PAPULAR PRURITIC ERUPTION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

SER LING CHUA

Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

DECEMBER 2015

Acknowledgements

I would first like to thank the participants of the studies presented in this thesis. Their time, patience and generosity in their participation have been and still are very much appreciated. I would also like to thank the Dr. David Bangsberg, Dr. Jeff Martin, Dr. Peter Hunt, Dr. Elvin Geng and Nneka Emenyonu who very kindly allowed me to recruit participants from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort and the use of office facilities in Mbarara, Uganda.

My research supervisor, Dr. Toby Maurer, who has supported me every step of the way and made all of this possible, has my greatest appreciation and gratitude. Dr. Kieron Leslie encouraged me to get on board with research, helped me with funding applications, writing protocols of the studies and has supported me from the start of my work as a doctor in dermatology. I would like to thank Prof. Kim Thomas being very patient with me, tirelessly reading through this thesis and providing very valuable advice.

I would like to acknowledge my colleagues and friends, especially Annet Kembabazi, Annet Kawuma and Nicholas Musinguzi, at the Mbarara University of Science and Technology and University of California, San Francisco research collaboration based in Mbarara, Uganda without

whose help and support I would not have managed to conduct the research studies and live in Mbarara, Uganda. Dr. Erin Amerson, the other study dermatologist in the research studies, has been key in keeping the studies going after I have had to leave Mbarara, Uganda. Christine Ngabirano, Shiphrah Nantongo and Nicholas Atwine, research assistants for the studies in this thesis, have been invaluable in the conduct of the research studies.

The doctors and nurses, in particular Dr. Grace Mulyowa and Jacqueline Chandari, at the Department of Dermatology, Mbarara National Referral Hospital, need special mention for allowing me to spend time in their department to learn more about dermatological needs of patients in Mbarara, Uganda.

Dr. Grace Mulyowa and Jacqueline Chandari at the Skin Clinic of Mbarara National Referral Hospital

I would like to thank Dr. Margaret Chren who allowed me to use Skindex-16 in the research studies and helped with the validation of the interviewer-administered Runyankore-version of Skindex-16 in Mbarara, Uganda. I am grateful to Pidson Mwebaze and Lilian Namukasa who translated Skindex-16 from English to Runyankore.

Dr. John Kornak and Dr. Stephen Shiboski provided valuable statistical advice in conjunction with the teaching I received in the Advanced Training in Clinical Research course at the University of California, San Francisco. I am immensely grateful to Dr. Philip LeBoit and Dr. Timothy McCalmont who provided us with their immense expertise and skill in dermatopathology and read the skin biopsy slides of the study participants. I would like to thank Douglas Grindlay who helped me formulate search strategies for the systematic review.

My roles in the research studies

I played a central role in the development and conduct of the research studies included within this thesis. I developed and wrote the study protocol with help from Dr. Kieron Leslie and Dr. Toby Maurer, my supervisors and principal investigators for the research studies from the Department of Dermatology, University of California, San Francisco. I completed applications to the Committee on Human Research at the University of California, San Francisco (where the principal investigators of the study are based) and the Institutional Ethical Review Committee of Mbarara University of Science and Technology (where the research studies were conducted) for approval to conduct the research studies. In order to travel to and live in Mbarara, Uganda for a year to conduct the research studies, I applied and was successful in obtaining the Roger Harman African Travelling Fellowship from the British Association of Dermatologists. I applied to the Trent Postgraduate Deanery for a one-year out of programme experience so that I could travel and live in Mbarara, Uganda in order to set up and conduct the research studies. I managed and trained the bilingual research assistants, with help from staff from the Mbarara University of Science and Technology-University of California, San Francisco Research Collaboration. They obtained informed consent from study participants and conducted participant interviews in Runyankore. They also assisted in clinical photography. Dr. Erin Amerson

and I were the study dermatologists for the research studies. We conducted clinical examinations of the skin and performed skin biopsies. I managed and analysed data collected, with help from Dr. John Kornak and Dr. Stephen Shiboski who advised on statistical analysis.

Education received for the purposes of research

- Diploma in Tropical Medicine and Hygiene

  - Liverpool School of Tropical Medicine, University of Liverpool (2006)

- Fundamentals in Epidemiology (Individual MSc Module by distance learning)

  - London School of Hygiene and Tropical Medicine, University of London (2008)

- Advanced Training in Clinical Research

  - University of California, San Francisco (2010-2011)

Supervisors

Prof. Kim Thomas, Centre of Evidence Based Dermatology, University of Nottingham

Dr. Toby Maurer, Department of Dermatology, University of California, San Francisco

Dr. Kieron Leslie, Department of Dermatology, University of California, San Francisco

Sources of funding

Uganda AIDS Rural Treatment Outcomes (UARTO) cohort is supported by the National Institute of Health (R01 MH054907, K24 MH87227 and P30 AI027763). The Roger Harman African Travelling Fellowship from the

British Association of Dermatologists supported my time in Mbarara, Uganda.

Funding from the British Association of Dermatologists Study Fellowship allowed me to undertake the Diploma in Tropical Medicine and Hygiene at the Liverpool School of Tropical Medicine in 2006. The British Epidermo-Epidemiology Society (BEES) Travelling Fellowship funded my travel to Moshi, Tanzania to present at their annual meeting in 2008. The British Association of Dermatologists and Dowling Club American Academy Registration Scholarship funded my registration fee and undertake an oral presentation at the 67th American Academy of Dermatology in 2009.

The World Health Organization commissioned and supported the systematic review of interventions for papular pruritic eruption of HIV so that it may contribute to the "Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults" published in 2014.

Output from research studies

- World Health Organization. (2014). Evidence and recommendations on papular pruritic eruption. In: *Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults*. Switzerland: World Health Organization. 31-34.

- Chua, S.L. et al., 2014. Factors associated with pruritic papular eruption of human immunodeficiency virus infection in the antiretroviral therapy era. *British Journal of Dermatology*, 170(4), pp.832–839.
- Chua, S.L., Maurer, T. & Chren, M.-M., 2011. Adaptation of a Runyankore version of Skindex-16 for oral administration in Mbarara, Uganda. *International Journal of Dermatology*, 50(10), pp.1249–1254.

Papers in preparation

- Systematic review of interventions for papular pruritic eruption of HIV and eosinophilic folliculitis. Chua SL, Zangenberg M, Maurer TA.
- Papular pruritic eruption of human immunodeficiency virus (HIV) infection over 2 years of antiretroviral therapy. Chua SL, Amerson EH, Leslie KS, Maurer TA

Oral and poster presentations at meetings

- Systematic review of interventions for papular pruritic eruption of HIV and eosinophilic folliculitis

  Chua SL, Zangenberg M, Maurer TA

  Oral presentation at the 23rd World Congress of Dermatology, 2015

- Papular pruritic eruption of human immunodeficiency virus (HIV) infection over 2 years of antiretroviral therapy

  Chua SL, Amerson EH, Leslie KS, Maurer TA

  Oral and poster presentation at the 73rd Annual Meeting of the American Academy of Dermatology, 2015

- Papular Pruritic Eruption of HIV

  Symposium: AIDS and Sexually Transmitted Diseases (STDs) Hot Topics

  71st Annual Meeting of the American Academy of Dermatology, Miami, 2013

- HIV dermatology research in the ART era in Mbarara, Uganda

  67th Annual Meeting of the American Academy of Dermatology (2009)

  Symposium: Organisational approaches to AIDS/STDs from a global perspective

- A study examining active skin disease as a predictor for treatment failure in HIV-infected individuals established on anti-retroviral therapy

Chua SL, Leslie K, Maurer T

5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (2009)

- Evaluating the effect of skin disease using a Runyankore-version of Skindex-16 in Mbarara, Uganda

  Chua SL, Maurer TA, Mulyowa GK, Chren MM

  5th International Dermato-Epidemiology Association Congress (2008)

  (J Invest Dermatol 2008; 128: 2554)

- Evaluating the effect of skin disease using Skindex-16 in Mbarara, Uganda

  Regional Dermatology Training Centre Annual CME meeting, Moshi, Tanzania (2008)

Table of Contents

List of tables

List of Figures

Abbreviations and Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CI	Confidence Interval
CINAHL	Cumulative Index To Nursing And Allied Health Literature
EMBASE	Excerpta Medica Database
FDC	Fixed-dose Combination
GRADE	Grading Of Recommendation, Assessment, Development And Evaluation
HIV	Human Immunodeficiency Virus
HIV-EF	Human Immunodeficiency Virus-Associated Eosinophilic Folliculitis
IRIS	Immune Reconstitution Inflammatory Syndrome
IQR	Interquartile Range
MEDLINE	Medical Literature Analysis And Retrieval System Online
NLM	National Library Of Medicine
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PPE	Papular Pruritic Eruption
PUVA	Psoralen And Ultraviolet A

RNA	Ribonucleic Acid
SMX-TMP	Sulphamethoxazole-Trimethoprim
SPT	Skin Prick Testing
STROBE	Strengthening The Reporting Of Observational Studies
Th1	T-helper 1
Th2	T-helper 2
UARTO	Uganda Aids Rural Treatment Outcomes
UNAIDS	Joint United Nations Programme On HIV/AIDS
UVB	Ultraviolet B
VAS	Visual Analogue Scale
WHO	World Health Organization

Abstract

Background

Papular pruritic eruption (PPE) of human immunodeficiency virus (HIV) infection is common HIV-infected populations who live in tropical and subtropical regions. It is characterized by chronic and intensely itchy papules that are usually more highly concentrated on the extremities, adversely impacting on quality of life. Its aetiology has been postulated to be an altered and exaggerated immunological response to insect bites or stings. It has been reported to diminish in severity or resolve with antiretroviral therapy (ART). Its presence after at least six months of ART has been proposed as one of several clinical markers of failure of antiretroviral treatment.

Objectives

1. To systematically summarise the evidence of interventions for PPE
2. To translate, culturally adapt, and test oral administration of a Runyankore-version of Skindex-16 for use in dermatology research in Mbarara, Uganda
3. To determine factors associated with PPE in HIV-infected Ugandan adults receiving ART for at least 15 months
4. To describe the natural history of PPE in HIV-infected Ugandan adults over two years from the time of ART initiation and explore the

association between recurrent or persistent PPE and antiretroviral treatment failure

Methods

Systematic review of interventions for PPE

Electronic searches of Medical Literature Analysis And Retrieval System Online (Medline), Excerpta Medica Database (Embase), Cumulative Index To Nursing And Allied Health Literature (CINAHL), Global Health Library, Cochrane Library, World Health Organization (WHO) International Clinical trials registry and National Library Of Medicine (NLM) gateway were carried out from January 1980 to July 2014. Studies of any design were included. The primary outcome measure for this review was resolution of skin disease. The quality of evidence was assessed using the Newcastle-Ottawa quality assessment scale and Grading Of Recommendation, Assessment, Development And Evaluation (GRADE) approach, where appropriate. Two authors carried out data extraction and quality assessment of studies independently.

Runyankore-version of Skindex-16 for oral administration in Mbarara, Uganda

Skindex-16 in English was translated to Runyankore, and then back-translated to English. The original and back-translated versions of

Skindex-16 were compared for fidelity of translation. The Runyankore-version was administered orally to 47 dermatology patients and 47 random hospital visitors. Study participants were also asked about the characteristics of their skin condition including its duration, presence of skin colour change and ease or difficulty of concealment as well as an open question on how their skin condition has affected them.

Case control study examining factors associated with PPE in the ART era

This is a case–control study nested within a 515-person cohort receiving care at the HIV clinic of a teaching hospital in Mbarara, Uganda. Forty-five cases and 90 controls were enrolled. Cases had received ART for ≥15 months, fulfilled the clinical case definition of PPE and had skin biopsy findings consistent with PPE. Each case was individually matched with two controls for age, sex and ART duration.

Cohort study describing the natural history of PPE over two years from ART initiation

This is a cohort study of HIV-infected Uganda adults initiating ART and receiving care at the HIV clinic of a teaching hospital in Mbarara, Uganda who fulfilled the clinical case definition of PPE and had skin biopsy findings consistent with PPE. Standardised interviews, clinical

photography, HIV viral load, CD4 counts and CD8+ T-cell activation markers were measured at three-month intervals for two years.

Results

Systematic review of interventions for PPE

No randomised controlled trials were identified. Thirteen studies with a total 188 participants were included. ART was associated with resolution of PPE in a prospective observational study that had high loss to follow-up rates. Two observational studies reported positive responses of PPE to oral antihistamines (promethazine and cetirizine). Pentoxifylline was associated with diminished signs and symptoms of PPE in an uncontrolled open trial and superior to dapsone and a combination of antihistamine and topical corticosteroids in a parallel group non-randomised trial. Resolution of PPE was reported with a combination of topical corticosteroids and oral antihistamines in a case report. The efficacy of ultraviolet B (UVB) phototherapy was reported in an observational study with eight participants and three case studies with a total of five participants.

Runyankore-version of Skindex-16 for oral administration in Mbarara, Uganda

Oral delivery was feasible, taking ≤10 minutes per subject. High Cronbach α values (0.86, 0.88 and 0.85 for Symptoms, Emotions and Functioning

subscales, respectively) demonstrated internal consistency reliability. As hypothesised, subjects with reported skin problems, dyspigmentation and difficulty in concealment had higher mean Skindex-16 scores, indicating construct validity. A large proportion (72.4%) of responses to the open-ended question were addressed in Skindex-16, indicating content validity.

Case control study examining factors associated with PPE in the ART era

Twenty-five of 45 cases (56%) had histological findings consistent with PPE (known as PPE cases). At skin examination and biopsy (study enrolment), a similar proportion of PPE cases and their matched controls had plasma HIV RNA <400 copies/ml (96% vs. 85%, p=0·31). The odds of having PPE increased four-fold 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 the presence of 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).

Cohort study of natural history of PPE over 2 years from ART initiation

Seventeen (15 female and 2 male) participants with a median age of 29.8 years were enrolled. Median CD4 count and HIV viral load at ART commencement was 108 cells/mm^3 and 114,442 copies/ml, respectively. Resolution of PPE occurred in 13 of 17 (76%) study participants at a median time of 8.5 months after ART initiation, although PPE recurrence was observed at seven participants during the study period. Two participants had persistent PPE. Virological failure was not detected in any study participant. HIV RNA was less than 400 copies/ml at a median time of three months from ART initiation in all study participants.

Conclusions

1. The evidence base of interventions for PPE is of low quality. There is some evidence of the efficacy of ART in the management of PPE. Pentoxifylline and phototherapy may have a role in its management but are unlikely to be available in resource-limited settings. Oral antihistamines and topical corticosteroids may be helpful in some individuals affected by PPE.
2. The orally administered Runyankore-version of Skindex-16 is reliable, with construct and content validity, and feasible for use in dermatology research in Mbarara, Uganda.

3. PPE in HIV-infected Ugandan adults receiving ART for at least 15 months was associated with reported daily insect bites and greater HIV viraemia at ART commencement, independent of CD4 count.
4. Recurrent or persistent PPE in HIV-infected Ugandan adults observed over two years from initiation of ART was not associated with virological failure in participants of this study.

1. Introduction

1.1 History of human immunodeficiency virus disease

Awareness of the phenomenon of human immunodeficiency virus disease began with reports of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma among previously healthy young homosexual men in New York City and California, United States of America (Gottlieb et al. 1981; Friedman-Kien et al. 1981). Between 1979 and 1983, previously healthy African persons in Belgium were admitted to hospital with opportunistic infections such as cryptococcosis, toxoplasmosis of the central nervous system and *Pneumocystis carinii* pneumonia, Kaposi's sarcoma and a syndrome of chronic lymphadenopathy, fever, weight loss and diarrhea (Clumeck et al. 1984).

From 1982, a new disease characterized by chronic diarrhoea, fever, weight loss and an itchy rash was seen with increasing frequency and known as Slim disease in Uganda (Serwadda et al. 1985). A similar phenomenon was noted in Kigali, Rwanda and Kinshasa, Democratic Republic of Congo; it was noted the male to female ratio was 1:1 and affected individuals had relatively high socioeconomic status and lived in urban areas (Piot et al. 1984; Van de Perre et al. 1984).

The phenomenon was attributed to a human retrovirus belonging to the family of human T-lymphotropic viruses (HTLV), initially designated as HTLV-III (Barré-Sinoussi et al. 1983; Gallo et al. 1984; Levy et al. 1984). It was also known as lymphadenopathy-associated virus (LAV) and acquired immunodeficiency syndrome retrovirus until the International Committee on the Taxonomy of Viruses officially proposed the use of the term human immunodeficiency virus (HIV) in 1986 (Coffin et al. 1986). HIV has been isolated from blood, seminal fluid, pre-ejaculate, vaginal secretions, cerebrospinal fluid, saliva, tears, and breast milk (Ho et al. 1985; Wofsy et al. 1986; Hollander & Levy 1987; Geier et al. 1992). The transmission of HIV infection may occur through the following routes; they have been listed in order of risk following a systematic review of “per act transmission risk” published in 2014: blood transfusion, vertical exposure (mother-to-child transmission), sexual exposure followed by other parenteral exposures (Patel et al. 2014).

Globally, heterosexual transmission of HIV is common, driving the HIV epidemic, not just in sub-Saharan Africa but also in the Asia-Pacific region and Caribbean (Piot et al. 2009; Kilmarx 2009). However, injecting drug users, men who have sex with men and sex workers are still disproportionately affected by HIV both in the developed and developing world (Kilmarx 2009).

The natural history of untreated HIV disease is chronic and progressive (Figure 1). With initial acquisition of HIV, the seroconversion illness that manifests as a mononucleosis-like syndrome may occur within weeks of exposure. Thereafter, the infection may enter a clinical latency period in which there may be little or no clinical manifestations of HIV infection for an average of ten years without intervention (Pantaleo et al. 1993). The disease then progresses to acquired immunodeficiency syndrome (AIDS), reclassified as stage III HIV disease by the Centres for Disease Control and Prevention (CDC) (Selik et al. 2014). Clinical events observed in the course of HIV disease have been classified by the World Health Organization (WHO) into four stages for adults (Appendix 1) to aid clinical assessment at initial diagnosis of HIV disease as well as to guide clinical decision making, especially the initiation of ART (World Health Organization 2007).

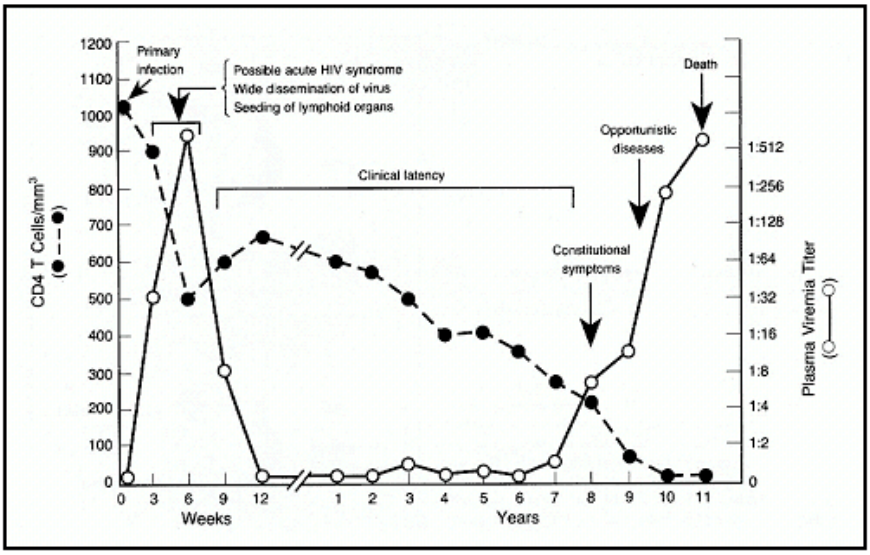


Figure 1 Clinical course of untreated human immunodeficiency virus infection

(From: Pantaleo, G., Graziosi, C. & Fauci, A.S., 1993. The Immunopathogenesis of Human Immunodeficiency Virus Infection. *New England Journal of Medicine*, 328(5), pp.327–335.)

Antiretroviral therapy (ART) for HIV disease first began with the use of zidovudine or azidothymidine (AZT) monotherapy in 1987 (Fischl et al. 1987); It was associated with increased survival initially (Creagh-Kirk et al. 1988) but its positive outcomes declined with prolonged use (Dournon et al. 1988). The use of combination ART the 1990s was responsible for dramatic reductions in the incidence of opportunistic infections and mortality in HIV-infected individuals (Palella et al. 1998).

1.2 HIV disease: the situation globally, in sub-Saharan Africa and Uganda

1.2.1 Global situation

HIV/AIDS remains a significant global public health issue. Figures published in 2014 by the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) are as follows: Over 78 million people have been infected with HIV since the disease was first recognised in 1981 (Friedman-Kien et al. 1981) and 39 million people have died as a result of HIV infection. There were an estimated 35 million people living with HIV by the end of 2013; of which 12.9 million (37%) were receiving ART, representing an increase in 5.6 million since 2010. The annual number of AIDS-related deaths has declined by 35% from 2.3 million in 2005 to 1.5 million in 2013. New HIV infections totaled 2.1 million in 2013, a reduction of 38% from 2001. The combination of longer life expectancy due to ART, coupled with new HIV infections account for the continued rise in numbers of people living with HIV (UNAIDS 2014b; World Health Organization 2014d).

