional Ethical Review Committee of Mbarara University of Science

and Technology have been obtained. Informed consent was obtained from all study participants.

Study Design and Setting

This is a case-control study nested within the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort, a 500-person cohort assembled at the time of ART initiation from adult Ugandan patients receiving medical care at the HIV clinic of Mbarara National Referral Hospital. Study participants lived within 20 km of Mbarara, a rural setting located 5 h by automobile from Kampala, the capital city of Uganda.¹⁷

Study Participants

All study participants had been receiving ART for at least 15 months. Inclusion criteria for cases were the presence of an active itchy papular skin rash for at least 1 month determined by self-report and clinical examination by a dermatologist (S.L.C. or E.H.A.). Controls were defined by the absence of an active skin rash at the time of study enrolment. Each case was individually matched with two controls for age, sex and duration of ART.

Study Procedures

All study participants completed standardized interviewer-administered instruments at 3-month intervals as part of the UARTO protocol. Study instruments were checked postinterview by study coordinators, and missing information was obtained from participants via telephone or at their next visit. The Filmer-Pritchett Asset Index,¹⁸ a proxy for household wealth, was derived from detailed information obtained during participant interviews. Blood was drawn from all participants at 3-month intervals for measurements including CD4 cell counts, plasma HIV RNA and percentage of CD 38⁺ HLA-DR⁺ CD8⁺ T cells. At the time of study enrolment, all study participants were examined by a study dermatologist (S.L.C. or E.H.A.) to confirm the presence or absence of a papular rash. Cases received clinical photography prior to a 4-mm punch biopsy of a new unexcori-ated primary lesion. Biopsies were reviewed by dermatopathologists at the University of California, San Francisco (T.H.M., P.E.L.), from whom all details of study participants were withheld apart from the body site from which the biopsy was taken.

Statistical Analyses

Statistical analyses were carried out with the Stata Statistical Software: Release 11 (StataCorp LP, College Station, TX, U.S.A.). Wilcoxon rank sum tests or Fisher's exact tests were used to compare characteristics of cases and controls. Cases with skin biopsy findings consistent with PPE were defined as PPE cases. The rest of the cases were known as non-PPE cases. Their matched controls were identified as PPE controls and non-PPE controls, respectively. PPE cases were also compared with non-PPE cases for a better understanding of PPE and its clinical mimickers.

Conditional logistic regression was used to explore predictors associated with cases and PPE cases compared with their matched controls, and logistic regression was used to compare PPE cases with non-PPE cases. Based on results from single-predictor analyses, we attempted to fit multipredictor conditional logistic regression models for cases and PPE

cases. Predictors that met the preset criterion of $P < 0.2$ were selected for inclusion. The contribution of each predictor to the multipredictor model was assessed using likelihood ratio tests, with the criterion for inclusion in the final multipredictor model set at $P < 0.2$.

Results

Twenty-five of the 45 cases (56%) had microscopic findings of urticarial hypersensitivity reaction or reaction to arthropod bite or sting, consistent with a diagnosis of PPE (Fig. 3). Twenty of the 45 cases (non-PPE cases) had the following microscopic findings: spongiotic dermatitis ($n = 11$), dermatophyte folliculitis ($n = 2$), intraepidermal pustular dermatitis ($n = 2$), pruriginous dermatitis ($n = 1$), excoriation ($n = 1$), secondary syphilis ($n = 1$), seborrhoeic keratosis ($n = 1$) and perniosis ($n = 1$).

A greater proportion of PPE cases (Table 1) reported that the rash present at study enrolment began prior to ART initiation compared with non-PPE cases [44% (11/25) vs. 15% (three of 20); $P = 0.05$]. The site of rash at onset was significantly different between PPE and non-PPE cases ($P = 0.002$). No PPE cases reported their rash starting in the head and neck region, compared with 30% (six of 20) of non-PPE cases. Nine of 25 PPE cases (36%) had a generalized rash at onset, in contrast with none of the non-PPE cases. At the time of study enrolment, body sites affected by the rash were similar between PPE and non-PPE cases ($P = 0.31$). The reported itch severity on a 10-cm visual analogue scale was similar with a median value of 10 cm, representing maximum itch severity ($P = 0.51$). The proportions who reported dyspigmentation due to the rash were also similar between PPE cases and non-PPE cases [84% (21/25) vs. 70% (14/20), respectively; $P = 0.30$].

Participant characteristics are presented in Table 2. Female participants accounted for 67% of all cases and controls, and 72% of PPE cases and PPE controls. Median age was similar between cases and controls (35.9 vs. 36.3 years; $P = 0.53$), as well as between PPE cases and PPE controls (35.8 vs. 36.0 years; $P = 0.61$). The median duration of ART was 1.4 years in both cases and controls ($P = 0.99$) and in PPE cases and PPE controls ($P = 0.81$).

Median plasma HIV RNA was higher at ART initiation when comparing PPE cases with PPE controls (390 398 vs. 109 615 copies mL^{-1} , $P = 0.002$), and PPE cases with non-PPE cases (390 398 vs. 71 006 copies mL^{-1} , $P = 0.01$). Plasma HIV RNA was < 400 copies mL^{-1} in a similar proportion of PPE cases and PPE controls (96% vs. 92%, $P = 0.66$), and in cases and controls (91% vs. 89%, $P = 0.77$) at the time of skin examination and biopsy (study enrolment). No PPE cases and two PPE controls had plasma HIV RNA > 5000 copies mL^{-1} , an indication of virological failure,¹¹ at the time of study enrolment. Sustained rebound in viraemia was not demonstrated in any cases or PPE cases after the suppression of plasma viraemia to < 400 copies mL^{-1} . Overall 92% (23/25) of PPE cases and 96% (48/50) of PPE controls had HIV RNA < 400 copies mL^{-1} 6 months after ART initiation.

Median CD4 counts at study enrolment were comparable between PPE cases and PPE controls (244 vs. 267 cells mm^{-3} , $P = 0.47$) and between cases and controls (257 vs. 265 cells mm^{-3} , $P = 0.84$). At ART initiation, median CD4 counts were also similar in PPE cases compared with PPE controls (93 vs. 124 cells mm^{-3} , $P = 0.19$), and in cases compared with

controls (110 vs. 121 cells mm⁻³, $P = 0.53$). CD8⁺ T-cell activation, measured as the percentage of CD38 HLA-DR⁺ CD8⁺ T cells, at ART commencement and 6 and 12 months after starting ART were similar between cases and controls, and between PPE cases and PPE controls.

Living and working conditions and dermatological history were remarkably similar between cases and controls, and between PPE cases and PPE controls with the exception of two predictors. A smaller proportion of cases than controls reported a history of skin disease [33% (15/45) vs. 49% (44/90), $P = 0.10$]. The difference was more marked in PPE cases compared with PPE controls [24% (six of 25) vs. 48% (24/50), $P = 0.05$]. Eczema had not been reported in the dermatological history of cases but was reported in 9% (eight of 90) of controls ($P = 0.05$).

As shown in Table 3, the odds of being a PPE case increased fourfold with every log increase in viral load at ART initiation [odds ratio (OR) 4.04, 95% confidence interval (CI) 1.29–12.68; $P = 0.02$]. This association was not evident in cases (OR 1.19, 95% CI 0.73–1.92; $P = 0.49$). There was no association between viral load at study enrolment and being a case (OR 0.90, 95% CI 0.51–1.60; $P = 0.73$), or being a PPE case (OR 0.95, 95% CI 0.35–2.60, $P = 0.93$). The odds of being a case or PPE case were not statistically significantly associated with CD4 counts, CD4 count gains after ART initiation or the proportion of CD38⁺ HLA-DR⁺ CD8⁺ T cells.

Among participants who reported daily insect bites, their odds of being a case or PPE case were 8.3-fold (95% CI 2.79–24.64, $P < 0.001$) and 8.6-fold (95% CI 1.85–39.71, $P = 0.01$) greater than those who did not report daily insect bites, respectively. Conversely, participants who reported a history of any skin disease were less likely to be cases (OR 0.53, 95% CI 0.25–1.11; $P = 0.09$) or PPE cases (OR 0.31, 95% CI 0.10–0.99; $P = 0.05$). Single-predictor analyses of immunological and environmental factors that fulfilled the criterion of $P < 0.2$ for inclusion in multipredictor model fitting, as well as HIV viral load and CD4 count at ART initiation and study enrolment, are presented in Table 3.

When attempting to fit a multipredictor model for all recruited cases, the dichotomous variable of reported bites was the only predictor that provided a consistently statistically significant effect across all conditional logistic regression models fitted (OR 8.29, 95% CI 2.79–24.64; $P < 0.001$). Two predictors, log viral load at ART initiation and self-reported history of skin disease, contributed in a statistically significant manner to the PPE cases' conditional logistic regression model, with OR 4.47 (95% CI 1.27–15.74, $P = 0.02$) and OR 0.28 (95% CI 0.07–1.06, $P = 0.06$), respectively).