Access to ART has dramatically increased globally since the launch of the “3 by 5” initiative by the WHO in 2002 that targeted the treatment of 3 million people with HIV/AIDS by 2005 (World Health Organization 2002). The achievements have been consolidated by the WHO 2006-2010 plan

for universal access to comprehensive treatment programmes, treatment, care and support by 2010 (World Health Organization 2006b). Between 2002 and 2012 in low to medium income countries, the number of people receiving ART has increased from 0.3 to 9.2 million and the consequent number of deaths averted is estimated at 4.2 million (World Health Organization 2013b). The ultimate goal of ending the HIV epidemic is now a realistic prospect. The HIV/AIDS response articulated by UNAIDS in 2010 is “getting to zero: zero new HIV infections, zero discrimination and zero AIDS-related deaths” (UNAIDS 2010). One of the targets presented in the United National 2011 political declaration on HIV/AIDS is to have 15 million people on ART by 2015. Steps taken toward this goal include a comprehensive global response to HIV outlined by UNAIDS in their “Treatment 2015 Initiative” and the strategic use of ART outlined by the WHO in 2012 that has been bolstered by their 2013 ART guidelines, which would increase the number of people eligible for ART in resource-limited settings (World Health Organization 2012; World Health Organization 2013a; UNAIDS 2013). WHO 2013 ART guidelines recommend initiating ART at CD4 cell counts ≤500 cells/mm^3, in serodiscordant couples irrespective of CD4 counts, pregnant women living with HIV, people with TB and HIV, people with HIV and hepatitis B, and children living with HIV who are younger than five years (World Health Organization 2013a). This is in contrast to WHO recommendations from 2002 to initiate ART in HIV-infected persons with WHO stage IV disease irrespective of CD4 count or

total lymphocyte count, WHO stage I, II or III disease with CD4 cell counts <200 cells/mm^3 and WHO stage II or III disease with total lymphocyte counts <1200/mm^3 (World Health Organization 2002). The 2013 guidelines are projected to increase the population eligible for ART in low and medium income countries from 16.7 to 25.9 million, with number peaking in 2021 and declining significantly after that (World Health Organization 2013a).

1.2.2 Sub-Saharan Africa

The heaviest burden of HIV/AIDS remains in sub-Saharan Africa (Health Statistics and Information Systems, World Health Organization 2013) where 24.7 million people live with HIV, accounting for 71% of the global HIV-infected population. Eighty-one percent of this population is located in 10 countries, namely South Africa (25%), Nigeria (13%), Kenya (6%), Uganda (6%), Tanzania (6%), Mozambique (6%), Zimbabwe (6%), Zambia (4%), Malawi (4%) and Ethiopia (3%). Women account for 58% of the HIV-infected population in sub-Saharan Africa (UNAIDS 2014b).

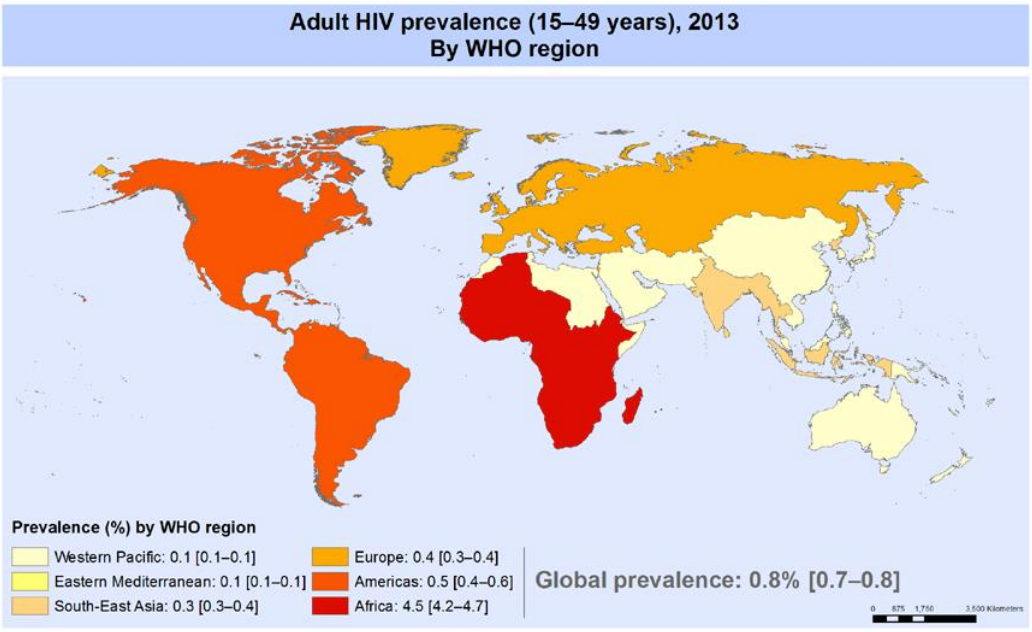


Figure 2 Global prevalence of human immunodeficiency virus infection

From: Health Statistics and Information Systems, World Health Organization, 2013. Adult HIV prevalence (15-49 years), 2013 by WHO region. Available at: http://www.who.int/gho/hiv/hiv_013.jpg?ua=1 [Accessed November 30, 2014].

AIDS-related deaths were estimated at 1.1 million in 2013, compared with total global estimates of 1.5 million. However, this was a reduction of 39% compared with 2005. Deaths averted from ART have been estimated at 7.6 million globally since 1995; that includes 4.8 million in sub-Saharan Africa. Thirty-seven percent of people living with HIV in sub-Saharan Africa are accessing ART, accounting for 75% of the total number receiving ART globally. New HIV infections were estimated at 1.5 million in

2013 (compared with global figures of 2.1 million), a reduction of 33% from 2005 and 19% compared with 2010. Angola and Uganda are the only two sub-Saharan African countries where new HIV infections have risen from 2005 to 2013 (UNAIDS 2014c).

The HIV epidemic in sub-Saharan Africa has been widely attributed to heterosexual contact, supported by the 1:1.7 male to female ratio compared to 16:1 in Europe recorded in 1986 (Quinn et al. 1986; Piot & Carael 1988). This mode of transmission has been reported to account for 80-90% of HIV infections (N'Galy & Ryder 1988; Buvé et al. 2002) although the basis for these estimates have been disputed (Gisselquist & Potterat 2003).

HIV infection in sub-Saharan Africa was initially more prevalent in urban areas and in people with higher educational attainment (Kirunga & Ntozi 1997; Fylkesnes et al. 1997), spreading along transport routes before becoming generalised (Carswell et al. 1989; Tanser et al. 2000; Colvin & Sharp 2000; Tanser et al. 2009). Other socio-economic factors that increase vulnerability to HIV infection include gender inequality, poverty (particularly urban poverty), inadequacy of social services, occupational travel, migration or displacement as well as wars or conflict (Buvé et al. 2002; Magadi 2013). The burden of HIV disease in these vulnerable and underserved groups, their impact in the dynamics of the HIV epidemic and

the importance of addressing their needs as an important part of the response to HIV has been recognised by WHO guidelines for the management of HIV disease in key populations published in July 2014 (World Health Organization 2014a).

HIV/AIDS has had a significant impact on development in sub-Saharan Africa. Gains in life expectancy were reversed in many sub-Saharan African countries by the HIV epidemic. Life expectancy at HIV-infected persons aged 15 years in South Africa in 1990 was 67.4 years and was reduced to 58.7 years in 2009 but this decline has been overturned by the scale-up of ART. This was well illustrated in Kwa-Zulu Natal where life expectancy gains of 11.3 years were recorded between 2003, the time of ART scale-up, and 2011 (Bor et al. 2013). The reduction in labour supply, productivity and increased health care costs due to mortality and morbidity from HIV infection is likely to have a significant economic impact that would compound the social and human consequences of HIV/AIDS. Estimates of its impact on reduction in economic growth have been estimated at 2-4% across Africa (Dixon et al. 2002). It is projected that continued investment in the rapid scaling up of ART, especially in low and middle income countries severely affected by HIV, would generate returns of up to three times the investment by increasing productivity as the health and well-being of working age adults improve, preventing children from

being orphaned and reducing health and social care costs with HIV-related morbidity (Resch et al. 2011).

1.2.3 Uganda

Uganda continues to have a generalised HIV epidemic. According to the 2013 UNAIDS Uganda Country Report, there were 1.6 million living with HIV and prevalence in adults aged 15-49 years was 7.4% (UNAIDS 2014a). This is in contrast to national HIV prevalence of 18.5% in 1992. Uganda was widely considered to be a success story in HIV control as the decline in national HIV prevalence began in the 1990s (Asiimwe-Okiror et al. 1997; Parkhurst 2002). However, apart from Angola, it was the only other country in sub-Saharan to have an increase in new HIV infections from 2005 to 2013, although a subsequent decrease in HIV incidence was recorded in 2013 (UNAIDS 2014b; UNAIDS 2014a). It is encouraging to note that 162,232 persons living with HIV were initiated on ART in 2013, more than the 140,908 new HIV infections recorded in the same year. The total number of people receiving ART by September 2013 was 570,373, representing 69.4% of HIV-infected persons eligible for ART according to WHO 2010 guidelines. HIV-related deaths have steadily declined from 72,928 in 2011 to 61,298 in 2013.

At the time of the inception of clinical research studies detailed in chapters 3, 4 and 5, the 2006 revision of WHO guidelines for ART in adults and

adolescents informed clinical practice at Mbarara National Referral Hospital, Mbarara, Uganda where the research studies were based (World Health Organization 2006a). These guidelines were formally incorporated into the Ugandan Ministry of Health's national antiretroviral treatment and care guidelines published in 2008 (Ministry of Health, Republic of Uganda 2008). The initiation of ART was recommended for adults and adolescents with documented HIV infection and

- WHO clinical stage IV disease irrespective of CD4 count
- WHO clinical stage III disease if CD4 testing is not available
- WHO clinical stage III disease, where CD4 testing is available, and CD4 count ≤200 cells/mm^3
- WHO clinical stage III disease, where CD4 testing is available, and CD4 count is between 200 and 350 cells/mm^3, only in patients who are co-infected with pulmonary tuberculosis, have severe bacterial infections or in women who are pregnant
- WHO clinical stage I or II disease and CD4 count ≤200 cells/mm^3 (if CD4 testing is unavailable, patients with WHO clinical stage I or II disease should not receive ART)

The choice of ART for HIV-infected patients receiving care at Mbarara National Referral Hospital were informed by the 2006 revision of WHO guidelines for ART in adults and adolescents, and Ugandan Ministry of Health's 2008 national antiretroviral treatment and care guidelines.

Recommended first-line ART regimens were comprised of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). This recommendation was based on available evidence of efficacy, low cost, availability of fixed-dose combinations (FDC) and preservation of protease inhibitor (PI)-based ART for second-line treatment (World Health Organization 2006a). Suggested combinations of NRTIs were lamivudine and either zidovudine, tenofovir or stavudine. Suggested NNRTIs were either nevirapine or efavirenz (Ministry of Health, Republic of Uganda 2008).

1.3 Significance of skin disease in human immunodeficiency virus infection

Skin disease has been one of the earliest recognised clinical manifestations of HIV infection since the beginning of the epidemic. AIDS was recognised as a new disease entity because of the recognition of epidemic Kaposi's sarcoma and pneumocystis pneumonia (Friedman-Kien et al. 1981).

1.3.1 Significance of skin disease in the diagnosis of human immunodeficiency virus infection

The skin can be the first manifestation of an otherwise asymptomatic HIV infection (Rigopoulos et al. 2004) and/or the event that brings the patient

to seek medical advice (Force et al. 1997). Skin disease is readily observable and provides the opportunity for early diagnosis of HIV (Ash & Hewitt 1994). Knowledge of one's HIV status is an entry point to accessing ART but also additional services such as the prevention and management of opportunistic infections and co-infections (UNAIDS 2013). Early diagnosis and treatment of HIV reduces risk of disease progression, morbidity and mortality associated with HIV disease as well as conferring public health benefits in the prevention of HIV transmission (World Health Organization 2013a).

1.3.2 Patterns of skin disease in human immunodeficiency virus disease

The vast majority of HIV-infected individuals will develop skin disease during the course of HIV infection; prevalence of over 90% have been reported in descriptive studies (Coldiron & Bergstresser 1989; Uthayakumar et al. 1997; Jensen et al. 2000; Sud et al. 2009). The frequency of skin disease has been quantified in HIV-infected individuals, mostly in single centre studies, during their course of HIV disease either over a defined period of time (Valle 1987; Coopman et al. 1993; Smith et al. 1994; Jensen et al. 2000; Kim et al. 2010) or at one time-point (Goodman et al. 1987; Matis et al. 1987; Coldiron & Bergstresser 1989; Fleischer et al. 1992; Goldstein et al. 1997; Rosatelli et al. 1997; Uthayakumar et al. 1997; Munoz-Perez et al. 1998; Spira et al. 1998; Jing

2000; Kumarasamy et al. 2000; Nnoruka 2004; Wiwanitkit 2004a; Mbuagbaw et al. 2006; Goh et al. 2007; Singh et al. 2009; Sud et al. 2009; Akinboro et al. 2014). Advancing HIV disease, determined by decreasing CD4 cell counts or clinical staging of HIV disease, has been associated with increased prevalence of skin disease (Alessi et al. 1988; Jing 2000; Raju et al. 2005; Akinboro et al. 2014), increased number of dermatological diagnoses per patient (Alessi et al. 1988; Coopman et al. 1993; Uthayakumar et al. 1997; Rosatelli et al. 1997; Nnoruka 2004; Goh et al. 2007; Sud et al. 2009), increased severity of skin disease (Uthayakumar et al. 1997; Kumarasamy et al. 2000; Jing 2000; Raju et al. 2005), atypical presentation of skin disease and diminished responsiveness to therapy (Kumarasamy et al. 2000). Other factors that may have influenced the proportion of study participants with skin disease and the number of dermatological diagnoses per study participant included the population from which study participants were drawn, for example HIV versus dermatology outpatient clinic (Spira et al. 1998), and 'blinding' of the assessor at the time of the skin examination to predictors such as CD4 cell count which may give rise to detection bias.

The type of skin diseases present may offer clues to the progression of HIV disease, and in turn have prognostic significance as opposed to just suggesting the presence of HIV disease. This took on practical importance as treatment, in particular ART and prophylaxis for opportunistic

infections, became available. As a result, the scope of clinical case definitions broadened from surveillance to determining eligibility for treatment. They are especially relevant in resource-limited settings where laboratory services are limited or unavailable. Skin (more accurately, mucocutaneous) diseases included within WHO clinical staging of HIV disease developed in 1990 include herpes zoster, angular cheilitis, recurrent oral ulceration, papular pruritic eruption, seborrhoeic dermatitis and fungal nail infection in clinical stage II, oral hairy leukoplakia, persistent oral candidiasis and acute necrotising stomatitis, gingivitis and periodontitis in clinical stage III as well as Kaposi's sarcoma and chronic herpes simplex infection in clinical stage IV (World Health Organization 2007).

Apart from mucocutaneous diseases mentioned in WHO clinical staging, other skin diseases have been described as clinical markers of the degree of immunosuppression from HIV disease. Molluscum contagiosum have been associated with advanced immunosuppression across multiple studies (Matis et al. 1987; Goldstein et al. 1997; Spira et al. 1998). Xerosis and pruritus were frequently described in HIV-infected study participants, more often in advanced immunosuppression in some studies (Uthayakumar et al. 1997; Spira et al. 1998; Wiwanitkit 2004a) but equally common regardless of level of immunosuppression in other studies (Coldiron & Bergstresser 1989).

1.3.3 Skin disease as a marker for response to antiretroviral therapy

The monitoring of response to ART has taken on greater importance since the global roll-out of ART and continued efforts to increase access to ART. This means that more HIV-infected individuals are likely initiate ART earlier and stay on it for longer. The prolonged use of failing ART regimens increase risk of HIV transmission and antiretroviral drug resistance, and need to be avoided with regular monitoring. Routine viral load monitoring at six- to twelve-month intervals has been recommended by the WHO but where resources do not permit, targeting viral load measurements at individuals who have fulfilled either immunological (based on CD4 counts) or clinical criteria for treatment failure has been suggested. WHO clinical criteria for treatment failure refers to new or recurrent WHO clinical stage IV or certain stage III conditions such as pulmonary tuberculosis and severe bacterial infections after at least six months of effective ART (World Health Organization 2013a).

The visibility of skin diseases makes them obvious candidates as clinical markers for response to ART. Treatment failure may cause certain skin diseases to present, recur or remain persistent and resistant to therapy. The challenge is to find skin diseases that would be good clinical markers for changes in immune status. Criteria for such skin diseases have been suggested by Rigopoulos et al. (2004). They are:

- High frequency in HIV patients compared to immunocompetent persons
- Atypical form of the skin disease or its relative resistance to common therapeutic modalities in HIV patients compared to immunocompetent persons
- Well-defined and proven epidemiological correlation with CD4 cell counts and HIV-RNA load
- Improvement due to immunological improvement because of ART
- Possible correlation to rapid progression of HIV disease and increased mortality

Colebunders et al. (2006) has included two skin conditions in a proposed algorithm for the monitoring of treatment failure at least 6 months after initiating ART: (1) appearance or worsening or prurigo, and (2) worsening of Kaposi's sarcoma (Colebunders et al. 2006).

HIV-associated skin conditions, especially those included in WHO clinical stages III and IV, may present for the first time, recur or persist after the initiation of ART, indicating either treatment failure as outlined above or immune reconstitution inflammatory syndrome and it is difficult to distinguish between the two possible causes. This is the rationale for evaluating clinical criteria for treatment failure at least six months after starting ART as immune reconstitution inflammatory syndrome usually occurs within four to eight weeks after initiating ART and may occur in 10-

27% (Haddow et al. 2012). Skin disease has been reported to account for 52-78% of all IRIS-associated events (French et al. 2004; Ratnam et al. 2006). Risk factors for IRIS include lower baseline CD4 counts, use of boosted protease inhibitors in ART, and greater magnitude of CD4 gains and viral load reductions with ART (Haddow et al. 2012).

1.3.4 Effect of skin disease on quality of life and attached stigma

As the life expectancy of HIV-infected persons has increased with ART, quality of life issues have become more important as health outcomes (Basavaraj et al. 2010). Quality of life has been defined by the WHO's constitution as "a state of complete physical, mental and social well-being, not merely the absence of disease" (World Health Organization 1997). Most HIV-infected individuals will develop skin disease during the course of the infection and it can have a profound impact on quality of life: affecting a person's physical, social and psychological well-being (Finlay & Khan 1994). Symptoms of skin disease, in particular pruritus, may result in depression, emotional distress and sleep impairment causing profound adverse effects on quality of life (Zachariae et al. 2004). Its impact has been compared with chronic pain (Kini et al. 2011).

Physical signs of skin disease that affects one's appearance may have complex effects on emotional and social functioning (Chren et al. 1996). It is made worse if associated with stigmatising diseases such as leprosy,

onchocerciasis and HIV due to associations with shame, immorality and exaggerated fear of contamination or contagion (Weiss 2008) . Stigma related to HIV has been defined by UNAIDS as “a process of devaluation of people living with or associated with HIV and AIDS”. It is often accompanied by discrimination, which refers to unfair and unjust treatment based on real or perceived HIV status (UNAIDS 2003). The adverse impact of stigma and discrimination on health-seeking behaviour is illustrated by reduced uptake of HIV testing, adopting preventive practices, accessing care and treatment, disclosure of HIV status and adherence to therapy. These are major obstacles to the implementation of universal HIV prevention, treatment, care and support. The reduction of HIV-related stigma and discrimination at every stage of the HIV care delivery is at the forefront of the UNAIDS “getting to zero” strategy and WHO treatment guidelines (UNAIDS 2007; World Health Organization 2013a). Therefore the understanding and management of HIV-related skin disease due to its impact on quality of life and potential as a source of stigma and discrimination is important and should not be neglected.

1.4 Papular pruritic eruption of human immunodeficiency virus infection

1.4.1 Background

Papular pruritic eruption (PPE) of human immunodeficiency virus (HIV) infection is a skin condition of unknown aetiology. It is characterised by intensely itchy papules that are usually most highly concentrated on the extremities (Colebunders et al. 1987; Liautaud et al. 1989).

1.4.2 Epidemiology

PPE is one of the most common skin diseases seen in HIV-infected persons in tropic and subtropical regions. Its association with HIV infection has been recognised and described since the beginning of the epidemic in countries within sub-Saharan Africa, Asia and the Caribbean, with reported prevalence of 11-46% (Colebunders et al. 1987; Liautaud B 1989; Sivayathorn et al. 1995; Rosatelli et al. 1997; Resneck et al. 2004a; Nnoruka et al. 2007; Goh et al. 2007; Akinboro et al. 2014). PPE has been reported to be highly predictive of HIV infection in African patients and a common first presentation of HIV infection in African and Haitian patients (Colebunders et al. 1987; Liautaud et al. 1989). However, over half of study participants with PPE in Hevia et al's (1991) study had an opportunistic infection prior to the onset of PPE.

1.4.3 Clinical presentation and clinical definition

The morphology of PPE lesions has been described as small, firm, well-demarcated papules. They may be “skin-coloured”, erythematous or hyperpigmented. Vesicles on top of these papules have also been described. The diameter of each lesion ranges from 1-10mm. The location of the earliest and largest numbers of these lesions is often on the extremities. On the upper limbs, they are usually localised on extensor surfaces. Palmar lesions have been reported to be rare and similar to dyshidrotic eczema. Facial lesions were mainly located on the forehead. The sparing of soles, interdigital areas, scalp and mucous membranes has been described. Severe pruritus was described as the predominant symptom, hence excoriations and the sequelae of chronic scratching were often seen including ulceration, lichenification and pruriginous lesions (Colebunders et al. 1987; Liautaud et al. 1989).

PPE as a disease entity has been poorly defined. Most studies relied on clinical case definitions, unsupported by correlation with biopsy findings. Clinical criteria for PPE used by Colebunders et al. (1987) were “generalised pruritic papular eruption of at least 1 month duration”. PPE was characterised by Liautaud et al. (1989) as “chronic disseminated intensely pruritic skin lesions of greater than 2 months but less than 5 years’ duration, without apparent cause or diagnostic category”. Clinical case definitions of PPE used by Hevia et al. (1991) and Boonchai et al.

(1999) were (1) HIV seropositivity, (2) chronic pruritic discrete papules on the trunk, extremities and face of at least 1 month's duration and (3) absence of another definable cause of the pruritus.

1.4.4 Histological features

Histological features of PPE, consistently described across multiple studies, were characterised by perivascular and interstitial mainly lymphocytic infiltrate with variable numbers of eosinophils seen within the superficial and deep dermis, sometimes extending into subcutaneous fat. As opposed to eosinophilic folliculitis, the inflammatory infiltrate is non-folliculocentric. Fungi, bacterial and virus, including HIV, were not seen in these lesions on microscopy with special (periodic acid-Schiff, Giemsa, Ziehl-Nielsen, Grocott-Gomori's methenamine silver) stains, as well as on electron microscopy (Colebunders et al. 1987; Liautaud et al. 1989; Hevia et al. 1991; Boonchai et al. 1999a; Resneck et al. 2004a; Ramos et al. 2005; Budavari & Grayson 2007).

Findings on examination of the epidermis have been described as largely normal. Other findings in the epidermis that have been described include acanthosis and spongiosis (Colebunders et al. 1987; Hevia et al. 1991; Boonchai et al. 1999a; Resneck et al. 2004a). Resneck et al (2004) has described a focal area of spongiosis located in the epidermis over the centre of the dermal inflammatory infiltrate, consistent with a punctum at

the site of an arthropod bite or sting, in eleven of 86 patients with PPE. The dermal inflammatory infiltrate may often include neutrophils and sometimes eosinophils may not be present, making biopsy findings more non-specific. Vasculitis is not a feature usually seen in PPE (Colebunders et al. 1987; Hevia et al. 1991; Boonchai et al. 1999a; Resneck et al. 2004b). Hevia et al. (1991) and Boonchai et al. (1999) have systematically described histologic findings of PPE in 28 and 20 persons with PPE, respectively. They are outlined in the table below (Table 1).

Table 1 Histological findings of papular pruritic eruption of human immunodeficiency virus infection

Histological findings (%)	Hevia et al. (1991) n=28	Boonchai et al. (1999) n=20
Epidermis		
Spongiosis	17 (61)	1 (5)
Parakeratosis	8 (28)	--
Hyperplasia	--	7 (35)
Erosion	--	2 (10)
Dermis		
Mononuclear cell infiltrate	--	--
Perivascular	28 (100)	--
Superficial perivascular	--	20 (100)
Deep perivascular	--	8 (40)
Perifollicular	24 (87)	10 (50)
Perieccrine	15 (55)	4 (20)
Perineural	16 (56)	--
Eosinophilic infiltrate	22 (79)	13 (65)
Neutrophilic infiltrate	--	5 (25)
Follicular spongiosis	13 (46)	--
Folliculitis	7 (25)	--

Features of PPE on immunohistochemical studies were examined in multiple studies with the aim of exploring the pathogenesis of PPE and distinguishing between PPE and HIV-EF. Greater numbers of lymphocytes especially CD8+ T-lymphocytes, eosinophils, mast cells, granulocytes, macrophages, Langerhans cells were seen in biopsies taken from lesional skin compared to non-lesional skin (Rosatelli & Roselino 2001). Ramos et al (2005) reported similar findings with elevated numbers of CD8+ and reduced numbers of CD4+ T-cells within the inflammatory infiltrate of PPE lesions. The predominant cytokine was interleukin-5. These findings suggest the activation of T-cells with T-helper (Th) 2 function (Ramos et al. 2005). Afonso et al (2012) found lower densities of inflammatory cell infiltration, tissue mast cell count by toluidine staining, expression of CD15, CD4 and CD7 in PPE compared with HIV-EF. However, these differences were purely quantitative and no qualitative differences were observed (Afonso et al. 2012).

1.5.5 Differential diagnoses

There is an extensive list of clinical differential diagnoses for papular pruritic eruptions associated with HIV. Eosinophilic folliculitis associated with HIV infection (HIV-EF) is a key differential diagnosis for PPE. It typically presents in individuals with advanced HIV disease with low CD4 counts of less than 250 cells/mm^3, which is similar to PPE. However, in contrast to PPE, most HIV-EF lesions are located on the head, neck,

upper trunk and proximal aspects of the upper arms, and rarely on the distal aspects of the extremities (Bason et al. 1993; Simpson-Dent et al. 1999). The histology of HIV-EF is characterised by follliculocentric infiltrates of eosinophils and lymphocytes (McCalmont et al. 1995). This is distinct from PPE where the dermal inflammatory infiltrate of lymphocytes and eosinophils is non-folliculocentric but mainly interstitial and perivascular (Resneck et al. 2004b). Other differential diagnoses for PPE are presented in Figure 3 (Bason et al. 1993; Fearfield et al. 1999; Simpson-Dent et al. 1999; Resneck et al. 2004b).

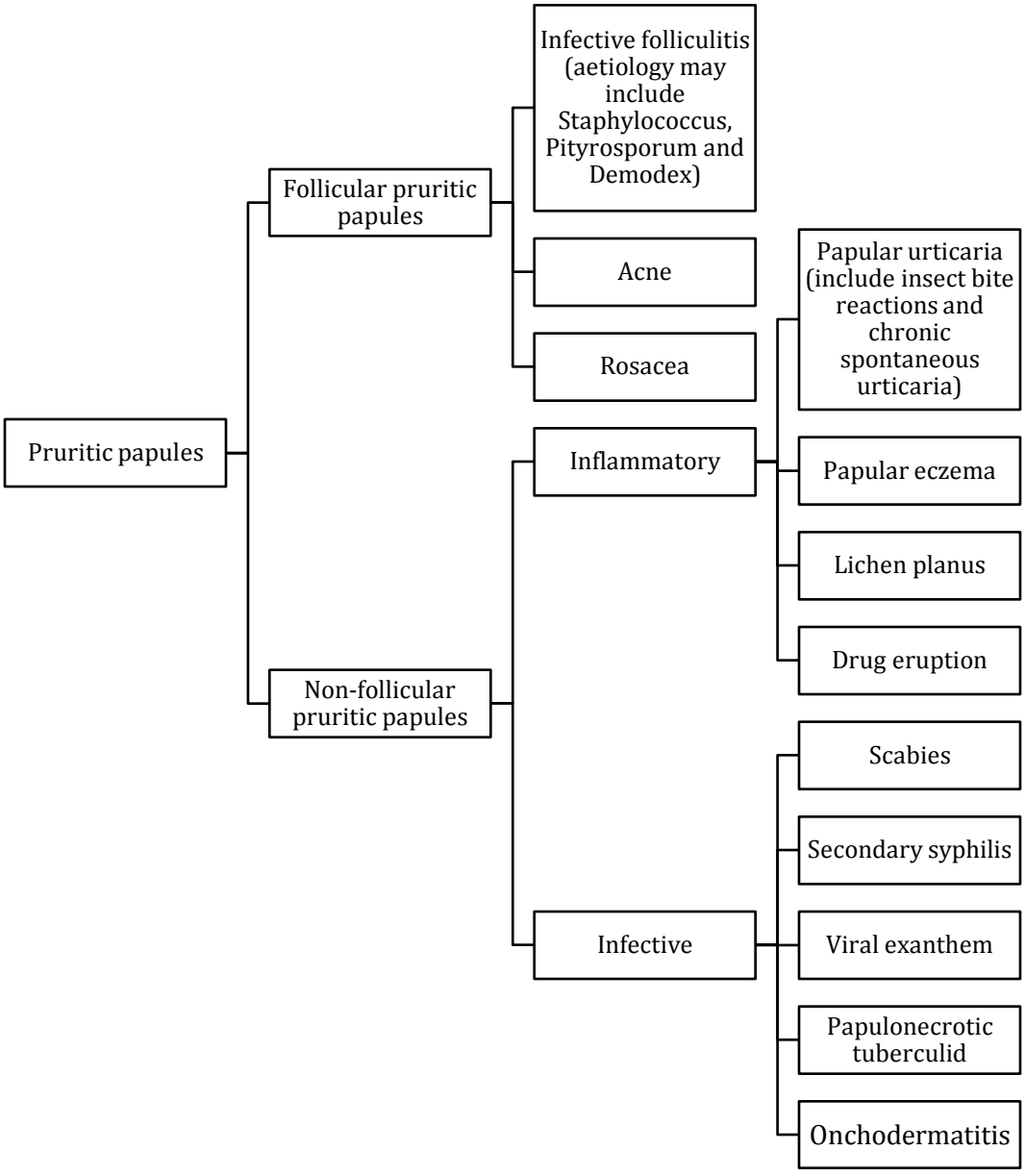


Figure 3 Differential diagnoses for papular pruritic eruption of human immunodeficiency virus infection

(Bason et al. 1993; Fearfield et al. 1999; Simpson-Dent et al. 1999; Resneck et al. 2004b)

1.5.6 Aetiology

The geographical distribution of HIV-infected populations affected by PPE in tropical and sub-tropical regions has suggested the contribution of exogenous factors to the development of PPE, in addition to HIV infection. The morphology of unexcoriated PPE lesions as well as histological features are similar to those found in arthropod bites or stings (Colebunders et al. 1987; Resneck et al. 2004a).

The possibility of PPE as a direct consequence of arthropod bites or stings has been suggested by findings of punctums on biopsy. This was found in eleven of 86 PPE patients in Resneck et al's (2004) study. However, the density of PPE lesions may be similar in both covered and covered areas in some affected individuals even though PPE lesions are more predominant on the extremities. Exposure to animals may predispose to insect bites and unpublished data from Kinshasa, Democratic Republic of Congo has reported no difference between the presence of animals and types of animals in the homes of HIV-infected individuals with or without PPE (Colebunders et al. 1987). Scabies has not been found in PPE lesions and HIV-negative close contacts have not reported similar lesions (Colebunders et al. 1987; Liautaud et al. 1989).

Hypersensitivity to arthropod bites or stings as a cause for PPE has been investigated by Rosatelli et al. (2001) with skin prick testing (SPT).

Antigens used included mites, fungi, feathers, epithelium (mixed) and insect body parts. A greater proportion of study participants with PPE (7/17, 41%) had a positive reaction to three or more antigens compared to those without PPE (2/8, 25%), and positive reactions to insect body parts were recorded in four of 17 (24%) participants with PPE compared to three of eight (38%) participants without PPE. Penneys et al. (1989) reported increased antibody titres to salivary antigens of a mosquito common to south Florida in five of seven patients with PPE resident in the area. A chronic recall reaction mediated by non-specific B-cell activation was suggested as a possible mechanism for the development of PPE in these patients (Penneys et al. 1989). This may add strength to the hypothesis that the well-described desensitization to repeated arthropod bites or stings (Peng et al. 2004) has been lost in individuals with PPE. Parallels between this and increased frequency drug hypersensitivity in HIV-positive persons have been drawn (Pirmohamed & Park 2001; Resneck et al. 2004a). Mechanisms suggested include chronic immune activation and immune dysregulation (Boasso et al. 2009) that has been well-described in HIV infection but not been specifically linked with PPE.

It has been suggested that PPE is an inflammatory process associated with the activation of T-cells with a Th2 pattern of cytokine expression, a feature of advanced HIV disease (Ramos et al. 2005). Immune dysregulation in the course of HIV disease that is characterised by the

decline of Th1 immune responses and the increasing predominance Th2 immune responses has been well-described (Clerici & Shearer 1993). Histological and immunohistochemical examination of PPE lesions have demonstrated a greater number of CD8+ T-cells compared to CD4+ T-cells in the inflammatory infiltrate, the presence of eosinophils and the predominance of interleukin-5 expression, which is consistent with a Th2 response (Ramos et al. 2005). This is in keeping with observations of greater prevalence of PPE with advancing HIV disease (Boonchai et al. 1999b; Wiwanitkit 2004b; Castelnuovo et al. 2008a; Akinboro et al. 2014).

1.5.7 Relationship with human immunodeficiency virus disease

The presence of PPE has been described in association with advanced HIV disease, especially prior to ART. Mean CD4 counts reported in ART-naïve HIV-infected individuals with PPE were generally low: 46 cells/mm^3 (Goldstein et al. 1997; Resneck et al. 2004a) , 52 cells/mm^3 (Castelnuovo et al. 2008b), 58 cells/mm^3 (Boonchai et al. 1999c), 124 cells/mm^3 (Ramos et al. 2005), 149 cells/mm^3 (Kumarasamy et al. 2000) and 225 cells/mm^3 (Farsani et al. 2013). Its frequency has been reported to increase with advancing HIV disease as demonstrated by its relationship to CD4 cell count (Table 2) and WHO clinical staging (Table 3).

Table 2 Frequency of papular pruritic eruption of human immunodeficiency virus infection in relation to CD4 cell counts

CD4 cell counts (cells/mm^3)	Akinboro et al. (2014)	Wiwanitkit (2004)	Boonchai et al. (1999)
<200	22/27 (81%)	30/37 (83%)	16/20 (80%)
200-500	4/27 (15%)	14/37 (34%)	4/20 (20%)
>500	1/27 (4%)	0/37 (0%)	0/20 (0%)

Table 3 Frequency of papular pruritic eruption of human immunodeficiency virus infection in relation to World Health Organization clinical staging

(From: Castelnuovo, B. et al., 2008. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? *AIDS (London, England)*, 22(2), pp.269–273.)

WHO clinical staging	Frequency of PPE (%)
I	0/53 (0%)
II	4/53 (8%)
III	25/53 (47%)
IV	24/53 (45%)

PPE, papular pruritic eruption of human immunodeficiency virus infection.

WHO, World Health Organization

Castelnuovo et al. (2008) has demonstrated the reduction in severity of pruritus six months after commencing ART and the resolution of PPE in 16 of 53 study participants (Ten participants had been lost to follow-up within six months of starting ART). Recurrent PPE has been described in Ugandan patients experiencing treatment failure with ART and its resolution with virological suppression following switching of ART regimens (Castelnuovo et al. 2008b; Chua & Maurer 2009).

PPE may fulfill Rigopoulos et al's (2004) criteria as a clinical marker of the course of HIV disease in tropical regions where it is prevalent as it is not present in HIV-negative individuals, more common with advancing HIV disease and improves with ART (Rigopoulos et al. 2004). Indeed, persistent or recurrent PPE after at least 6 months of ART has been suggested as part of a proposed clinical algorithm to detect virological failure (Colebunders et al. 2006). However, the case control study presented in chapter 4 of this thesis has reported persistent or recurrent PPE after at least 15 months ART that was not associated with treatment failure. It was associated with greater HIV viraemia at ART initiation and participant reports of daily insect bites, and was independent of CD4 gains, CD8+ T-cell activation markers measured at six and twelve months after initiation of ART (Chua & Maurer 2009).

1.6 Knowledge gaps

PPE is a highly symptomatic and stigmatising skin disease that is prevalent in HIV-infected populations that live in tropical and subtropical regions. Summarizing current available evidence of effective interventions would aid decision-making by health care providers and policy makers, and identify research gaps that may direct future research efforts. A systematic review of interventions for PPE (chapter 2) was performed to address this need.

The clinical studies of PPE described below enrolled Ugandan study participants based in Mbarara, Uganda where the predominant language used is Runyankore and literacy rates are low. In order to measure the impact of skin disease on their quality of life, Skindex-16, a one-page dermatology-specific quality of life instrument, was translated into Runyankore and adapted for oral administration. It was tested for practicability of use, reliability, construct and content validity in Mbarara, Uganda prior to commencement of clinical studies of PPE. This study is reported in chapter 3.

The presence of PPE has been proposed as one of several clinical markers of virological failure after at least six months of ART (Colebunders et al. 2006). There are gaps in existing knowledge of factors that predict

the presence of PPE in ART-treated HIV-infected persons. It is also unclear if PPE is associated with virological failure in HIV-infected persons receiving ART. A case control study of Ugandan adults receiving ART was carried out with the aim of answering these questions and is described in Chapter 4.

Symptom improvement and resolution of PPE has been reported with ART, although the speed of improvement and factors affecting its response to ART is unclear. The proportion of PPE patients who will experience recurrent or persistent PPE despite virologically suppressive ART is as yet unknown, as is the risk of recurrent or persistent PPE with treatment failure. A 2-year cohort study of Ugandan HIV-infected adult participants initiating ART was performed with the objective of describing the natural history of PPE and the relationship between recurrent or persistent PPE and virological response to ART. The study is reported in Chapter 5.

2. Systematic review of interventions for papular pruritic eruption of human immunodeficiency virus infection

2.1 Background

2.1.1 Description of condition

Papular pruritic eruption (PPE) of human immunodeficiency virus (HIV) infection is a chronic skin condition characterized by intensely pruritic papular lesions that are mostly distributed on the extremities and trunk (Colebunders et al. 1987; Liautaud et al. 1989; Hevia et al. 1991; Boonchai et al. 1999b). It is associated with lower CD4 counts and advanced HIV disease (Boonchai et al. 1999b; Resneck et al. 2004b; Wiwanitkit 2004a). PPE is prevalent in tropical and subtropical regions, with reported prevalence of 11-46%. It has been reported to be highly predictive of HIV infection and a common initial presentation of AIDS in Haiti and the Democratic Republic of Congo (Colebunders et al. 1987; Liautaud et al. 1989).

2.1.2 Describe interventions

Multiple studies of PPE have described the lack of success of interventions such as topical corticosteroids, topical antiparasitic agents including lindane cream, topical antifungal agents, oral antihistamines and

systemic antibiotics including co-trimoxazole, rifampicin and ampicillin (Colebunders et al. 1987; Liautaud et al. 1989; Hevia et al. 1991). However, the efficacy of oral antihistamines, topical corticosteroids and topical antifungal agents have also been reported (Uchigasaki et al. 1996; Dagatti et al. 2000; Navarini et al. 2010). Phototherapy, oral pentoxifylline and dapsone have also been reported to help with symptoms and skin lesions of PPE (Pardo et al. 1992; Ishii et al. 1994; Berman et al. 1998; Aquilina 1998; Lakshmi et al. 2008a; Bellavista et al. 2013). ART has been associated with resolution of PPE, although it may persist or recur despite virologically suppressive ART (Castelnuovo et al. 2008b).

2.1.3 Rationale for review

PPE is one of the most common skin conditions associated with HIV in tropical and subtropical regions. These geographical regions include sub-Saharan Africa and south Asia where approximately three-quarters of the global population of persons living with HIV/AIDS reside (UNAIDS 2014b). According to the 2010 global burden of disease study, HIV/AIDS was the leading cause of disability-adjusted life years (DALYs) in 21 countries that were located in sub-Saharan Africa, the Caribbean and Thailand where PPE has been reported to be prevalent (Colebunders et al. 1987; Hevia et al. 1991; Sivayathorn et al. 1995; Rosatelli et al. 1997; Goh et al. 2007; Nnoruka et al. 2007; Ortblad et al. 2013; Akinboro et al. 2014).

Severe pruritus, characteristic of PPE, adversely impacts on quality of life, and has the potential to result in depression, distress and sleep impairment (Zachariae et al. 2004). The impact of chronic pruritus on quality of life is substantial and comparable with chronic pain (Kini et al. 2011). Skin diseases are a source of stigma in many communities, especially if they cause visible skin changes that are difficult to conceal and suggest the possibility of stigmatising diseases such as HIV (Ginsburg & Link 1993; Chaturvedi et al. 2005; Weiss 2008; Mahajan et al. 2008; Roosta et al. 2010).