Discussion

The odds of having PPE in HIV-infected persons treated with ART were increased fourfold with every log increase in plasma HIV RNA at ART initiation. This suggests that higher levels of HIV viraemia pretreatment may have long-term effects that persist well after ART initiation and virological suppression. The mechanism of this effect on PPE is not known. Viral loads of over 100 000 copies mL⁻¹ at ART commencement have been linked with a

greater likelihood of HIV disease progression.¹⁹ It is for this reason that we explored the association between PPE in ART-treated persons and predictors of HIV disease progression linked with pre-ART HIV viraemia.

Pre-ART plasma HIV RNA levels have been positively correlated with T-cell activation, especially CD8⁺ T-cell activation.²⁰ After ART initiation, both CD4⁺ and CD8⁺ T-cell activation levels have been reported to remain higher than those of HIV-uninfected persons, despite treatment-induced virological suppression.²⁰ CD8⁺ T-cell activation has been shown to predict HIV disease progression²¹ more strongly than viral load or CD4 count. Higher T-cell activation levels have also been associated with lower CD4⁺ cell T gains during ART.^{14,16} We have not found an association between CD8⁺ cell activation and CD4⁺ cell gains measured at ART commencement or after 6 and 12 months of ART, and PPE in ART-treated study participants. It is likely that PPE in ART-treated HIV-infected persons is not associated with the immune activation markers measured in this study.

HIV viral load and CD4 count at the time of skin examination and biopsy were similar between PPE cases and PPE controls. A similar proportion of both groups had plasma HIV RNA < 400 copies mL⁻¹ at the time of study enrolment and 6 months after starting ART. Therefore, the presence of PPE in HIV-infected persons receiving ART is unlikely to be a marker for treatment failure. The small number of PPE cases and PPE controls with virological failure at the time of study enrolment (one PPE case and two PPE controls) does not allow for further evaluation of the association between PPE and virological failure.

Study participants who reported daily insect bites or stings had an eightfold increase in their odds of having a chronic itchy papular rash (case) and a similar increase in the odds of that rash being PPE (PPE case). A link between arthropod bites or stings and PPE has been suggested.²² However, the similarity in the magnitude of association between reported insect bites and any chronic itchy papular rash, as well as PPE, does not fully support that theory. It may be that study participants with an itchy papular rash find it difficult to distinguish between the rash and itchy insect bites or stings. Although desensitization to insect bites with repeated exposure over time is well described,²³ it is possible that this may have been lost in some HIV-infected individuals, allowing immunological reactions from insect bites to result in an itchy skin eruption.

To explore further the postulated link between insect bites or stings and PPE, information regarding environmental characteristics in our participants' lives that may predispose them to insect bites was elicited. A similarly large proportion of PPE cases and PPE controls worked outdoors during the day, used bed (or mosquito) nets and did not use insect repellents. Housing characteristics and sanitation facilities were also comparable between PPE cases and PPE controls. It is possible that environmental factors more closely associated with insect bites or stings were not explored in this study. Based on our findings, it would be difficult to draw any conclusions about the relationship between insect bites or stings and PPE in HIV-infected individuals on ART.

Confirming clinical diagnoses of PPE with skin biopsies has been one of the strengths of this study. Participants on ART for at least 15 months with a pruritic papular rash for a month or

more were enrolled as cases in this study, irrespective of the study dermatologists' level of suspicion of PPE, to avoid inconsistencies in enrolment to the study. This may explain the lower than expected proportion of cases with microscopic findings consistent with PPE. There were few differences in clinical presentation of the skin eruption in PPE cases and non-PPE cases with regard to timing, persistence, itch severity or dyspigmentation. The only difference found in our study was that PPE was not localized to the head and neck at commencement of the rash; rather, it was localized to the extremities or was generalized. While this may be a clinical clue to the diagnosis, microscopic confirmation of PPE occurred in only 56% of the cases. This underscores the importance of skin biopsies to avoid misdiagnosing treatable conditions such as dermatophytic folliculitis and syphilis, which were found in our non-PPE cases. However, this may not be practical in resource-limited settings with limited or no access to pathology services. In research studies of PPE, confirming clinical diagnoses of PPE by biopsy is important for study validity.

This case-control study was nested within a well-established cohort (UARTO)¹⁷ with excellent adherence to ART²⁴ and from which blood draws were carried out on all participants at 3-month intervals for measurement of CD4 counts, plasma HIV RNA and other immunological factors. This enabled the study of predictors measured not only at study enrolment, but also at other time points.

Limitations of this study include a small sample size, contributing to the lack of association between multiple predictors and the odds of being a case or PPE case due to lack of power. The small number of study participants with virological failure at study enrolment would also have made this study underpowered to study the association between PPE in ART-treated persons and virological failure. As study participants were examined and biopsied only once, the natural history of their rash could not be studied objectively. Characteristics of the rash reported by study participants, especially with regard to past events such as time and site of rash onset, are subject to recall bias.

In conclusion, the presence of PPE in ART-treated HIV-infected persons was associated with higher viral loads at ART initiation in this study. No other immunological markers measured in this study, including CD4⁺ T-cell gains and CD8⁺ T-cell activation, were found to be associated with PPE in ART-treated persons. Confirmation of clinical diagnoses of PPE by biopsy is encouraged, as clinical diagnosis alone is not optimal.

Large gaps remain in our understanding of PPE: its aetiology, immunological factors that shape its natural history and its potential as a prognostic indicator. Further studies correlating the natural history of PPE with immunological markers and prognostic indicators for HIV disease may be helpful.

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What's already known about this topic?

- Papular pruritic eruption (PPE) of HIV is common in HIV-infected populations living in the tropics.
- PPE is characterized by symmetrically distributed itchy papules, worst on the extremities, with similar microscopic findings to insect bites or stings.

What does this study add?

- Persistent or recurrent PPE in antiretroviral therapy (ART)-treated persons is associated with greater HIV RNA load at ART commencement but not during treatment.
- No association was found with CD4 count, CD4 gains and T-cell activation markers.



Fig 1. Papular pruritic eruption of HIV. This is characterized by symmetrically distributed pruritic, often excoriated, papules, which are most concentrated on the extensor aspects of the extremities but may also be generalized.

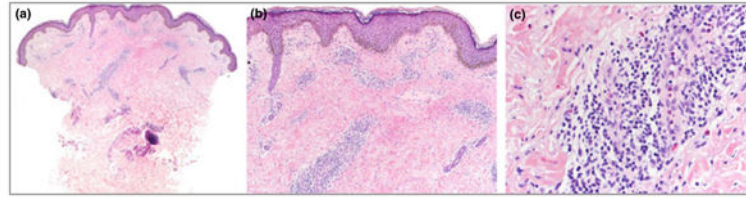


Fig 2.

Photomicrographs of skin biopsy specimens (a) This shows a roughly wedge-shaped superficial and deep infiltrate of lymphocytes and eosinophils that is characteristic of a reaction to arthropod bites or stings. Study participants who had skin biopsies with this appearance and no other obvious cause of their itchy papular eruptions were considered PPE cases. (haematoxylin-eosin, original magnification 4×) (b) (haematoxylin-eosin, original magnification 10×) (c). Dermal infiltrate of lymphocytes and eosinophils (haematoxylin-eosin, original magnification 40×).

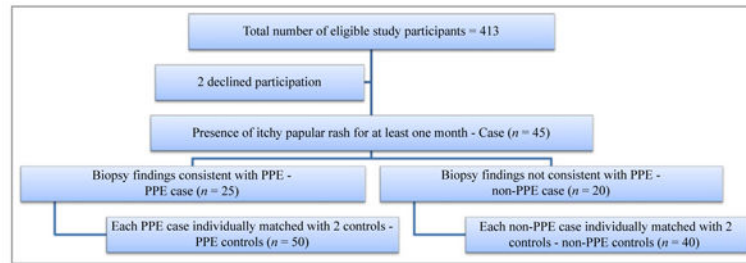


Fig 3. Study participants. Participants of the Uganda AIDS Rural Treatment Outcomes cohort who had received antiretroviral therapy (ART) for at least 15 months were eligible for inclusion in the study. Cases had an itchy papular rash for at least 1 month that was still present at study enrolment. Cases with biopsy findings consistent with papular pruritic eruption (PPE) of HIV were known as PPE cases. Cases with other biopsy findings were known as non-PPE cases. Each case was individually matched with two controls by age, sex and duration of ART.