Stigmatised persons are more likely to experience discrimination, loss of status and reduction in life chances. This has a negative impact of quality of life and contributes to poor uptake and adherence to HIV/AIDS prevention and treatment programmes (Link & Phelan 2006; Mahajan et al. 2008).

The WHO has highlighted the global demand for guidance in the treatment of skin conditions associated with HIV as they are currently lacking. As a result, systematic reviews were commissioned by the WHO for ten main HIV-associated skin and oral conditions, including PPE. This review has contributed the WHO's guidelines on the treatment of HIV-associated skin and oral conditions published in 2014 (World Health Organization 2014c).

2.2 Objectives

The objective of this review was to systematically summarise the evidence for interventions for PPE in HIV-infected adults and children, and identify knowledge gaps in its management.

2.3 Methods

2.3.1 Search strategy

Electronic databases were searched for published studies of interventions for PPE. Studies in all languages published between 1 January 1980 and 1 September 2014 were included. The databases searched included Medical Literature Analysis and Retrieval System Online (Medline), Excerpta Medica Database (Embase), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Global Health Library, Cochrane Library, National Library of Medicine (NLM) gateway and WHO International Clinical Trials Registry that provides access to www.clinicaltrials.gov, European Union, Australian, New Zealand, Brazilian, Chinese, Cuban, German, Iranian, Indian, Japanese, Korean, Sri Lankan, Dutch and Thai clinical trials registers.

Key search terms used were papular, pruritic, eruption, insect bites, HIV and AIDS. The exact search strategy used was “((pruri* AND papul*) OR

(pruri* AND erup*) OR (papul* AND erup*) OR (insect bite*)) AND (HIV OR AIDS)". The aim of this search strategy was to capture all studies of and relating to PPE where possible. The Boolean operators, "AND" and "OR", as well as truncation symbols, "*", were included to ensure that various combinations, permutations and variants of key words that describe PPE were accounted for. Reference lists of included studies and review articles were reviewed to identify further publications. Study authors were contacted if necessary for more data or clarification of data presented.

2.3.2 Inclusion criteria - types of studies, participants, interventions and outcome measures

All studies of human subjects that examined interventions for PPE were included, irrespective of study design and even if the evaluation of interventions for PPE was not one of the objectives of the study. There were no restrictions on the number of study participants in each study or types of study participants with regard to age, sex or ethnicity. This meant the inclusion of studies ranging from case reports of a single patient to observational studies and randomised controlled trials. All interventions for PPE were considered, including combinations of multiple interventions. Studies that did and did not compare one group of study participants with another group receiving different interventions were included. There were no restrictions placed on the interventions received by the comparison

group, which may include no intervention, placebo or another active intervention(s).

The primary outcome of interest for this review was the resolution of PPE: its symptoms, physical signs or both. However, there were no restrictions placed on the types of outcome measures used in studies of interventions of PPE identified for inclusion in this review. The timing of outcome assessment and reporting of adverse events were recorded but did not impact on selection of studies for inclusion.

2.3.3 Data extraction and analysis

Data from full texts of included studies were extracted and independently evaluated by two authors in duplicate (Dr. Mike Zangenberg and I). If there were disagreements between the two authors extracting the data on whether a study should be included, and a consensus could not be reached, it was adjudicated by a third author (Dr. Toby Maurer). Extraction of data was based on the “Checklist of items to consider in data collection or data extraction” in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green 2011). The following data were extracted: first author, year of publication, location of study, study design, number of study participants, method of ascertainment of diagnosis (clinical criteria and/or biopsy findings), reported previous unsuccessful interventions, study intervention(s), outcome(s), length of follow-up period, results and

adverse effects of intervention(s) (Table 4). Due to the heterogeneous nature of study designs and reported outcome measures of included studies, quantitative synthesis of the data collected was not carried out. Instead, a descriptive qualitative approach was used in the analysis of data collected.

Quality assessment of included studies was carried out using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (GRADE Working Group 2004). If included studies were randomised controlled trials, the Cochrane collaboration's risk of bias assessment tool (Higgins & Green 2011) was used to evaluate their quality. If included studies were non-randomised studies such as case control or cohort studies, the Newcastle-Ottawa scale (Wells et al. 2000) was used to assess their quality.

The GRADE approach is a systematic and explicit way of making judgments about the quality of evidence and strength of recommendations. This involves making judgments about the following: quality of evidence across studies for each important outcome, which outcomes are critical to a decision, overall quality of evidence across the critical outcomes, balance between benefits and harm, and strength of recommendations. Authors of the GRADE approach have defined the quality of evidence as the extent to which one can be confident that the

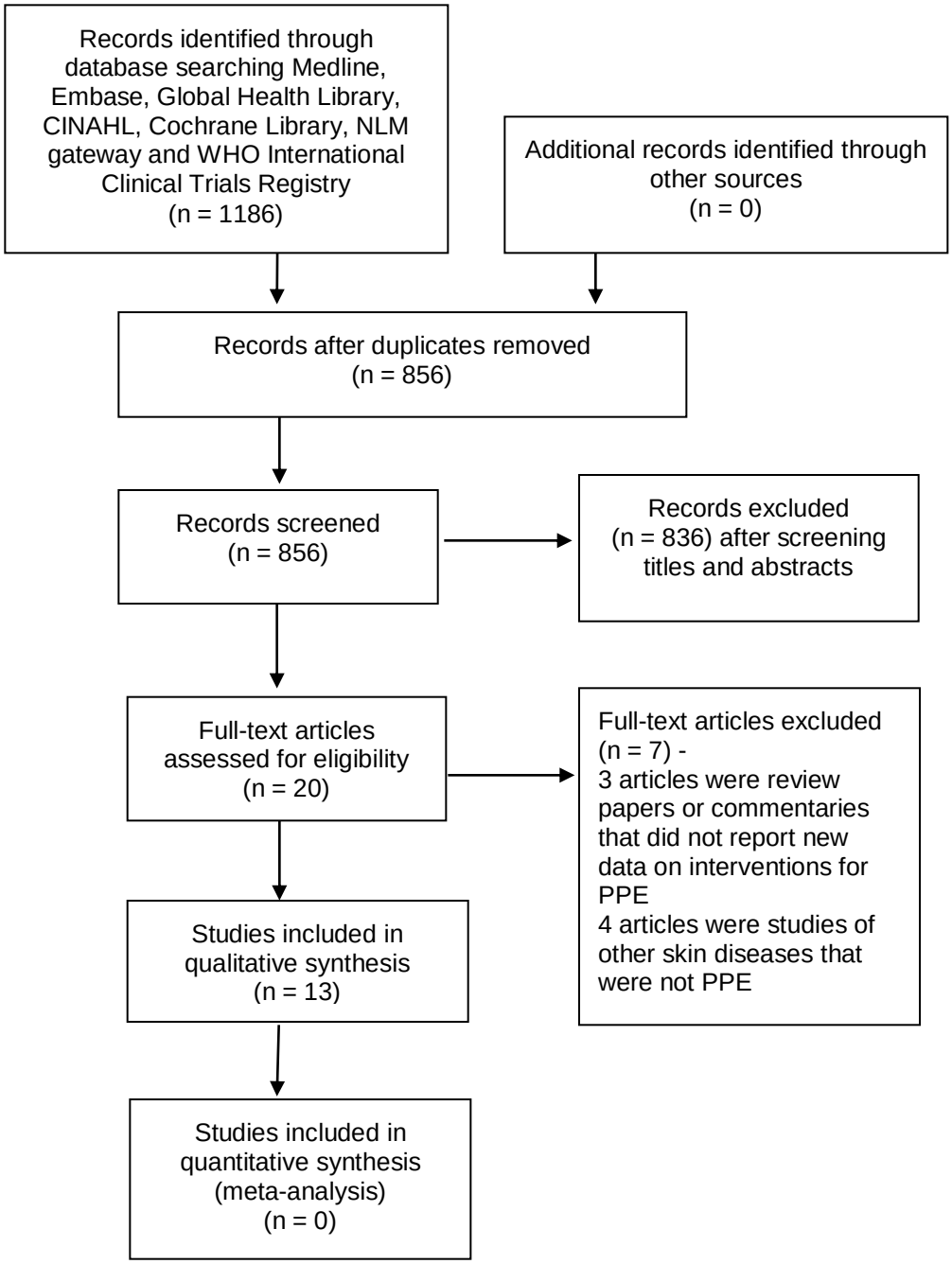
estimate of the effect is correct. They have defined the strength of a recommendation as the extent to which one can be confident that adherence to the recommendation will do more good than harm. These judgments are contingent upon having a clearly defined question that identifies interventions being compared, for whom, in what setting and the consideration of all outcomes likely to be important to those affected (GRADE Working Group 2004).

The Cochrane collaboration's risk of bias tool aims to determine the extent to which a study has answered its research question in a manner that is free from bias, otherwise known as the "internal validity" of a study. It addresses seven domains, namely sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), addressing incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential risks of bias. The evaluation of the validity of studies included within a systematic review is an essential part of the review as it determines the extent to which a review may draw conclusion about the effects of an intervention (Higgins & Green 2011).

The Newcastle-Ottawa Scale is a validated scale that was developed to assess the quality of non-randomised studies such as case control and

cohort studies in a systematic review. The evaluation of each study is based on eight items that are categorised into three main domains: selection of study groups, comparability of the groups and the ascertainment of either exposure or outcome of interest for case control or cohort studies, respectively. The number of stars awarded for each study out of a maximum of nine stars provides a quick visual assessment of its quality (Wells et al. 2000).

Figure 4 Study flow diagram of systematic review of interventions for papular pruritic eruption of human immunodeficiency virus infection



CINAHL, Cumulative Index to Nursing and Allied Health Literature. Embase, Excerpta Medica Database. Medline, Medical Literature Analysis and Retrieval System Online. NLM, National Library of Medicine. PPE, papular pruritic eruption of human immunodeficiency virus disease. WHO, World Health Organization.

2.4 Results

2.4.1 Included studies

2.4.1.1 Study participants

Thirteen studies of interventions for PPE were included in this review (Figure 4). They included a total of 188 participants. All study participants were adults apart from one study whose study subject was 13 years old (Naswa et al. 2011). Confirmation of the clinical diagnosis of PPE with histological examination was carried out in nine of thirteen included studies.

2.4.1.2 Study design

None of these studies were randomised controlled trials (Table 4). There were two uncontrolled non-randomised trials that studied UVB phototherapy (Pardo et al. 1992) and oral pentoxifylline (Berman et al. 1998) as interventions for PPE. One parallel-group study, in which randomisation was not mentioned, compared oral dapsone versus oral pentoxifylline versus a combination of topical corticosteroids and oral antihistamines for PPE (Lakshmi et al. 2008b). Three observational studies were included; interventions for PPE described were ART (Castelnuovo et al. 2008b), oral cetirizine (Dagatti et al. 2000) and oral promethazine compared with topical hydrocortisone therapy (Navarini et

al. 2010). Seven single-patient case reports were included. Three case reports described the response of PPE to UVB phototherapy (Ishii et al. 1994; Aquilina 1998; Bellavista et al. 2013). The other four case reports described the use of ART (Naswa et al. 2011), oral isotretinoin (Harindra & Roy 1992), oral thalidomide (Wernham & Chua 2014) and a combination of oral antihistamines and topical corticosteroids (Uchigasaki et al. 1996).

2.4.1.3 Outcome measures

Reported outcomes were heterogeneous across studies. Two studies reported global clinical response without specific reference to symptoms or physical signs (Dagatti et al. 2000; Lakshmi et al. 2008a). Five studies reported global reduction in pruritus and PPE lesions (Harindra & Roy 1992; Ishii et al. 1994; Aquilina 1998; Naswa et al. 2011; Bellavista et al. 2013). Participant-reported pruritus severity was reported in five studies with the use of numerical rating scales (Pardo et al. 1992; Navarini et al. 2010), 4-point verbal rating scale (Castelnuovo et al. 2008b) and 10-cm visual analogue scale (VAS) (Berman et al. 1998; Wernham & Chua 2014). Reported outcomes of physical signs of PPE included papule count in a $100cm^2$ area (Pardo et al. 1992), morphology of skin lesions (healed lesions, macules, papules or excoriated lesions) (Navarini et al. 2010) and presence or absence of skin lesions (Castelnuovo et al. 2008b). The Dermatology Life Quality Index and use of treatment for PPE were also reported as outcomes by Wernham et al. (2014) and Castelnuovo et al. (2008), respectively.

2.4.2 Excluded studies

A total of seven studies or articles were excluded after their full texts were reviewed. They included Bason et al's (1993) review article on PPE, Rosen's (1991) item of correspondence on the diagnosis of different papular pruritic eruptions associated with AIDS and Colebunders et al's (1987) observational study of key characteristics of PPE. Four studies described skin conditions other than PPE, including HIV-associated eosinophilic folliculitis (Sears et al. 2014), scabies (del Pozo et al. 1992), Demodex-associated folliculitis (Bañuls et al. 1991), papular mucinosis and secondary syphilis (Binet et al. 1987).

2.4.3 Risk of bias

According to the GRADE approach, the quality of evidence for each main outcome may be assessed by considering four elements: study design, study quality, consistency and directness. Due to the heterogeneous nature of outcomes measured, it was not possible to assess the quality of evidence across multiple studies for each main outcome. Therefore, the overall quality of evidence was assessed for all included studies.

Overall, the quality of evidence included in this review may be considered very low quality. In the GRADE approach, evidence from randomised trials are considered high quality, observational studies are considered low

quality and all other studies are considered very low quality. No randomised controlled trials were included in this review. There were three non-randomised trials, three observational studies and seven case reports. As the observational studies included in this review were not clearly defined as case control or cohort studies, the Newcastle-Ottawa scale (Wells et al. 2000) could not be used to evaluate their quality. None of the studies had clearly defined primary and/or secondary outcomes, which limited study quality. Apart from one parallel group study, none of the studies had comparisons of outcomes between two or more groups that allowed comparative risk or effect size measurements.

Consistency, which refers to the similarity of effect across studies for a particular outcome, could not be determined in this review. It was not possible to compare the effect of interventions across multiple studies for each main outcome due to the heterogeneous nature of outcome measurements in studies included in this review. Lastly, directness refers to the extent to which the people, interventions and outcome measures are similar to those of interest. Generalisability is limited in single-centre studies with small numbers of participants and case reports, which characterize the studies included in this review. The interventions described in studies of this review, including ART, antihistamines, dapsone, pentoxifylline, phototherapy and topical corticosteroids are relevant to clinical practice. Outcome measures across included studies

addressed the main symptoms of pruritus and signs of PPE, which are clinically relevant even though the specific outcome measures used varied across studies.

2.4.4 Effect of interventions

2.4.4.1 Systemic therapy

Antiretroviral therapy

Castelnuovo et al. (2008) evaluated the effect of ART, comprising lamivudine, stavudine and nevirapine or efavirenz, on PPE in 53 Ugandan adults with PPE. The proportion of study participants who reported the presence of PPE after six, twelve, eighteen and twenty-four months of receiving ART were 27/43 (63%), 10/43 (23%), 2/39 (5%) and 2/29 (7%). The use of medications for PPE was reported by 53/53 (100%), 23/43 (53%), 9/43 (20%), 1/39 (3%) and 1/29 (4%) of study participants at baseline, six, twelve, eighteen and twenty-four months of starting ART, respectively. PPE severity was the third outcome reported. It was defined as the sum of itch severity during the day and at night measured with a four-point verbal rating scale (0=not at all, 1=a little, 2=a lot, 3=very much). Mean PPE severity scores were 3.9, 0.9, 0.5, 0.1 and 0.1 at baseline, six, twelve, eighteen and twenty-four months after ART initiation.

Naswa et al. (2011) reported the reduction of pruritus and healing of PPE lesions in a 13-year old female HIV-positive patient on initiation of ART

(stavudine, lamivudine and efavirenz). The patient's PPE had previously failed to respond to oral and topical corticosteroids as well as oral dapsone 50mg per day. The duration of her treatments have not been specified.

Antihistamines

Dagatti et al. (2000) observed a positive response of to cetirizine 20mg per day in eight participants whose CD4 counts were less than 200 cells/mm^3. The duration of therapy, time of outcome evaluation and whether study participants were receiving ART was not reported.

Pentoxifylline

Berman et al. (1998) evaluated oral pentoxifylline therapy, 400mg three times per day over eight weeks, in twelve participants over an eight-week period. Three participants had been receiving UVB phototherapy without improvement in their PPE for at least a month prior to starting oral pentoxifylline; they continued with phototherapy without changes to the treatment protocol during the study period. Mean pruritus score measured on a 10cm VAS declined from 6.5cm at baseline to 3.6cm at the end of eight weeks of treatment. The physical extent of PPE after eight weeks of treatment, evaluated by a study investigator in 11/12 study participants, decreased by 0-24% in seven participants and 25-49% in three participants, and increased by 1-24% in one participant.

Other systemic therapy

Wernham and Chua (2014) reported the use of thalidomide, 100mg per day over three months, in one female patient receiving virologically suppressive ART. Her DLQI scores declined from 26/30 at the start of treatment to 2/30 at the end of treatment. Her pruritus score decreased from 7/10 to 1/10 from the start to the end of the treatment period.

Harindra et al (1992) reported the use of isotretinoin for PPE, starting at 0.5mg/kg/day, in one patient who was also receiving oral doxycycline for other reasons. After six weeks of treatment, the patient hardly mentioned itch and the skin lesions had almost completely healed. Isotretinoin was subsequently continued at 0.25mg/kg/day.

2.4.4.2 Topical therapy

None of the included studies investigated the use of topical therapy only for PPE.

2.4.4.3 Phototherapy

Pardo et al. (1992) evaluated the use of UVB phototherapy (whole body) in a series of eight patients with PPE. All patients experienced a significant reduction in papule count in a 100cm^2 area ($p<0.0014$). Seven of eight patients reported a significant reduction in pruritus severity assessed with

a numeric rating scale ($p<0.0022$). PPE recurred in half of these patients after an average of eight weeks (range: 4-12 weeks) from the discontinuation of phototherapy.

There were two case reports that described the use of UVB phototherapy (Ishii et al. 1994; Aquilina 1998) and one case report that described the use of narrowband UVB phototherapy for PPE (Bellavista et al. 2013) included within this review. The reduction of pruritus and skin lesions was reported in all patients.

2.4.4.4 Comparisons between different modalities of treatment

Pentoxifylline versus dapsone versus antihistamines and topical clobetasol propionate

Lakshmi et al. (2008) compared oral pentoxifylline 400mg three times per day with oral dapsone 100mg per day, as well as a combination of oral antihistamines and topical clobetasol proprionate in 30 ART-naïve participants (ten participants per group) over eight weeks. The pentoxifylline group was reported to have a faster response and longer remission than the other two groups when assessed six weeks after discontinuation of the interventions. No further details of outcome measures were reported.

Promethazine versus topical hydrocortisone 1% ointment

Navarini et al. (2010) compared the responses of PPE to oral promethazine in 50 participants and topical hydrocortisone 1% ointment in 18 participants receiving ART. Mean participant-reported itch severity (±standard deviation) on a ten-point numerical rating scale (0=least severe, 9=most severe) decreased from 6.6±3.0 to 2.8±3.1 in the promethazine group and from 6.2±2.6 to 5.2±2.7 in the topical hydrocortisone group over one month of treatment. Clinical intensity of PPE, based on the morphology of skin lesions (0-healed, 1-macules, 2-papules, 3-excoriated lesions), was evaluated at the end of one-month period. Mean intensity scores (±standard deviation) were 1.3±1.0 in the promethazine group and 1.87±1.1 in the topical hydrocortisone group.

2.4.4.5 Combination of oral antihistamines and topical corticosteroids

The resolution of PPE lesions after treatment with a combination of oral antihistamines and topical corticosteroids (no further details available) was reported in a single-patient case report (Uchigasaki et al. 1996).

2.4.5 Adverse events

Adverse events associated with interventions for PPE were reported in one study included in this review. Berman et al. (1998) reported drowsiness in one participant and increased duration of menses in one out of twelve participants who received oral pentoxifylline therapy for PPE.

Table 4 Studies included in the systematic review of interventions for papular pruritic eruption of human immunodeficiency virus infection

Reference / Setting	Study Design (#)	Receiving ART or OI prophylaxis (#)	Biopsy	Unsuccessful Interventions (#)	Interventions (#)	Outcomes	Follow up	Results (#)	Adverse effects (#)
Systemic therapy									
Wernham et al. 2014 Birmingham, United Kingdom	Case report (1)	Yes	Yes	Topical betamethasone valerate 0.1% NB-UVB	Thalidomide 100mg/day for 3mo	DLQI Pruritus score (0-10)	4mo post-Tx	Start of Tx, DLQI 26/30, pruritus 7/10 End of Tx, DLQI 2/30, pruritus 1/10 Remission lasted 4mo	NR
Naswa et al. 2011 Gujarat, India	Case report (1)	No	Yes	Intermittent oral and topical corticosteroids Dapsone 50mg/day	ART: Stavudine, Lamivudine, Efavirenz	Reduction of pruritus and lesions	NR	Healing lesions and minimal pruritus on ART initiation	NR
Castelnuovo et al. 2008 Kampala, Uganda	Prospective Observational (53)	Yes Co-trimoxazole (48) Dapsone (5)	No	Oral antihistamines (53) Topical corticosteroids (37)	ART: Lamivudine, Stavudine and Nevirapine (51) Lamivudine, Stavudine and Efavirenz (2)	Presence of PPE Medication use for PPE Severity score = Day + night itch score (Itch score: 3=very much, 2=a lot, 1=a little, 0=not at all)	24mo	At 0, 6, 12, 18 and 24mo: PPE present in 53/53, 27/43, 10/43, 2/39 and 2/29, respectively Medication use in 53/53, 23/43, 9/43, 1/39 and 1/29, respectively Mean severity score = 3.9, 0.9, 0.5, 0.1 and 0.1, respectively	NR
Dagatti et al. 2000 Rosario, Argentina	Observational (8)	NR	Yes	NR	Cetirizine 20mg/d	NR	NR	Responded well (8)	NR

Reference / Setting	Study Design (#)	Receiving ART or OI prophylaxis (#)	Biopsy	Unsuccessful Interventions (#)	Interventions (#)	Outcomes	Follow up	Results (#)	Adverse effects (#)
Berman et al. 1998 Miami, Florida, USA	Uncontrolled trial (12)	Yes	Yes	UVB therapy (3) - stable disease but no improvement	Pentoxifylline 400mg tid for 8w Concurrent UVB, if started just prior to study, without change to treatment protocol (3)	Pruritus: 10cm VAS (0cm: no itch, 10cm: worst itch ever experienced) Physician global assessment of PPE extent	8w	Pruritus score Mean at 0w (12): 6.5cm Mean at 8w (11): 3.6cm Decrease over 8w (10) = 22.6-87.3% Increase over 8w (1) = 13.1% Physician global assessment at 8w vs. 0w: Decreased 0-24% in 7/11, 25-49% in 3/11 Increased 1-24% in 1/11	Drowsiness (1) Increased duration of menses (1)
Harindra et al. 1992 Bournemouth, United Kingdom	Case report (1)	NR	NR	NR	Isotretinoin 0.5mg/kg/day, then continued at 0.25mg/kg/day and long term doxycycline for other infection	Reduction of itch and skin lesions	NR	Lesions healed and itch hardly mentioned by 6w of Tx	NR

Reference / Setting	Study Design (#)	Receiving ART or OI prophylaxis (#)	Biopsy	Unsuccessful Interventions (#)	Interventions (#)	Outcomes	Follow up	Results (#)	Adverse effects (#)
Phototherapy									
Bellavista et al. 2013 Bologna, Italy	Case report (1)	Atazanavir Ritonavir Tenofovir/ Emtricitabine	Yes	Chlorphenamine 4mg bid and Desoximetasone cream – 3mo	NB-UVB Dosing: Initial: 0.4J/cm^2 0.1J/cm^2 3 times/w for 2w 0.9J/cm^2 twice/w for 7w Total: 12.9J/cm^2	Reduction of itch and skin signs	6mo	Reduction of skin signs and resolution of itch in 2w and maintained through follow-up	NR
Aquilina et al. 1998 Toulouse, France	Case report (1)	Yes (1)	NR	ART (1)	UVB 100Tx (1)	Improvement of itch and skin lesions	NR	Improvement (1)	NR
Ishii et al. 1994 Yokohama, Japan	Case report (1)	Zidovudine	Yes	Zidovudine	UVB twice/w for 1mo Initial dose 67% MED 5% increment at each Tx	Resolution or reduction of itch and skin lesions	1mo – LTFU	Resolution of new skin lesions Reduction in itch	NR
Pardo et al. 1992 Miami, Florida, USA	Uncontrolled trial (8)	NR	Yes	NR	UVB 3Tx/w start at 60%MED 10% increment/Tx until erythema or pruritus relief Stopped 1mo after pruritus resolved Continued for 1mo if persistent pruritus	Pruritus score (0: none, 1-2: mild, 4-6: moderate, 7-10: severe) Papules count in 100cm^2 area	NR	Outcomes at 1mo vs. 0mo Pruritus score sig decrease in 7/8 (p<0.0022) Papule count sig decrease in 8/8 (p<0.0014) Pruritus recurred in 4/8 after tx stopped. Mean time to recurrence = 8w (range 4-12w)	NR

Reference / Setting	Study Design (#)	Receiving ART or OI prophylaxis (#)	Biopsy	Unsuccessful Interventions (#)	Interventions (#)	Outcomes	Follow up	Results (#)	Adverse effects (#)
Multiple modalities									
Navarini et al. 2010 Ifakara, Tanzania	Observational (68)	Some pts	No	NR	Oral promethazine 25mg bid (50) vs. topical HC 1% (18)	Pt-reported itch score (0-9) Clinical intensity: 0=healed lesions, 1=macules, 2: papules, 3: excoriated lesions	1mo	Change in itch score over 1mo of tx Promethazine: 6.6±3.0 to 2.8±3.1 Topical HC 6.2±2.6 to 5.2±2.7 Clinical intensity at 1mo Promethazine: 1.3±1.0 Topical HC: 1.87±1.1	NR
Lakshmi et al. 2008 Andhra Pradesh, India	Parallel group trial (30)	No	Yes	NR	Dapsone 100mg/d (10) vs. Pentoxifylline 400mg bid (10) vs. oral antihistamine & topical clobetasol propionate (10) Duration: 8w	Speed of response Duration of remission	6w	Pentoxifylline group responded faster and remission lasted longer than the other groups (but poorer compliance)	NR
Uchigasaki et al. 1996 Tokyo, Japan	Case report (1)	Zidovudine Didanosine	Yes	NR	Oral antihistamines and topical corticosteroids	Resolution of skin lesions	NR	Resolution of skin lesions	NR

#, number of study participants; ART, antiretroviral therapy; bid, twice daily; d, day; DLQI, Dermatology Life Quality Index; HC, hydrocortisone; HIV, human immunodeficiency virus; LTFU, lost to follow-up; MED, minimal erythema dose; mo, month; NR, not reported; PPE, papular pruritic eruption of human immunodeficiency virus infection; pt, participant; sig, significant; tid, three times a day; tx, treatment; UVB, ultraviolet B; VAS, visual analogue scale; vs, versus; w, week

2.5 Discussion

The body of evidence for interventions for PPE is of very low quality, mainly derived from case reports, observational studies and uncontrolled non-randomised trials, which are prone to selection and performance bias.

The widespread use of ART is has reduced the prevalence of skin diseases associated with HIV and their associated morbidity (Calista et al. 2002; Maurer et al. 2004; Zancanaro et al. 2006). The impact of the roll-out of ART on PPE has been described anecdotally (Resneck et al. 2004b) but not quantified and documented systematically in the form of population-based studies or randomised controlled trials. Castelnuovo et al's (2008) prospective observational study of ART described the resolution of PPE in 33 of 43 participants, and 27 of 29 participants after twelve and 24 months of ART, respectively. Despite the limitations of this study, including its high losses to follow-up (10/53 and 24/53 participants at twelve and 24 months of follow-up) and lack of ascertainment of clinical diagnoses of PPE by biopsy, it has provided evidence of ART as an effective intervention for PPE.

Oral pentoxifylline was reported to reduce the symptoms and signs of PPE in an uncontrolled trial (Berman et al. 1998). In a non-randomised trial, participants treated with pentoxifylline experienced more rapid resolution

and longer remission of PPE compared to participants treated with oral dapsone or a combination of oral antihistamines and topical corticosteroids (Lakshmi et al. 2008b). This has been attributed to pentoxifylline's effect on reduction of tumour necrosis factor alpha expression (Berman et al. 1998). However, pentoxifylline is unlikely to be the treatment of choice in sub-Saharan Africa as it is not included in the WHO's list of essential medicines (World Health Organization 2013c) and unlikely to be easily available in resource-limited settings located in tropical regions such as sub-Saharan Africa where the burden of HIV and PPE is greatest.

UVB phototherapy was reported to be helpful in one uncontrolled non-randomised trial of eight participants (Pardo et al. 1992) and three case studies of a total of five participants (Ishii et al. 1994; Aquilina 1998; Bellavista et al. 2013). Pardo et al. (1992) reported PPE recurrence in four of eight (50%) participants at average of eight weeks after discontinuation of phototherapy. Economic analysis of UVB phototherapy for psoriasis carried out in the Netherlands have quoted average costs of 800 and 752 euros per patient per course of phototherapy for treatment at home and in a hospital outpatient setting, respectively (Koek et al. 2010). Phototherapy requires the procurement and maintenance of expensive equipment, reliable supply of electricity and well-trained staff, hence it is unlikely to be a practicable treatment option in resource-limited settings.

Both first- and second-generation antihistamines, specifically promethazine and cetirizine, have been reported to be helpful in the management of PPE (Dagatti et al. 2000; Navarini et al. 2010). However, oral antihistamines have often been reported to be ineffective for PPE (Colebunders et al. 1987; Liautaud et al. 1989; Castelnuovo et al. 2008b). Oral antihistamines in combination with topical corticosteroids have been used in the management of PPE with mixed outcomes (Uchigasaki et al. 1996; Bellavista et al. 2013).

In summary, there is evidence that ART is an effective intervention for PPE. Oral antihistamines and topical corticosteroids may be of limited benefit but are easily available in resource-limited settings. This is in keeping with WHO guidelines for the management of PPE which recommends the initiation of ART and symptomatic therapy with oral antihistamines and topical corticosteroids if needed (World Health Organization 2014c). Pentoxifylline and UVB phototherapy are unlikely to be practicable treatment options in resource-limited settings in tropical regions where the burden of HIV and PPE is greatest.

It is evident from this review that there is a lack of high quality published evidence of interventions for PPE. Well-designed studies that document the effect of ART on PPE, as well as randomised controlled trials of other

modalities of treatment would help in bridging the existing research and knowledge gaps. HIV-infected persons receiving virologically suppressive ART regimens but continue to have persistent or recurrent PPE should be targeted as a subject of study as they are likely to be most severely affected by PPE in the era of widespread ART use. As the burden of PPE is greatest in resource-limited settings such as sub-Saharan Africa, the cost and practicability of interventions need to be taken into account in the design of research studies that may eventually translate into viable treatment options for PPE.

3. Adaptation of a Runyankore version of Skindex-16 for oral administration in Mbarara, Uganda

3.1 Background

Skin disease can have a significant impact on quality of life, in chronic and complex ways (Chren et al. 1996). The burden of skin disease is more often from its morbidity than mortality (Chren & Weinstock 2004). Physical and psychosocial well-being are subjectively affected by skin disease (Chren et al. 1996). They may be influenced by one's experiences, beliefs, expectations and perceptions. Therefore, people with the same health status may have very different qualities of life as it reflects the unique perception and reaction of individuals to their health status and other non-medical aspects of life (Gill & Feinstein 1994; Testa & Simonson 1996).

Health-related quality of life measurements are an integral part of patient-reported outcomes which are important in the delivery of patient-centred care and appraisal of interventions for aspects of health care including prevention, diagnosis and treatment, with implications for healthcare business and policy decisions (Gabriel & Normand 2012). Most of these instruments have been developed in English for use in English-speaking communities and in resource-replete settings. As perceptions of quality of life and expressions of health concerns may vary greatly between different

cultural groups and healthcare systems, there is a need to translate and adapt these instruments for use in different circumstances (Guillemin et al. 1993).

Most health-related quality of life instruments are administered in a written format and require functional literacy skills. In communities with low literacy levels, patient-centred outcomes have been successfully assessed using computer-based audio questionnaires in which questions were read aloud as they appear on screen. Response categories to each question such as “yes/no” and “never/sometimes/often/always” were also read aloud and selected using “buttons” on a touchscreen (Hahn et al. 2004; Edwards et al. 2007).

For the purposes of conducting clinical dermatology research studies in Mbarara, Western Uganda (chapter 5 and 6), it was necessary to find or develop a dermatology-specific quality of life instrument that was suitable for use in this setting. The predominant spoken language in this region is Runyankore and literacy rates are not high. Oral transmission of knowledge and culture is the norm in this region. Written versions of the language and development of its orthography were first developed by Christian missionaries in the early 20th century (Bernstein 1998). The estimated total adult literacy rate in Uganda from 2008 to 2012 was 73.2%, but the figure is likely to be lower in women and rural populations

(UNICEF 2013). According to the Uganda 2010 National Household Survey, literacy rates in men were 77% and 65% in women in Western Uganda and levels of educational attainment in the region were as follows: 21.9% no formal education, 54.1% primary school education, 20.4% secondary school education and 3.7% above secondary school education (Uganda Bureau of Statistics 2010).

Skindex is a self-administered dermatology-specific survey instrument that measures the effect of skin disease on quality of life (Chren et al. 1996). It has been extensively revised and shortened from 61 to 29 items and then to 16 items. Skindex-29 has been extensively studied, translated and validated in many different countries, cultural settings and languages (Both et al. 2007) and has been considered the “most valuable dermatology-specific quality of life questionnaire” for psoriasis research (De Korte et al. 2004). Skindex-29 measures the frequency with which various aspects of skin disease are experienced (Chren et al. 1997). It was further developed and refined to form Skindex-16, which enquires about how much one is bothered by the skin disease. This modification was intended to improve Skindex-16’s ability to evaluate the perception of handicap (defined as disadvantage resulting from an impairment or disability) due to skin disease, Its brevity may also help with practicability of use (Chren et al. 2001).

3.2 Objectives

This study aimed to translate, culturally adapt and test an orally administered Runyankore-version of Skindex-16 for use in Mbarara, Uganda. First, the aim was to translate Skindex-16 from English to Runyankore with semantic, idiomatic, experiential and conceptual equivalence (Guillemin et al. 1993). The second aim was to administer the Runyankore-version of Skindex-16 orally and test its practicability, reliability and validity.

3.3 Methods

3.3.1 Institutional approval and informed consent

This study was approved by the Institutional Ethical Review Committee of Mbarara University of Science and Technology as part of pre-study plans for the case control and cohort study presented in chapters 5 and 6, respectively. Bilingual research assistants obtained informed consent from all study participants. Guidelines for the cross-cultural adaptation of health-related quality of life measures (Guillemin et al. 1993) and methods used to translate and culturally adapt Skindex-29 from English to Spanish (Jones-Caballero et al. 2000) informed the methods chosen and detailed below.

3.3.2 Translation

Skindex-16 was translated from English to Runyankore and then back translated by two translators (Lilian Namukasa and Pidson Mwebaze) who worked independently. The back-translated version was compared with the original version of Skindex-16. Equivalence of translation was graded as satisfactory, almost satisfactory or doubtful. Items for which equivalence were judged as doubtful or almost satisfactory were reviewed and revised by Dr. Mary Margaret Chren, both translators and I, with the aim of arriving at satisfactory equivalence where possible.

3.3.3 Pre-test interviews

To ensure that Skindex-16 comprehensively addresses the ways in which skin conditions affect the quality of life of typical patients from Mbarara, clinical staff in the Dermatology Outpatients Clinic of Mbarara National Referral Hospital (four dermatologists and one nurse) and two research assistants working on this study were asked an open question, “In what way(s) do the skin conditions of patients bother them?” There was consensus that patients were most bothered by itch and the effect of their skin condition(s) on their appearance, especially if the skin condition(s) was associated with dyspigmentation and difficult to conceal due to stigma associated with skin disease. Many local people link skin disease with syphilis or HIV. In addition to the effect of skin disease on appearance, Jones-Caballero et al. (2007) elicited participants’ concerns about

chronicity of skin disease when assessing content validity of the Spanish-version of Skindex-16. Based on this information, additional questions regarding the duration, ease of concealment and presence of dyspigmentation of their skin condition were composed. The information obtained was used to generate hypotheses to test the construct validity of the adapted Runyankore-version of Skindex-16.

3.3.4 Data collection

Trained bilingual (Runyankore and English) research assistants administered Skindex-16 orally to 47 consecutive patients attending Mbarara National Referral Hospital's Dermatology Outpatients Clinic and 47 randomly selected non-patient visitors to the hospital (non-patient participants). Research assistants were asked to adhere strictly to the translated version of Skindex-16. Study participants were prohibited from completing Skindex-16 independently in writing.

Basic demographic information was also collected from study participants. Non-patient participants were asked to report if they had any skin conditions at the time of the study. Medical records of patient participants were reviewed to abstract data on diagnoses of their skin conditions.

3.3.5 Scoring

The scoring of Skindex-16 has been described by Chren et al. (2001) and adhered to in this study. There are seven response categories for each item anchored by “never bothered” and “always bothered” at each end. Responses were transformed to a linear scale of zero to 100 where zero corresponds to “never bothered” and 100 corresponds to “always bothered” (Chren et al. 2001).

Questions that addressed a similar aspect of skin disease that has an effect on quality of life were grouped together. They were known as subscales. Questions one to four addressed the effect of symptoms associated with skin disease on quality of life (symptoms subscale). Questions five to eleven enquired about the emotional aspects of skin disease (emotions subscale). Questions twelve to sixteen explored functional impairment associated with skin disease (functioning subscale). The average scores of questions in each group was known as the scale score (Chren et al. 1996).

3.3.6 Measurement of properties of Skindex-16

3.3.6.1 Reliability

The assumption of internal consistency reliability is that all items of a questionnaire should be measuring the same theoretical construct, otherwise known as a concept or hypothesis. In Skindex-16, items within

each subscale should address the same construct. If there is internal consistency reliability, the responses to each item in each subscale should be highly correlated with each other. This was determined using Cronbach's alpha coefficient (Cronbach 1951; Bland & Altman 1997). Cronbach alpha values of 0.7 to 0.8 are considered satisfactory as research tools to compare groups (Bland & Altman 1997).

3.3.6.2 Construct Validity

The validity of an instrument refers to the extent to which it measures what it intends to measure. Construct validity refers to the extent to which a theoretical concept or framework is being adequately measured (De Korte et al. 2004). The following hypotheses, generated from information obtained during pre-test interviews, were tested to determine construct validity:

1. Participants with skin conditions would have poorer quality of life and higher Skindex-16 scores than those without skin conditions
2. Participants who reported difficulty in concealing their skin conditions would have higher Skindex-16 scores than those who did not report difficulty with concealment
3. Participants who reported skin colour change as a result of their skin conditions would have higher Skindex-16 scores than those who did not report skin colour change

3.3.6.3 Content validity

Content validity refers to the extent to which a theoretical construct is addressed by items in the instrument (De Korte et al. 2004). Ideally, a dermatology-specific quality of life instrument should measure the entire spectrum of how people might be affected by skin problems. This was explored by asking every participant an open question “In what way(s) does your skin condition bother you?” The participants’ responses were compared with items in Skindex-16 to check if they had been addressed. Additionally, study participants were asked how much they were bothered by the duration of their skin condition, presence of skin colour change and ease of concealment of affected areas of skin.

3.3.6.4 Statistical analysis

SAS® 9.0 (Statistical Analysis Systems, SAS Institute Inc., Cary, NC) was used for all statistical analyses. Multivariate linear regression was used to test hypotheses with adjustments made for age, sex and ethnicity (tribe).

3.4 Results

3.4.1 Translation

Four items in Skindex-16 presented challenges in translation from English to Runyankore (Table 5). This was due to the lack of semantically equivalent words in Runyankore for the following English words: “irritated”

(question 4), “frustration” (question 8), “embarrassment” (question 9) and “affection” (question 14). There was no equivalent word in Runyankore for “frustration”, “irritated” and “affection”, hence an explanation of the concepts was attempted in Runyankore. Both “embarrassed” and “ashamed” translated into the same word in Runyankore, which explained the disparity between the original and back-translated versions (Table 5). After discussion between translators and research staff, satisfactory agreement was reached for two of the words and almost satisfactory agreement in the other two words. The final Runyankore-version of Skindex-16 is presented in Table 6.

Table 5 Agreement between original and back-translated version of Skindex-16

Items in original Skindex-16	Back-translated version	Agreement
4. Your skin being irritated	Your skin failing to get peace	Satisfactory
8. Frustration about your skin condition	Hating yourself and everything around you because of your skin condition	Almost satisfactory
9. Embarrassment about your skin condition	Feeling ashamed of your skin condition	Almost satisfactory
14. Your skin condition making it hard to show affection	You skin condition making it hard to show your love for others	Satisfactory

Table 6 Final Runyankore-version of Skindex-16

1. Omubiri gwawe kukurya
2. Omubiri gwawe kukwotsya nings kukutonera
3. Omubiri kukushasha
4. Omubiri kuburwa obusingye
5. Okugumizamu ninga kugarukwamu oburwire bwomubiri
6. Okwerarikirira ahabwe embera yomubiri. Ekyokureberaho: Okujanjara, okweyongera kubakubi, enkojo, obutatebereza embera nebinidi
7. Endebuka yomubiri gwawe
8. Okweyanga ahabwomubiri gwawe
9. Okushwara ahabwomubiri gwawe
10. Okunyiga ahabwomubiri gwawe
11. Okugira enaku ahabwomubiri gwawe
12. Omubiri gwawe kuteganisa okukwatanisa nabandi, Ekyokureberaho: Okukwatanisa nabeka yawe, banywani bawe, nabandi abanyabuzare abakuhikire, nabandi
13. Ekyomubiri gwawe giresire obutenda kuba nabantu
14. Omubiri gwewe kukuremesa kworeka okukunda
15. Ahabwomubiri gwawe gukozire aha mirimo yaburijo
16. Omubiri gwawe kukugumiza okukora ninga kukoraekyorikukunda

3.4.2 Practicability

Oral administration of the Runyankore-version of Skindex-16 took less than ten minutes per participant. This included a brief explanation to participants of how to respond to each item in the questionnaire as well as eliciting their responses. None of the study participants withdrew from the study or failed to respond to items in the questionnaire due to lack of understanding.