Table 1
Participant-reported characteristics of rash in all cases, cases of pruritic papular eruption (PPE) of HIV and non-PPE cases

	Cases (n=45)	PPE (n=25)	Non-PPE (n=20)	P-value
Onset before ART initiation	14 (31)	11 (44)	3 (15)	0.05
Onset after ART initiation	31 (69)	14 (56)	17 (85)	0.05
Itch severity on a 10-cm visual analogue scale, median (IQR)	10 (8–10)	10 (8–10)	10 (7–10)	0.51
Dyspigmentation	35 (78)	21 (84)	14 (70)	0.30
Site of rash at onset				0.002
Head and neck only	6 (13)	0 (0)	6 (30)	
Trunk only	6 (13)	4 (16)	2 (10)	
Extremities only	18 (40)	8 (32)	10 (50)	
Generalized	9 (20)	9 (36)	0 (0)	
Site of rash at study enrolment				0.31
Head and neck only	6 (13)	1 (4)	5 (25)	
Trunk only	6 (13)	5 (20)	1 (5)	
Extremities only	17 (38)	9 (36)	8 (40)	
Generalized	11 (24)	8 (32)	3 (15)	

Values are n (%) unless stated otherwise. ART, antiretroviral therapy; IQR, interquartile range.

Table 2

Characteristics of study participants

	Cases (n=45)	Controls (n=90)	P-value	PPE cases (n=25)	PPE controls (n=50)	P-value ^a	Non-PPE cases (n=20)	P-value ^b
Female	30 (67)	60 (67)	1.00	18 (72)	36 (72)	1.00	12 (60)	0.53
Ethnicity Banyankore	34 (76)	66 (73)	0.83	18 (72)	36 (72)	1.00	16 (80)	0.47
Age (years), median (IQR)	36 (34–40)	36 (32–41)	0.53	36 (34–41)	36 (31–39)	0.61	37 (34–40)	0.57
Duration of ART (years), median (IQR)	1.4 (1.2–1.7)	1.4 (1.2–1.7)	0.99	1.4 (1.2–1.8)	1.4 (1.2–1.8)	0.81	1.4 (1.2–1.7)	0.56
Socioeconomic status: Filmer–Pritchett Asset Index quintile			0.15			0.14		0.61
1	13 (29)	13 (14)		7 (28)	7 (14)		6 (30)	
2	4 (9)	19 (21)		3 (12)	10 (20)		1 (5)	
3	7 (16)	20 (22)		2 (8)	15 (30)		5 (25)	
4	11 (24)	23 (26)		7 (28)	11 (22)		4 (20)	
5	9 (20)	14 (16)		5 (20)	7 (14)		4 (20)	
Missing data	1 (2)	1 (1)		1 (4)	0 (0)		0 (0)	
CD4 count (cells mm ⁻³), median (IQR)								
At ART initiation	110 (73–175)	121 (76–186)	0.53	93 (66–167)	124 (82–187)	0.19	128 (100–183)	0.20
At study enrolment	257 (179–379)	265 (178–373)	0.84	244 (159–379)	267 (215–373)	0.47	270 (214–371)	0.60
HIV RNA load at ART initiation (log ₁₀ copies mL ⁻¹), median (IQR)	5.3 (4.8–5.8)	5.1 (4.6–5.6)	0.20	5.6 (5.1–5.9)	5.0 (4.5–5.5)	0.002	4.9 (4.4–5.6)	0.01
HIV RNA < 400 copies mL ⁻¹ 6 months after starting ART	40 (89)	86 (96)	0.16	23 (92)	48 (96)	0.60	17 (85)	0.18
At study enrolment	41 (91)	80 (89)	0.77	24 (96)	46 (92)	0.66	17 (85)	0.31
Percentage CD38 ⁺ HLA-DR + CD8 ⁺ T cells, median (IQR)								
At ART initiation	67 (62–74)	71 (60–80)	0.41	67 (60–79)	71 (61–77)	0.65	66 (64–72)	0.92
6 months after starting ART	52 (42–62)	48 (40–56)	0.07	54 (47–60)	52 (43–58)	0.22	47 (41–62)	0.48
12 months after starting ART	41 (30–46)	41 (31–48)	0.99	41 (32–50)	40 (32–47)	0.69	42 (28–46)	0.72
Outdoor work	30 (67)	56 (62)	0.71	15 (60)	32 (64)	0.80	15 (75)	0.35
Work in daytime	39 (87)	81 (90)	0.57	20 (80)	45 (90)	0.32	19 (95)	0.21
Livestock ownership	19 (42)	41 (46)	0.85	10 (40)	19 (38)	1.00	9 (45)	0.77
Insect repellent use	2 (4)	3 (3)	1.00	1 (4)	1 (2)	1.00	1 (5)	1.00
Bed net use	42 (93)	84 (93)	1.00	22 (88)	46 (92)	0.68	20 (100)	0.24
Roof material metal	43 (96)	89 (99)	0.26	24 (96)	50 (100)	0.33	19 (95)	1.00
Wall material			0.77			0.29		0.90