3.4.3 Participant characteristics

Seventy-two of 94 (77%) study participants were female. Their median age was 30 years. There were 47 patient participants and 47 non-patient participants. A significantly greater proportion of non-patient participants were female compared with patients (94% versus 60%, respectively; $p<0.01$). The median age of non-patients was 30 years compared to 25 years in patients ($p=0.03$). Thirty-two of 47 (68%) non-patient participants reported current skin conditions and none had sought medical attention for them. Clinical dermatological diagnoses of patient participants obtained from review of medical records are listed in Table 7. More than one dermatological diagnosis was recorded in 17 of 47 (36%) patients.

Table 7 Dermatological diagnoses of patient participants

Diagnoses	Frequency
Dermatitis (including atopic, seborrhoeic, irritant contact and allergic contact dermatitis)	18
Fungal infection (of skin, scalp, hair and/or nails)	11
Folliculitis (of any cause)	5
Other inflammatory skin conditions	
Acne	3
Urticaria	2
Anogenital lichen sclerosus	1
Cutaneous adverse drug reactions	1
Cutaneous lupus erythematosus	1
Cutaneous sarcoidosis	1
Viral exanthems	1
Prurigo nodularis	1
Panniculitis	1
Pityriasis rosea	1
Pityriasis versicolor	1
Psoriasis	1
Isolated lesions	
Hypertrophic scars or keloids	4
Kaposi's sarcoma	2
Pyogenic granuloma	1
Other skin infections or infestations	
Impetigo	2
Condyloma acuminata	1
Scabies infestation	1
Other skin conditions	
Acrodermatitis verruciformis	1
Cushing's syndrome due to oral corticosteroids	1
Hyperhidrosis	1
Psychogenic or senile pruritus	1

3.4.4 Measurements properties

3.4.4.1 Reliability

High Cronbach alpha values were obtained for all three subscales (α - 0.86, 0.88 and 0.85 for symptoms, emotions and functioning, respectively).

3.4.4.2 Construct validity

The first hypothesis was that participants with skin conditions would have higher Skindex-16 scores than those without skin conditions. Patient participants had the highest mean Skindex-16 scores in all three subscales, followed by non-patient participants who had reported current skin conditions and then non-patients participants without skin problems (Table 8). Their differences in Skindex-16 scores were statistically significantly different in all three subscales ($p<0.01$).

Table 8 Mean Skindex-16 scores in patients and non-patient participants with and without self-reported skin conditions

Mean Skindex-16 scale scores (± standard deviation)	Patients (n=47)	Non-patients with self-reported skin conditions (n=32)	Non-patients without self-reported skin conditions (n=15)	Adjusted p values
Symptoms	68 ± 26	60 ± 27	10 ± 14	p<0.01
Emotions	55 ± 27	39 ± 27	7 ± 17	p<0.01
Functioning	36 ± 30	31 ± 28	3 ± 7	p<0.01

The next hypothesis was that participants who reported skin colour change as a result of their skin conditions would have higher Skindex-16 scores than those who did not report skin colour change. The proportion of participants with skin problems reporting the presence and absence of dyspigmentation was almost equal (48% versus 52%, respectively). Higher mean Skindex-16 scores in all three subscales were recorded in participants with dyspigmentation compared to those without dyspigmentation (symptoms subscale p=0.03, emotions subscale p<0.01 and functioning subscale p<0.01; Table 9).

Table 9 Mean Skindex-16 scores in participants who did and did not report dyspigmentation due to their skin condition

Mean Skindex-16 scale scores (± standard deviation)	Dyspigmentation (n=45)	No dyspigmentation (n=49)	Adjusted p values
Symptoms	73 ± 27	41 ± 29	p=0.03
Emotions	57 ± 27	28 ± 27	p<0.01
Functioning	39 ±29	20 ± 27	p<0.01

The third hypothesis was that participants who reported difficulty in concealing their skin conditions would have higher Skindex-16 scores than those who did not report difficulty with concealment. One-third of study participants reported concealment difficulty of their skin condition. Higher mean Skindex-16-scores were recorded for these participants in all three sub-scales (Table 10) but this was statistically significant only in the symptoms subscale (p-0.02).

Table 10 Mean Skindex-16 scores in participants with and without concealment difficulty of their skin condition

Mean Skindex-16 scale scores (± standard deviation)	Concealment difficulty (n=31)	No concealment difficulty (n=62)	Adjusted p values
Symptoms	73 ± 27	41 ± 29	p=0.02
Emotions	57 ± 27	28 ± 27	p=0.28
Functioning	39 ± 29	20 ± 27	p=0.43

The duration of skin conditions ranged from 0.01 to 23 years. Median duration of skin conditions in participants with skin problems was one year (interquartile range [IQR] 2.83-5.65 years). There were no significant associations between the duration of skin conditions and Skindex-16 scores in symptoms, emotions and functioning subscales (p=0.33, 0.49 and 0.43, respectively). Adjustments were made for age, sex and ethnicity (or tribe) in all the above analyses.

3.4.4.3 Content validity

Sixty-eight of 94 (72%) participants responded to the open question “In what way(s) does your skin condition bother you?” There were a total of 58 skin-related responses; of these, 42 (72%) were addressed in Skindex-16. Responses that were mentioned by more than one participant and not addressed by Skindex-16 included sores or wounds, malodour and swelling. Each of the following responses not addressed by Skindex-16

was mentioned by a single participant: bleeding, weeping, scarring, dry skin, change in skin texture and discomfort that is exacerbated by cold weather or footwear. Responses classified as non-skin-related were headache, backache, stomachache, body pain, fever, leg pain, loss of appetite, body weakness, chest pain, difficulty sleeping, difficulty walking, joint pain and swelling.

3.5 Discussion

A Runyankore-version of Skindex-16 was developed, adapted and tested in a predominantly Runyankore-speaking population of Mbarara, Uganda. This instrument was found to be feasible, reliable and have construct and content validity.

Measuring dermatology-specific quality of life in Uganda with conventional written instruments often developed in English in resource-replete settings pose many challenges. This is due to the disparity in socio-economic context, literacy rates and the predominance of oral rather than written communication in Uganda. This study aimed to address the gap in available tools for the measurement of dermatology-specific quality of life. The orally administered Runyankore-version of Skindex-16 was found to be practicable for use in Mbarara, Uganda. These findings provide a basis

for further studies of the effects of skin disease on the quality of life in Ugandan patients.

Pre-test interviews of clinicians and research staff were helpful in understanding social issues surrounding skin disease such as stigma. Patients often associated skin disease with syphilis or HIV, which adds to the stigma experienced. We learned that dyspigmentation and concealment difficulty appeared to have a profound impact on quality of life as skin disease is stigmatising in itself. We hypothesised that dyspigmentation and concealment difficulty of skin condition would be associated with higher Skindex-16 score (greater impact on quality of life) and used these hypotheses to test the construct validity of the adapted Runyankore-version of Skindex-16.

Fidelity of translation is essential for the meaningful use of instruments in different language and cultural groups. Direct translation of four items in Skindex-16 from English to Runyankore was difficult. Difficulties with the translation of similar items in Skindex-16 into Turkish and Arabic have been reported. The word “irritated” (question 4 of Skindex-16) was translated to Arabic and then back translated as “agitation”, classified as an almost satisfactory translation. “Frustration” (question 8) could not be directly translated into Turkish; the word depressed was used with an explanation within parentheses. There were difficulties with translating

“embarrassment about your skin condition” (question 9), as distinguishing between “embarrassment” and “shame” in Turkish was difficult, just as in Runyankore. “Show affection” (question 14) was translated into Arabic and back-translated as “difficulty in expressing your emotions”, and considered a doubtful translation (Aksu et al. 2007; AlGhamdi & AlShammari 2007).

Oral administration of the Runyankore-version of Skindex-16 was feasible, taking less than ten minutes per participant. By adhering to the adapted Runyankore-version of Skindex-16, research assistants ensured that the questionnaire was administered in a consistent manner. Only one interviewer was present with each participant so that consecutive patients attending the dermatology clinic would be enrolled and interviewed in a time-efficient manner. It would have been ideal to have the interviewer observed by a second interviewer to minimize interviewer bias.

The measurement properties of the adapted questionnaire were found to be satisfactory. All three subscales had Cronbach alpha values of 0.85 to 0.88, demonstrating good internal consistency reliability. Cronbach alpha values of 0.7 to 0.8 are considered satisfactory in scales used as research tools to compare between groups (Bland & Altman 1997). Construct validity was demonstrated by higher Skindex-16 scores (greater impact on quality of life) in participants with skin problems and dyspigmentation. This was tested based on *a priori* hypotheses. A majority of participant

responses to the question “In what way(s) does your skin condition(s) bother you?” were addressed in Skindex-16, demonstrating content validity.

The three most frequent responses to the open question above were sores, malodour and swelling, which are likely to be associated with infection. This may account for a larger proportion of skin conditions in Uganda compared to the United States of America where Skindex-16 was developed and validated. To provide an even more comprehensive understanding of overall quality of life effects of skin disease in Uganda, items reflecting the responses above could be appended onto Skindex-16.

Interestingly, 68% of non-patient participants had reported skin conditions for which they had not sought medical attention. The severity and type of skin conditions present in non-patient participants at the time of the study was not known, as they were not subject to clinical examination of their skin. The prevalence of their reported skin conditions was higher than the prevalence of skin disease detected on clinical examination, which was 37.4%, in a study of 800 villagers in southwest Tanzania (Satimia F et al. 1998). However, it is worth noting that skin disease was reported to be the fourth leading cause of non-fatal disease burden globally in 2010 (Hay et al. 2014). Their Skindex-16 scores were lower than those of patient participants but higher than non-patient participants without self-reported

skin conditions. Seeking healthcare may in itself be an indicator of the impact of skin disease on quality of life.

Limitations of the study included a relatively small sample size that was drawn from patients and visitors of a teaching hospital, and so may not be typical of the average Ugandan person. There was a far greater proportion of women compared to men, especially in non-patient participants. This is probably because most non-patient participants were visiting and caring for family and friends who were receiving care at the hospital, and it is likely that women were more likely to be caregivers compared to men. As a consequence, the impact of skin conditions on quality of life in women was probably over-represented in this study. The outcomes of this study might have been different if more men were enrolled as study participants as men may respond differently to quality of life issues related to their skin conditions.

In conclusion, the culturally adapted and orally administered Runyankore-version of Skindex-16 was found to be reliable and have construct and content validity. It is feasible for use in dermatology research in Mbarara, Uganda. Orally administered quality of life instruments have the potential to be very useful for conducting research in groups of people with low literacy levels across the world whose healthcare needs may be chronically underserved.

4. Factors associated with papular pruritic eruption of human immunodeficiency virus infection in the antiretroviral therapy era - a case control study

4.1 Background

PPE has been suggested as a marker for advanced HIV disease due to its association with low CD4 cell counts (Boonchai et al. 1999b; Resneck et al. 2004a; Wiwanitkit 2004b) and WHO clinical stages III and IV (Castelnuovo et al. 2008b). The place of PPE in the clinical evaluation of HIV disease is substantiated by its inclusion in stage II of WHO's clinical staging of HIV (World Health Organization 2013a).

PPE has been reported to resolve within a few months of starting ART. Its recurrence has also been described within weeks of discontinuation of ART (Colebunders et al. 2006). Castelnuovo et al. (2008) described the resolution of PPE in 27 of 53 Ugandan adults within 24 months of ART initiation; two study participants had persistent PPE which became severe PPE and the other participants were lost to follow-up (Castelnuovo et al. 2008b). The response of PPE to ART has been suggested as a clinical marker for the virological outcome of ART. Indeed, its recurrence, worsening or onset after at least 6 months of ART has been proposed as part of a clinical algorithm for assessing virological failure in settings

where access to viral load testing is limited (Colebunders et al. 2006; Labhardt et al. 2012).

4.2 Objectives

The primary objective of this study was to explore factors associated with the presence of PPE in HIV-infected adults receiving ART. They included

1. Higher viral load compared with ART-treated HIV-infected adults without PPE
    i. Greater probability of virological failure, defined as plasma viral load >1000 copies/ml detected on two consecutive measurements carried out within a three-month interval, after at least 6 months of ART (World Health Organization 2013a)
2. Lower CD4 counts compared with ART-treated HIV-infected adults without PPE
    i. Greater likelihood of immunological failure, defined as defined as the fall of CD4 count to baseline levels (or below) or persistent CD4 levels below 100 cells/mm^3 (World Health Organization 2013a)
3. Greater CD8+ T-cell activation compared with ART-treated HIV-infected adults without PPE, which was measured with proportion

of CD38+ HL-DR+ CD8+ T-cells (Deeks et al. 2004; Hunt et al. 2003)

4. Greater exposure to arthropod bites or stings due to environmental factors including housing characteristics, bed net use, time and type of work
5. Different dermatology-related characteristics including history of skin disease especially conditions that may manifest as chronic itchy papules such as papular eczema and lichenoid dermatoses

4.3 Methods

4.3.1 Institutional approval and informed consent

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 were obtained for this study. Informed consent was obtained from all study participants.

4.3.2 Study design and setting

This was a case control study nested within the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort, a prospective observational study of 515 HIV-infected Ugandan adults. The cohort was consecutively sampled from patients receiving normal standard of care at the HIV

outpatients' clinic of Mbarara National Referral Hospital at the time of ART initiation. All UARTO study participants received first-line ART regimens, which consist of two NRTIs (lamivudine/zidovudine, lamivudine/stavudine or emcitricitabine/tenofovir) and one NNRTI (either nevirapine or efavirenz), in accordance with the Ugandan Ministry of Health's 2008 national antiretroviral treatment and care guidelines (Ministry of Health, Republic of Uganda 2008). Study participants resided within 20km of Mbarara, a rural setting located approximately 270km from Kampala, the capital of Uganda (Google Maps 2014).

4.3.3 Study Participants

UARTO study participants who had received ART for at least 15 months were screened for inclusion to this study. This timing was chosen to capture participants who may be experiencing treatment failure and require switching from first to second line ART. A cohort study of 17 ART programmes in lower income countries reported the median time for switching to second line ART was 16.3 months after first line ART initiation in programmes with viral load monitoring and 21.8 months in programmes without viral load monitoring. Switching was due to treatment failure in 74%, drug toxicity in 10% and other reasons in 15% (Keiser et al. 2009). The median time for switching to second line ART was 20 months in a study of 62 Médecins Sans Frontières-supported HIV programmes (Pujades-Rodríguez et al. 2008).

Clinical case definitions of PPE used by Hevia et al. (1991) and Boonchai et al. (1999) informed the inclusion criteria for cases in this study. They were 1) HIV seropositivity, (2) chronic pruritic discrete papules on the trunk, extremities and face of at least one month's duration and (3) absence of another definable cause of the pruritus. The presence of the skin eruption in all cases was confirmed by clinical examination by a dermatologist (Dr. Erin Amerson or me).

Each case was individually matched with two controls for age, sex and duration of ART. Controls were UARTO study participants who did not have an active skin rash at the time of enrolment to the study.

4.3.4 Study Procedures

Information regarding the demographic, occupational, housing and socioeconomic characteristics of study participants was obtained from data collected during participant interviews conducted at three-month intervals as part of the UARTO study. Additional information obtained at the time of study enrolment included self-reported daily exposure to insect bites, bed net usage, history of skin disease, time of onset of skin rash (before or after ART initiation), site of skin rash at onset and study enrolment. Study participants were asked about their use of prophylactic sulphamethoxazole-trimethoprim (or co-trimoxazole) as this might have an

impact on the prevalence of skin infections such as bacterial folliculitis, which may present similarly to PPE. Study participants were also asked about the severity of their itch on a 10-cm VAS, presence of dyspigmentation due to their skin rash and impact of their skin eruption on their quality of life via the Runyankore-version of Skindex-16. Study instruments were checked for missing information immediately after the interview, and research assistants obtained missing information from study participants in person or over the telephone.

Detailed information about household assets obtained during participant interviews had previously been used to determine household wealth, using the Filmer-Pritchett Asset Index (Filmer & Pritchett 2001) for all UARTO participants. The asset index placed individual UARTO participants on a continuous scale of relative wealth, which was then divided into five quintiles (1=poorest and 5=wealthiest quintile). Socioeconomic status of UARTO participants was measured using the Filmer-Pritchett asset index because these participants were based in rural Uganda where subsistence farming is the main economic activity and educational attainment is generally low (Uganda Bureau of Statistics 2010). As a consequence, measurement of socioeconomic status by income, occupation or educational attainment might be challenging and might not reflect socioeconomic status accurately. Additionally, asset-based wealth indices have been widely used in health research and has been

acknowledged to be “measuring an important determinant of health” (Howe et al. 2009).

Blood was routinely drawn from all UARTO study participants at three-month intervals for measurements including CD4 cell counts, plasma HIV RNA and proportion of CD38+ HLA-DR+ CD8+ T-cells. CD4 counts and plasma HIV RNA levels were shared with participants’ health care providers to avoid duplication of investigations.

All cases had their skin eruption (Figure 5) photographed by research assistants using a point-and-shoot digital camera, prior to a 4mm punch biopsy of an unexcoriated primary lesion[1] (Figure 6) to confirm the diagnosis of PPE. Biopsies were reviewed by Dr. Phillip LeBoit and Dr. Timothy McCalmont, dermatopathologists at the University of California, San Francisco from whom all details of study participants were withheld, apart from the body site from which the biopsy was taken.

[1] A primary lesion refers to a physical change in the skin directly cause by the disease process (Department of Dermatology, University of California, San Francisco 2015).

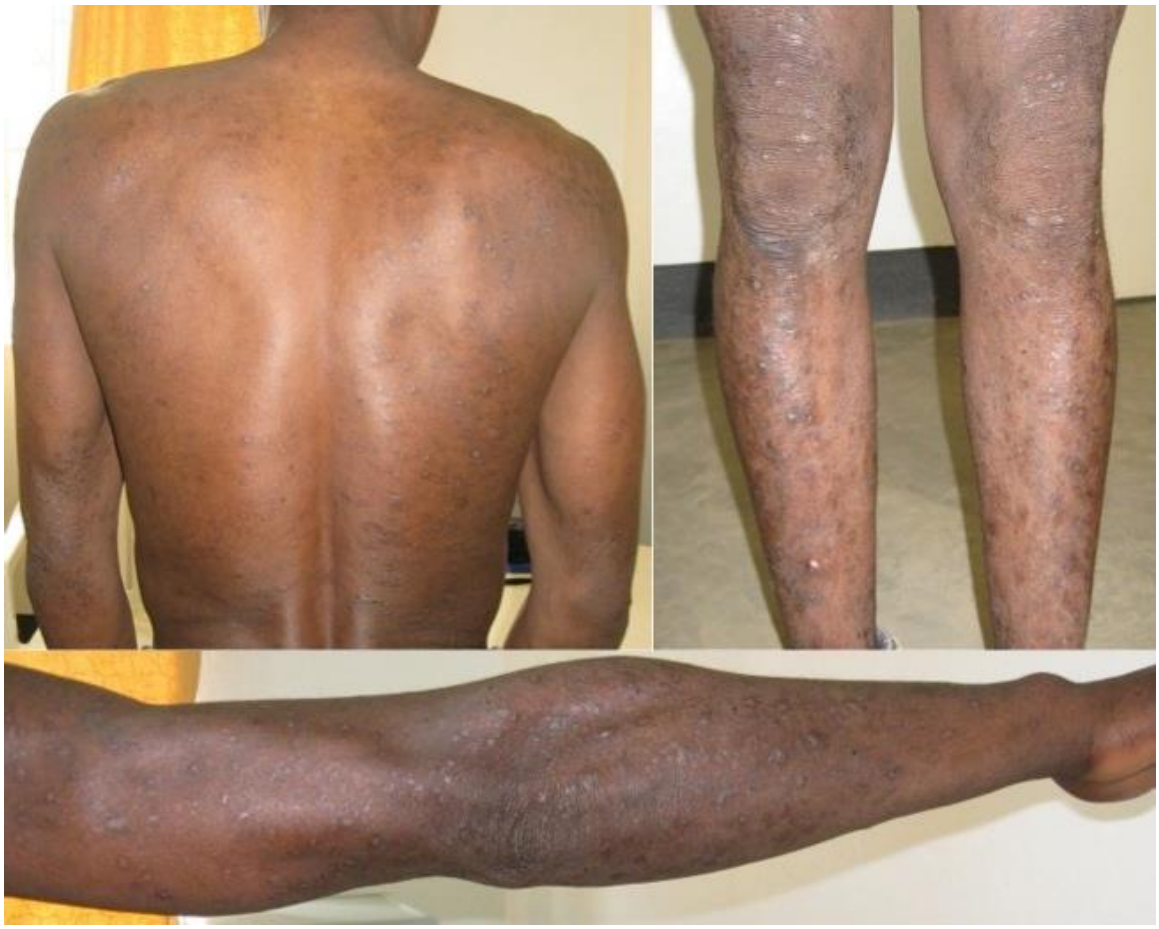


Figure 5 Papular pruritic eruption of human immunodeficiency virus infection

Clinical photographs of a study participant with papular pruritic eruption of human immunodeficiency virus infection affecting the trunk and limbs. Informed consent for clinical photography has been obtained from all study participants.

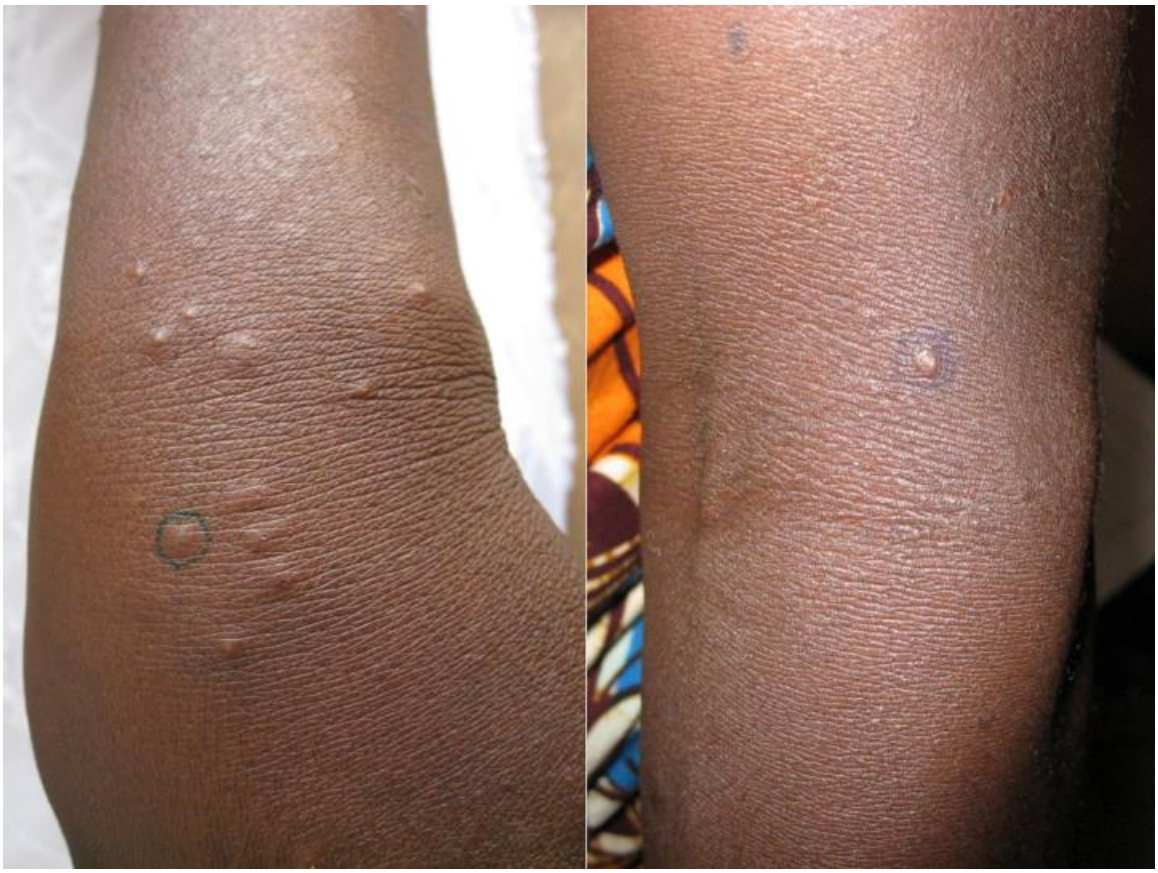


Figure 6 Examples of lesions of papular pruritic eruption of human immunodeficiency virus infection that were biopsied

Clinical photographs of two study participants with papular pruritic eruption of human immunodeficiency virus infection. Lesions that were biopsied have been marked with a skin marker pen. Informed consent for clinical photography has been obtained from all study participants.

4.3.5 Statistical analyses

Statistical analyses were carried out with Stata Statistical Software Release 11 (StataCorp LP, College Station, TX USA). STROBE (Strengthening the Reporting of Observational Studies) guidelines informed the reporting of this study (Elm et al. 2007).

Although this was an exploratory study of factors associated with the presence of PPE in HIV-infected Ugandan adults who have received ART for at least 15 months, sample size calculations were carried out to inform the number of study participants anticipated for enrolment. Sample size calculations were based on the hypothesis that the presence of PPE in ART-treated HIV-infected adults was associated with virological failure of antiretroviral treatment. We hypothesised that the probability of virological failure would exceed the probability of absence of virological failure in an ART-treated HIV-infected adult with PPE. Therefore, the probability of virological failure was hypothesised to exceed 50% in an ART-treated HIV-infected adult with PPE.

A systematic review of virological follow-up in ART programmes reported that the overall proportion of adult HIV-infected patients in sub-Saharan Africa who experienced virological failure, defined by the rebound of HIV RNA >1000 copies/ml, was 15% (Barth et al. 2010). This is consistent with reported proportions of virological failure in Ugandan HIV-infected adults

of 6-17% after receiving ART for one to three years (Jaffar et al. 2009; Reynolds et al. 2009; Ahoua et al. 2009; Mermin et al. 2011).

In order to detect virological failure in 50% of the group with PPE versus 15% in the group without PPE with 80% power (1-β) and two-sided 5% type I error rate (α), 33 participants would be needed in each group if they had equal numbers of participants. If the ratio of participants in the group without PPE compared to the group with PPE were 2:1, numbers of participants required would be 48 in the group without PPE and 24 in the group with PPE.

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 known as PPE cases. The other cases were known as non-PPE cases. Their individually matched controls were identified as PPE controls and non-PPE controls, respectively. PPE cases were compared with non-PPE cases to explore characteristics of participants with PPE or other chronic pruritic papular eruptions.

Conditional logistic regression was used to explore predictors associated with cases and PPE cases, compared with their matched controls. Logistic regression was used to compare PPE cases with non-PPE cases. Single predictor analyses were used to identify potential predictors for inclusion in

a multi-predictor model. Predictors that met the pre-set criterion of $p<0.2$ were selected for inclusion in a multi-predictor conditional logistic regression models for cases and PPE cases. The contribution of each predictor to the multi-predictor model was assessed using likelihood ratio tests.

4.4 Results

4.4.1 Screening and enrolment of study participants

The total number of UARTO study participants who had had ART for at least 15 months and eligible for inclusion in this study was 413 of the available 515 UARTO cohort study participants (Figure 7).

Forty-seven of 413 (11%) eligible UARTO study participants fulfilled the clinical case definition of PPE. Two participants declined participation; therefore 45 cases were enrolled. Twenty-five of 45 (56%) enrolled cases had histological findings compatible with reactions to arthropod bite or stings, or urticarial hypersensitivity reaction, consistent with a diagnosis of PPE (Figure 8). The other 20 cases (non-PPE cases) had the following histological diagnoses: spongiotic dermatitis (n=11), dermatophyte folliculitis (n=2), intraepidermal pustular dermatitis (n=2), pruriginized dermatitis (n=1), excoriation (n=1), secondary syphilis (n=1), seborrhoeic keratosis (n=1) and perniosis (n=1).

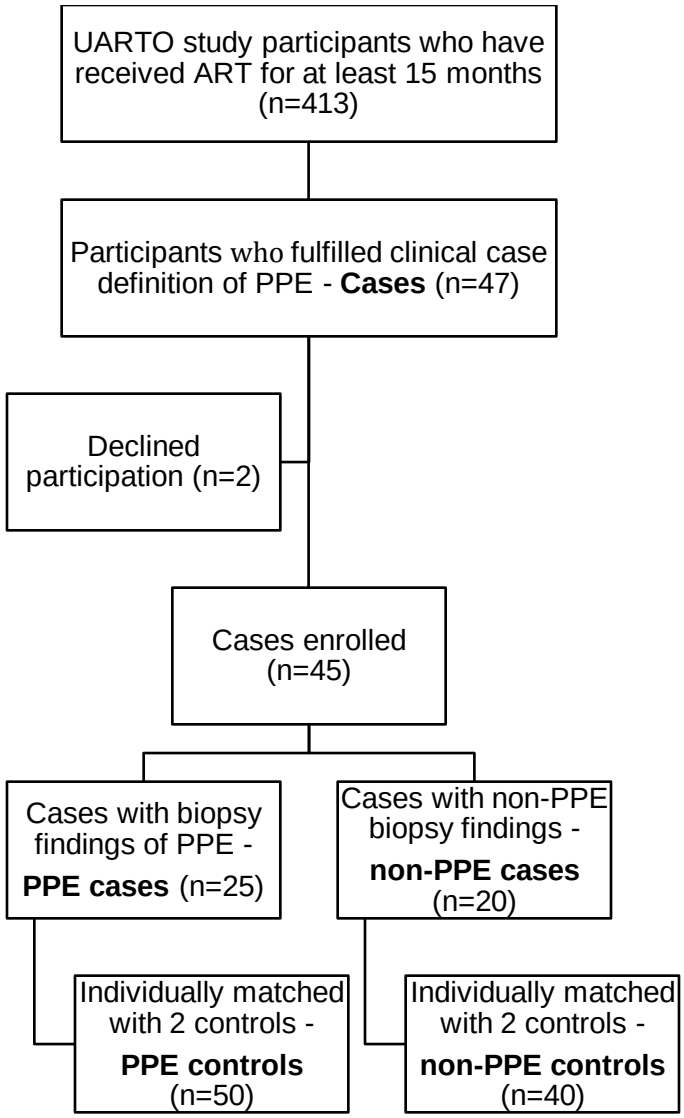


Figure 7 Flow diagram of study participants

PPE, papular pruritic eruption of human immunodeficiency virus infection.

UARTO, Uganda AIDS Rural Treatment Outcomes

Each case was individually matched with two controls for age, sex and duration of ART. Controls were UARTO study participants who did not have an active skin rash at the time of enrolment to the study.

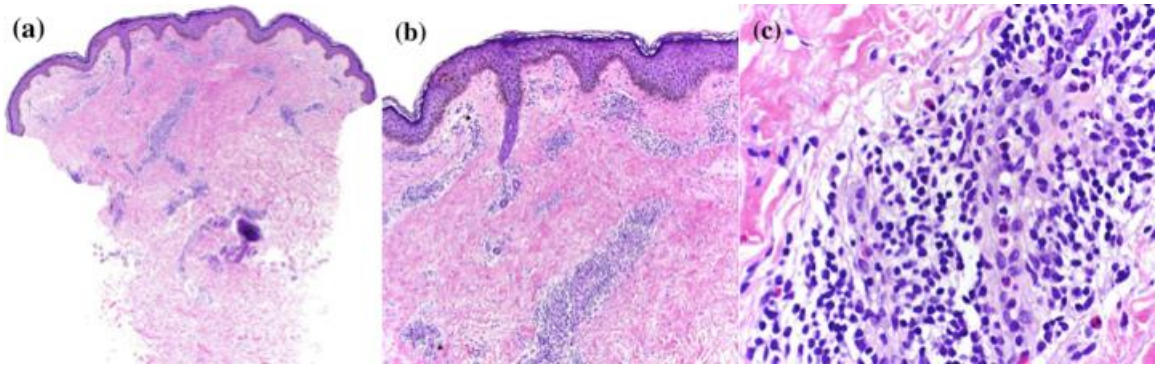


Figure 8 Photomicrograph of skin biopsy consistent with papular pruritic eruption of human immunodeficiency virus infection

(a) This shows a wedge-shaped superficial and deep infiltrate of lymphocytes and eosinophils that is characteristic of a reaction to arthropod bites or stings, or papular pruritic eruption of human immunodeficiency virus infection (haematoxylin-eosin, original magnification 4X) (b) (haematoxylin-eosin, original magnification 10X) (c). Dermal infiltrate of lymphocytes and eosinophils (haematoxylin-eosin, original magnification 40X)

4.4.2 Dermatological characteristics of cases - Comparisons between PPE cases and non-PPE cases

A greater proportion of PPE cases (Table 11) reported that their skin eruption or rash, which was present at study enrolment, began prior to ART initiation compared with non-PPE cases (11/25 [44%] vs. 3/20 [15%]; p=0.05). The site of rash at onset was significantly different between PPE and non-PPE cases (p=0.002). None of the PPE cases reported that their rash was located in the head and neck region at onset compared with 6/20 (30%) of non-PPE cases. Nine of 25 (36%) PPE cases had a generalised rash at onset, in contrast with none of the non-PPE cases. At the time of study enrolment, body sites affected by the skin eruption were similar between PPE and non-PPE cases (p=0.31). Their median reported itch severity at study enrolment was similar at 10cm on a 10-cm VAS (p=0.51), as well as the proportion that reported dyspigmentation secondary to the rash (21/25 [84%] in PPE cases vs. 14/20 [70%] in non-PPE cases, p=0.30). Median Skindex-16 scores were not statistically significantly different between PPE cases and non-PPE cases (Symptoms subscale: 63 [IQR 50-96] vs. 90 [IQR 50-100], p=0.34; Emotions subscale: 57 [IQR 33-71] vs. 30 [IQR 15-71], p=0.27; Functioning subscale: 0 [IQR 0-23] vs. 0 [0-20], p=0.33).

Table 11 Characteristics of skin eruption in cases, PPE cases and non-PPE cases

	Cases (n=45)	**PPE cases (n=25)**	**Non-PPE cases (n=20)**	***p***
Onset before ART initiation (%)	14 (31)	11 (44)	3 (15)	0.05
Onset after ART initiation (%)	31 (69)	14 (56)	17 (85)	0.05
Duration of ART, years (IQR)	1.4 (1.2-1.7)	1.4 (1.2-1.8)	1.4 (1.2-1.8)	0.55
Median itch severity on 10-cm visual analogue scale (IQR)	10 (8-10)	10 (8-10)	10 (7-10)	0.51
Dyspigmentation (%)	35 (78)	21 (84)	14 (70)	0.30
Skindex-16 scores (IQR)				
Symptoms	75 (50-100)	63 (50-96)	90 (50-100)	0.34
Emotions	48 (29-71)	57 (33-71)	30 (15-71)	0.27
Functioning	0 (0-23)	0 (0-23)	0 (0-20)	0.33
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)	
Generalised	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)	
Generalised	11 (24)	8 (32)	3 (15)	

ART, antiretroviral therapy. IQR, inter-quartile range. *p*, p-value. PPE, papular pruritic eruption of human immunodeficiency virus infection

4.4.3 Comparisons between cases versus controls and PPE cases versus PPE controls

Participant characteristics have been outlined in Table 12 and described below. For ease of comparison, characteristics of cases versus controls, PPE cases versus PPE controls, as well as PPE cases versus non-PPE cases have been presented in adjacent columns in Table 12.

Female participants accounted for 67% of all cases and controls, and 72% of PPE cases and PPE controls. Median age was similar in cases and controls (35.9 vs. 36.3 years; p=0.53), as well as 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).

4.4.3.1 Virological failure and HIV viral load

The median plasma HIV RNA was significantly greater at ART initiation in PPE cases than PPE controls (390,398 vs. 109,615 copies/ml, p=0.002), and also greater in PPE cases compared to non-PPE cases (390,398 vs. 71,006 copies/ml, p=0.01). Plasma HIV RNA was <400 copies/ml in a similar proportion of PPE cases and PPE controls (96% vs. 92%; p=0.95), and in cases and controls (91% vs. 89%; p=0.90) at the time of skin examination and biopsy (study enrolment).

Antiretroviral treatment (or virological) failure has been defined by the WHO as plasma HIV RNA >1000 copies/ml in two consecutive measurements within a three-month interval after at least six months of ART with adherence support (World Health Organization 2013a). One PPE cases and three PPE controls had plasma HIV RNA >1000 copies/ml at the time of study enrolment. However, sustained rebound in HIV viraemia was not demonstrated in any cases or PPE cases after the suppression of plasma HIV RNA to <400 copies/ml. Within six months of ART, 23/25 (92%) of PPE cases and 48/50 (96%) of PPE controls had HIV RNA <400copies/ml.

4.4.3.2 Immunological failure and CD4 counts

The median CD4 count at study enrolment was similar 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 comparable 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).

4.4.3.3 CD8+ T-cell activation

CD8+ T-cell activation, measured with proportion of CD38+HLA-DR+CD8+T-cells, at ART commencement, six and twelve months after

starting ART was similar between cases and controls, and between PPE cases and PPE controls.

4.4.3.4 Environmental characteristics

Living conditions were very similar between cases and controls, PPE cases and PPE controls, and PPE cases and non-PPE cases. At least 95% of all study participants lived in houses with roof made of metal. Between 40-52% of participants in each group lived in houses with walls made of mud and another 40-50% had walls made of unfinished brick, and between 40-55% in each group lived in houses with mud floors and 38-44% lived in houses with cement floors. Approximately half of participants in each group shared toilets with other households. Bed net use was reported by 88-100% of participants in each group. In contrast, insect repellant use was reported by only 2-5% in each group. Working conditions were comparable between cases and controls, PPE cases and PPE controls, and PPE cases and non-PPE cases; 60-75% in each group worked outdoors, 87-95% in each group worked in the day and 38-46% in each group reported livestock ownership.

4.4.3.5 Dermatological history

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% [6/25] vs. 48%

[24/50]; p=0.05). A history of specific skin diseases such as eczema, psoriasis, scabies and adverse cutaneous drug reactions were sought. Eczema had not been reported in the dermatological history of cases but was reported in 9% (8/90) of controls (p=0.05). The use of suphamethoxazole-trimethoprim (or co-trimoxazole) prophylaxis was ubiquitous among all participants with 95-100% coverage across different groups. This is in line with Ugandan and WHO co-trimoxazole prophylaxis guidelines. According to Uganda's Ministry of Health's guidelines on HIV care published in 2008, co-trimoxazole prophylaxis should be used in HIV-infected persons who are symptomatic (irrespective of CD4 count) or started ART when their CD4 count was <250 cells/mm^3 (Ministry of Health, Republic of Uganda 2008). In settings where malaria and/or severe bacterial infections are highly prevalent, the WHO recommend that co-trimoxazole prophylaxis should be initiated and continued regardless of CD4 count or WHO stage (World Health Organization 2014b).