	Cases (n=45)	Controls (n=90)	P-value	PPE cases (n=25)	PPE controls (n=50)	P-value ^a	Non-PPE cases (n=20)	P-value ^b
Mud	20 (44)	43 (48)		10 (40)	26 (52)		10 (50)	
Unfinished brick	21 (47)	39 (43)		12 (48)	20 (40)		9 (45)	
Floor material			0.67					0.75
Mud	22 (49)	36 (40)		11 (44)	24 (48)		11 (55)	
Cement	19 (42)	39 (43)		11 (44)	19 (38)		8 (40)	
Shared toilet with other households	21 (47)	46 (51)	0.85	12 (48)	23 (46)		9 (45)	0.77
History of any skin disease	15 (33)	44 (49)	0.10	6 (24)	24 (48)		9 (45)	0.21
History of specific skin disease								
Eczema	0 (0)	8 (9)	0.05	0 (0)	5 (10)		0 (0)	–
Psoriasis	4 (9)	10 (11)	0.77	1 (4)	6 (12)		3 (15)	0.31
Scabies	7 (16)	22 (24)	0.27	3 (12)	11 (22)		4 (20)	0.68
Drug reaction	1 (2)	5 (6)	0.66	0 (0)	3 (6)		1 (5)	0.44
Sulfamethoxazole–trimethoprim prophylaxis	44 (98)	90 (100)	0.33	25 (100)	50 (100)		19 (95)	0.44

Values are n (%) unless otherwise stated. ART, antiretroviral therapy; HLA, human leucocyte antigen; IQR, interquartile range; PPE, pruritic papular eruption of HIV.

^aPPE cases vs. PPE controls.

^bPPE cases vs. non-PPE cases.

Table 3
Single-predictor analyses using conditional logistic regression for all cases and cases of pruritic papular eruption (PPE) of HIV

Predictor	Cases vs. controls		PPE cases vs. PPE controls		PPE cases vs. non-PPE cases	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Log HIV viral load						
At ART initiation	1.19 (0.73–1.92)	0.49	4.04 (1.29–12.68)	0.02	3.41 (1.22–9.58)	0.02
At study enrolment	0.90 (0.51–1.60)	0.73	0.95 (0.35–2.60)	0.93	0.95 (0.34–2.66)	0.93
CD4 count in 50 cells mm ⁻³ intervals						
At ART initiation	0.94 (0.76–1.16)	0.56	0.86 (0.63–1.16)	0.32	0.88 (0.62–1.25)	0.48
At study enrolment	0.99 (0.88–1.11)	0.84	0.98 (0.84–1.14)	0.75	1.01 (0.82–1.25)	0.90
CD4 count gains in 50 cells mm ⁻³ intervals						
18 months after ART initiation	1.13 (0.95–1.33)	0.16	1.16 (0.94–1.42)	0.16	1.10 (0.84–1.42)	0.49
24 months after ART initiation	1.13 (0.97–1.32)	0.12	1.20 (0.95–1.53)	0.13	1.11 (0.86–1.42)	0.43
Percentage CD38 ⁺ HLA-DR ⁺ CD8 ⁺ T cells						
3 months after ART initiation	1.02 (0.99–1.06)	0.20	1.04 (0.99–1.09)	0.11	1.05 (0.99–1.11)	0.11
6 months after ART initiation	1.02 (0.99–1.06)	0.17	1.03 (0.98–1.08)	0.23	1.02 (0.97–1.07)	0.41
Reported bites	8.29 (2.79–24.64)	<0.001	8.58 (1.85–39.71)	0.01	1.00 (0.30–3.32)	1.00
History of skin disease	0.53 (0.25–1.11)	0.09	0.31 (0.10–0.99)	0.05	0.39 (0.11–1.38)	0.14

ART, antiretroviral therapy; CI, confidence interval; HLA, human leucocyte antigen; IQR, interquartile range; OR, odds ratio.