Table 12 Characteristics of study participants

	Cases (n=45)	**Controls (n=90)**	***p***	**PPE Cases (n=25)**	**PPE Controls (n=50)**	***p***	**PPE cases (n=25)**	**Non-PPE cases (n=20)**	***p***
Female (%)	30 (67)	60 (67)	1.00	18 (72)	36 (72)	1.00	18 (72)	12 (60)	0.53
Ethnicity Banyankore (%)	34 (76)	66 (73)	0.83	18 (72)	36 (72)	1.00	18 (72)	16 (80)	0.47
Median age, years (IQR)	36 (34-40)	36 (32-41)	0.53	36 (34-41)	36 (31-39)	0.61	36 (34-41)	37 (34-40)	0.57
Median duration of ART, years (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 (1.2-1.8)	1.4 (1.2-1.7)	0.56
Socio-economic status: Filmer Pritchett Asset Index quintile **(%)**			0.15			0.14			0.61
1	13 (29)	13 (14)		7 (28)	7 (14)		7 (28)	6 (30)	
2	4 (9)	19 (21)		3 (12)	10 (20)		3 (12)	1 (5)	
3	7 (16)	20 (22)		2 (8)	15 (30)		2 (8)	5 (25)	
4	11 (24)	23 (26)		7 (28)	11 (22)		7 (28)	4 (20)	
5	9 (20)	14 (16)		5 (20)	7 (14)		5 (20)	4 (20)	
Missing data	0 (0)	0 (0)		1 (4)	0 (0)		1 (4)	0 (0)	
HIV-associated characteristics									
Median CD4 count, cells/mm^3 (IQR)									
At ART initiation	110 (73-175)	121 (76-186)	0.53	93 (66-167)	124 (82-187)	0.19	93 (66-167)	128 (100-183)	0.20
At study enrollment	257 (179-379)	265 (178-373)	0.84	244 (159-379)	267 (215-373)	0.47	244 (159-379)	270 (214-371)	0.60
HIV RNA load at ART initiation, copies/ml (IQR)	185,060 (69557 - 586768)	138,610 (43,823 - 398,332)	0.20	390,798 (113,888 - 750,000)	109,615 (30,691 - 352,625)	0.002	390,798 (113,888 - 750,000)	71006 (27955 - 361831)	0.01
HIV RNA load at ART initiation, log_{10} copies/ml (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	5.6 (5.1-5.9)	4.9 (4.4-5.6)	0.01

	Cases (n=45)	Controls (n=90)	*p*	PPE Cases (n=25)	PPE Controls (n=50)	*p*	PPE cases (n=25)	Non-PPE cases (n=20)	*p*
HIV RNA <400 copies/ml (%)									
6 months after starting ART	40 (89)	86 (96)	0.16	23 (92)	48 (96)	0.60	23 (92)	17 (85)	0.18
At study enrollment	41 (91)	80 (89)	0.77	24 (96)	46 (92)	0.66	24 (96)	17 (85)	0.31
Median %CD38+ HLA-DR+ CD8+T-cells (IQR)									
At ART initiation	67 (62-74)	71 (60-80)	0.41	67 (60-79)	71 (61-77)	0.65	67 (60-79)	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	54 (47-60)	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	41 (32-50)	42 (28-46)	0.72
Environmental Characteristics									
Daily insect bites (%)	18 (40)	6 (7)	<0.001	10 (40)	4 (8)	0.002	10 (40)	8 (40)	1.00
Outdoor work (%)	30 (67)	56 (62)	0.71	15 (60)	32 (64)	0.80	15 (60)	15 (75)	0.35
Work in daytime (%)	39 (87)	81 (90)	0.57	20 (80)	45 (90)	0.32	20 (80)	19 (95)	0.21
Livestock ownership (%)	19 (42)	41 (46)	0.85	10 (40)	19 (38)	1.00	10 (40)	9 (45)	0.77
Insect repellant use (%)	2 (4)	3 (3)	1.00	1 (4)	1 (2)	1.00	1 (4)	1 (5)	1.00
Bed net use (%)	42 (93)	84 (93)	1.00	22 (88)	46 (92)	0.68	22 (88)	20 (100)	0.24
Roof material (%) - metal	43 (96)	89 (99)	0.26	24 (96)	50 (100)	0.33	24 (96)	19 (95)	1.00
Wall material (%)			0.77			0.29			0.90
Mud	20 (44)	43 (48)		10 (40)	26 (52)		10 (40)	10 (50)	
Unfinished brick	21 (46)	39 (43)		12 (48)	20 (40)		12 (50)	9 (45)	
Floor material (%)			0.67			0.96			0.75
Mud	22 (49)	36 (40)		11 (44)	24 (48)		11 (44)	11 (55)	
Cement	19 (42)	39 (43)		11 (44)	19 (38)		11 (44)	8 (40)	
Shared toilet with other households (%)	21 (47)	46 (51)	0.85	12 (48)	23 (46)	0.81	12 (50)	9 (45)	0.77

	Cases (n=45)	Controls (n=90)	*p*	PPE Cases (n=25)	PPE Controls (n=50)	*p*	PPE cases (n=25)	Non-PPE cases (n=20)	*p*
Dermatological history									
History of any skin disease (%)	15 (33)	44 (49)	0.10	6 (24)	24 (48)	0.05	6 (24)	9 (45)	0.21
History of specific skin disease (%)									
Eczema	0 (0)	8 (9)	0.05	0 (0)	5 (10)	0.16	0 (0)	0 (0)	-
Psoriasis	4 (9)	10 (11)	0.77	1 (4)	6 (12)	0.41	1 (4)	3 (15)	0.31
Scabies	7 (6)	22 (24)	0.27	3 (12)	11 (22)	0.36	3 (12)	4 (20)	0.68
Drug reaction	1 (2)	5 (6)	0.66	0 (0)	3 (6)	0.55	0 (0)	1 (5)	0.44
SMX-TMP prophylaxis (%)	44 (98)	90 (100)	0.33	25 (100)	50 (100)	--	25 (100)	19 (95)	0.44

ART, antiretroviral therapy. IQR, interquartile range. p, p-value. PPE, pruritic papular eruption of human immunodeficiency virus infection. SMX-TMP, sulphamethoxazole-trimethoprim.

4.4.3.6 Conditional logistic regression models for cases and PPE cases

Single predictor analyses were performed for all predictors outlined in Table 12. Additional predictors screened included CD4 gains and proportion of CD38+ HLA-DR+ CD8+ T-cells measured at three-month intervals for 24 and 12 months, respectively. Single predictor analyses of factors that fulfilled the criterion of $p<0.2$ for inclusion in multi-predictor model fitting, as well as HIV viral load and CD4 counts measured at ART initiation and study enrolment have been presented in Table 13.

Key findings in single-predictor analyses were as follows:

1. The odds of reporting daily insect bites or stings were 8.3 times greater in cases than controls and 8.6 times greater in PPE cases then PPE controls (OR 8.29, 95%CI 2.79-24.64, $p<0.001$ and OR 8.58, 95%CI 1.85-39.71, $p=0.01$, respectively).
2. With every log increase in viral load at ART initiation, the odds of being a PPE case increased four-fold (OR 4.04, 95%CI 1.29-12.68, $p=0.02$). This association was not found in cases (OR 1.19, 95%CI 0.73-1.92, $p=0.49$).

Multi-predictor model fitting for cases or PPE cases demonstrated that only two predictors (reported daily insect bites or stings and history of any skin disease) had a statistically significant effect in the conditional logistic

regression model for cases. The same two predictors had a statistically significant effect in the conditional logistic regression model for PPE cases. When both of these predictors were included in the conditional logistic regression model for cases, the odds of reported daily insect bites or stings were 10.7 times greater in cases than controls (OR 10.70, 95%CI 3.25-35.19, p<0.001), but the odds of a history of any skin disease were 2.9 times greater in controls compared with cases (OR 2.90, 95%CI 1.10-7.63, p=0.03). In the conditional logistic regression model for PPE cases, the odds of reported daily insect bites or stings were 11.7 times greater in cases compared with controls (OR 11.71, 95%CI 2.02-68.00, p=0.01), but the odds of a history of any skin disease were 5.6 times greater in PPE controls than PPE cases (OR 5.58, 95%CI 1.08-28.81, p=0.04).

Table 13 Single predictor analyses using conditional logistic regression for cases and PPE cases

Predictors	Case (vs. Controls) OR	95% CI	*p*	PPE Case (vs. PPE controls) OR	95%CI	*p*	PPE Case (vs. non-PPE Cases) OR	95%CI	*p*
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 50cells/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 50cells/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
%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
Daily bites or stings	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. IQR, interquartile range. OR, odds ratio. *p*, p-value. 95% CI, 95% confidence interval.

4.5 Discussion

The presence of PPE in HIV-infected persons who have received ART for at least 15 months has not been found to be associated with virological failure of ART in this study. Plasma HIV RNA levels and CD4 count at the time of skin examination and biopsy (study enrolment) were similar between PPE cases and PPE controls. The proportion of participants in both groups that had plasma HIV RNA <400 copies/ml at study enrolment were comparable. The small number of study participants with virological failure at study enrolment did not allow for further evaluation of the association between PPE and virological failure.

The odds of having PPE in HIV-infected participants after at least 15 months of ART were increased four-fold with every log increase in HIV viral load at ART initiation. This suggests that greater HIV viraemia pre-ART may have effects that persist well after ART initiation and virological suppression. The mechanism of this effect on PPE is not known. HIV viral loads of greater than 100,000 copies/ml at ART commencement have been linked with a higher risk of HIV disease progression (Egger et al. 2002).

Pre-ART plasma HIV RNA levels have been positively correlated with T-cell activation, especially CD8+ T-cell activation, which has in turn been shown to predict HIV disease progression more strongly than viral load or CD4 count (Hunt et al. 2003; Deeks et al. 2004). Higher T-cell activation levels have also been associated with lower CD4 gains during ART (Giorgi et al. 1993; Liu et al. 1998; Giorgi et al. 1999). CD8+ T-cell activation as well as CD4 gains at ART initiation, and six and twelve months after that have not been found to be associated with the presence of PPE in ART-treated study participants in this study. It is possible that the immune activation marker measured in this study (%CD38+ HLA-DR+ CD8+ T-cells) was not associated with PPE in ART-treated study participants.

Study participants who reported daily insect bites or stings had increased odds of having a chronic itchy papular rash of any cause and similarly increased odds if that rash was biopsy-proven PPE. The similarity in magnitude of association between daily insect bites and PPE as well as any chronic itchy eruption does not fully support the theory of PPE being a reaction to insect bites that has been suggested by Colebunders et al. (1987), Rosatelli and Roselino (2001) and Resneck et al. (2004). It was postulated that some HIV-infected persons might have lost the desensitization to insect bites acquired with repeated exposure over time (Peng & Simons 1998), allowing an exaggerated reaction to insect bites to eventuate in a pruritic skin eruption (Resneck et al. 2004a). It is possible

that study participants found it difficult to distinguish between any itchy papular eruption and insect bites or stings.

Information regarding environmental exposures that may predispose study participants to insect bites or stings was elicited so as to explore the postulated link between insect bites and PPE further (Colebunders et al. 1987; Rosatelli & Roselino 2001; Resneck et al. 2004a). A similarly large proportion of PPE cases and PPE controls worked outdoors during the day, used bed nets and did not use insect repellants. Housing characteristics, sanitation facilities and levels of animal ownership were also similar between PPE cases and PPE controls. Colebunders et al. (1987) presented similar findings in Kinshasa, Democratic Republic of Congo where a comparable proportion of patients with and without a generalised papular pruritic eruption had at least one animal in the house and kept similar types of animals (mainly chickens and dogs). It is possible that environmental factors explored in this study were not associated with exposure to insect bites or stings.

Confirmation of the clinical diagnosis of PPE with histological examination of skin biopsies in all study participants has been one of the strengths of this study. Study participants that fulfilled the clinical case definition of PPE and had received ART for at least 15 months were enrolled as cases, regardless of the study dermatologists' degree of suspicion for PPE as a

diagnosis, so as to avoid inconsistencies in enrolment to the study. This may explain the lower than expected proportion of cases with histological findings consistent with PPE.

There were few differences in the clinical presentation of the skin eruption in PPE cases and non-PPE cases with regard to onset, persistence, itch severity, dyspigmentation and effect on quality of life. The only difference found was that PPE was not located at the head and neck at onset, but was either generalised or localised to the extremities. Although this may be a clinical clue, histological confirmation of the diagnosis of PPE is still important. Additionally, biopsies would help to avoid misdiagnosing treatable conditions such as secondary syphilis and dermatophytic folliculitis found in non-PPE cases of this study. However, this may not be practicable in resource-limited settings with limited or no access to histopathology services. In research studies of PPE, ascertainment of clinical diagnoses of PPE by biopsy is important for study validity.

This case control study was nested within a well-established cohort (UARTO) with excellent adherence to ART (Ware et al. 2009). As part of the UARTO study, detailed structured interviews and measurements of laboratory parameters such as CD4 counts and HIV RNA were carried out at three-month intervals allowing the accumulation of valuable data from

study participants. This enabled the study of predictors at time points other than at enrolment to the case control study.

Limitations of this study include a small sample size, possibly contributing to a 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 study participants and virological failure.

Additionally, study participants were examined at one point in time and only one lesion was biopsied. As PPE is an intensely pruritic skin condition, the number of excoriated primary lesions that may be selected for biopsy in each case was limited therefore standardisation of the site biopsied (for example, extensor aspects of the extremities) was not possible. As a consequence, the lesion biopsied may not be representative of the participant's skin eruption and may lead to inappropriate classification of the study participant as a PPE case or non-PPE case, resulting in selection bias. There may be differences in the histological findings of PPE lesions from different body sites that have not been accounted for in this study, although there have not been published reports of how these differences might lead to the misdiagnosis of PPE. In addition, information obtained from study participants based on self-

reports and interviews such as time of onset and site of their skin eruptions may be subject to recall bias.

In conclusion, the presence of PPE in ART-treated HIV-infected study participants was associated with higher HIV viral loads at ART initiation. No other immunological markers measured in this study, including CD4 cell counts, CD4 cell gains and CD8+ T-cell activation markers, were found to be associated with PPE in ART-treated participants. Confirmation of clinical diagnoses of PPE by biopsy should be encouraged, as clinical diagnosis alone cannot be regarded as optimal. Large gaps remain in our understanding of PPE: its aetiology and immunological factors that shape its natural history. Larger studies correlating the natural history of PPE with immunological markers and prognostic indicators for HIV disease would be helpful.

5. Cohort study describing the natural history of papular pruritic eruption of human immunodeficiency virus infection over two years of antiretroviral therapy

5.1 Background

Little has been published on the natural history of PPE with the initiation of ART. The resolution of PPE after a few months of ART and its recurrence within weeks of ART discontinuation has been described (Colebunders et al. 2006). A prospective study of 53 participants from Kampala, Uganda with a clinical diagnosis of PPE noted resolution of PPE without recurrence in 27 of 29 participants that were followed up at 24 months (Castelnuovo et al. 2008b). This study aims to add to the body of knowledge on PPE by enrolling participants with a clinicopathological diagnosis of PPE and close follow-up over a two-year period to document the response of PPE to ART initiation.

5.2 Objectives

The objective of this study was to describe the natural history of PPE in HIV-infected Ugandan adults over two years from the time of ART initiation. Another aim of this study was to explore the presence of an

association between recurrent or persistent PPE and virological failure of ART.

5.3 Methods

5.3.1 Institutional approval and informed consent

This study has received 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. Informed consent was obtained from all study participants.

5.3.2 Study design and setting

This was a cohort study of Ugandan HIV-infected adults enrolled at the time of ART initiation and followed up at three-month intervals for two years. All study participants were also part of the UARTO cohort, a 515-person cohort consecutively sampled at the time of ART initiation from HIV-infected adult patients receiving care at the HIV clinic of Mbarara National Referral Hospital (UARTO 2014). All UARTO study participants received first-line ART regimens, which consist of two NRTIs (lamivudine/zidovudine, lamivudine/stavudine or emcitricitabine/tenofovir) and one NNRTI (either nevirapine or efavirenz), in accordance with the

Ugandan Ministry of Health's 2008 national antiretroviral treatment and care guidelines (Ministry of Health, Republic of Uganda 2008). Study participants resided within 20km of Mbarara, a rural setting located approximately 270km from Kampala, the capital of Uganda (Google Maps 2014).

These study participants were distinct from those enrolled in the case control study (chapter 4); they were enrolled at initiation of ART as opposed to at least 15 months after initiation of ART in the case control study.

Inclusion criteria for this study were UARTO participants who fulfilled the clinical case definition of PPE used by Hevia et al. (1991) and Boonchai et al. (1999), which were 1) HIV seropositivity, (2) chronic pruritic discrete papules on the trunk, extremities and face of at least one month's duration and (3) absence of another definable cause of the pruritus. The presence of their papular rash was established on clinical examination by a dermatologist (Dr. Erin Amerson or me), and their diagnosis of PPE confirmed on histological examination.

5.3.3 Study procedures

Standardised interviews and the Runyankore-version of Skindex-16 were administered by research assistants to all study participants at three-

month intervals. The validation of the interviewer-administered Runyankore-version of Skindex-16 is presented in chapter 3. Information elicited from standardised interviews included demographic, occupational and housing characteristics. The Filmer-Pritchett Asset Index, a proxy for household wealth, was derived from information obtained in standardised interviews (Filmer & Pritchett 2001). Information regarding the characteristics of the study participants' skin eruption including duration, site, and severity of itch, sleep impairment and dyspigmentation was also obtained during standardised interviews.

Blood was drawn from all study participants at three-month intervals, as part of UARTO protocol, for measurements that included CD4 cell counts, plasma HIV RNA and proportion of CD8+ T-cells expressing CD38+ HLA-DR+. Clinical photography of all affected areas was performed at study enrolment and at three-month intervals. A 4mm punch biopsy was taken from an unexcoriated primary lesion[2] of recent onset. Biopsies were reviewed by dermatopathologists at the University of California, San Francisco. Details of study participants were withheld from the dermatopathologists apart from the body site from which the biopsy had been taken.

[2] A primary lesion refers to a physical change in the skin directly cause by the disease process (Department of Dermatology, University of California, San Francisco 2015).

5.3.4 Statistical analyses

As this is an exploratory descriptive study of the natural history of PPE with ART initiation, it would be difficult to quantify the sample size required in order to describe the behaviour of PPE over a 24-month period and draw meaningful conclusions from it. At the inception of this study, the number of UARTO participants who were about to initiate ART and were available for screening and enrolment to this study was between 140 to 150. As the prevalence of PPE was reported to be 11-46% (Colebunders et al. 1987; Liautaud B 1989; Sivayathorn et al. 1995; Rosatelli et al. 1997; Goh et al. 2007; Nnoruka et al. 2007; Akinboro et al. 2014; Resneck et al. 2004a), it was anticipated that between 17 to 69 study participants may be eligible for enrolment.

Statistical analyses were carried out with Stata Statistical Software Release 11 (StataCorp LP, College Station, TX, USA). Descriptive statistics were used to outline characteristics of study participants. Time to resolution of PPE was defined as the time from ART initiation to the first follow-up visit at which study participants reported the absence of an active skin rash, regardless of whether the rash recurred or remained absent. A Kaplan-Meier survival curve was used to demonstrate this graphically. STROBE (Strengthening the Reporting of Observational Studies) guidelines were observed in the reporting of this study (Elm et al. 2007).

5.4 Results

The total number of UARTO participants screened for inclusion to the study was 146 (Figure 9). Thirty-three of these 146 participants (23%) fulfilled the clinical case definition for PPE. Eight participants did not have a skin biopsy performed. Seventeen participants had skin biopsy findings consistent with PPE. Eight participants had histological diagnoses of spongiotic dermatitis (n=4), interface dermatitis (n=1), psoriasis (n=1), folliculitis (n=1) and arteriolitis (n=1).

Among the 17 participants with biopsy-proven PPE enrolled to this study, 15 were female and two were male. Their median age was 29.8 years. Information collected from all study participants at ART initiation on their HIV-related, dermatological, occupational and housing characteristics are presented in Table 14.

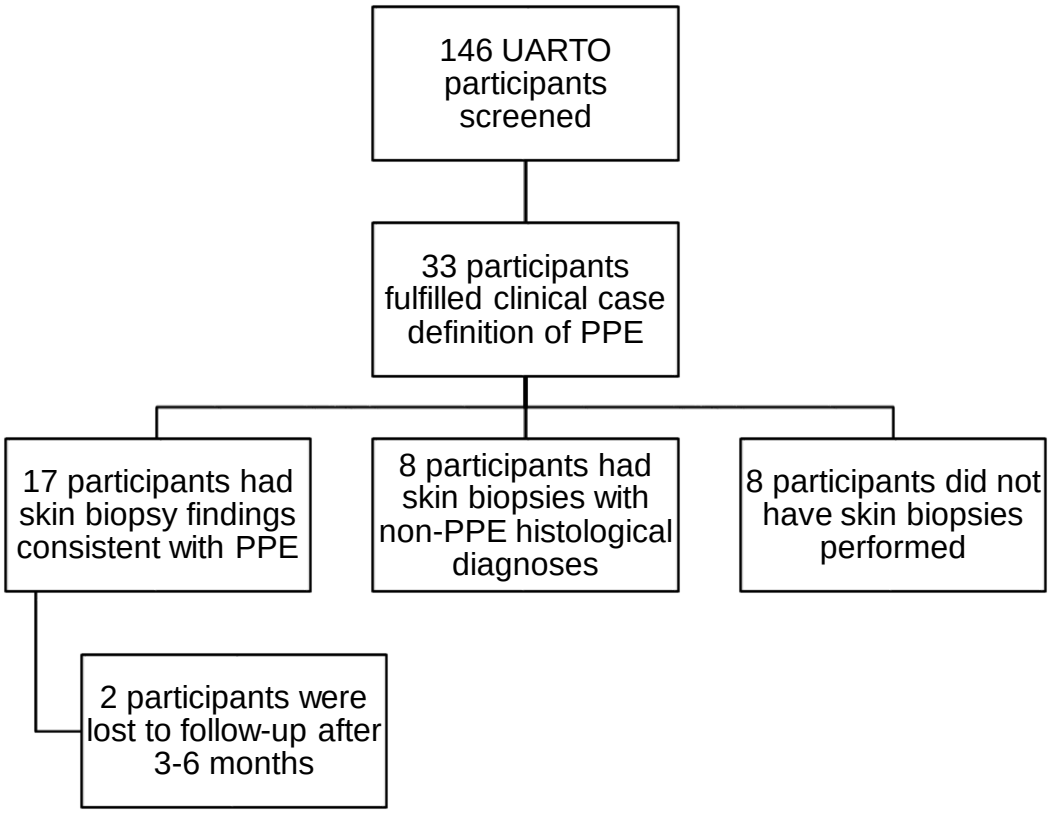


Figure 9 Flow diagram of study participants

PPE, papular pruritic eruption of human immunodeficiency virus infection.

UARTO, Uganda AIDS Rural Treatment Outcomes.

Table 14 Characteristics of study participants

Characteristics of study participants at initiation of ART	All participants (n=17)
Female (%)	15 (89)
Ethnicity Banyankore (%)	12 (71)
Median age, years (IQR)	29.8 (26.2, 34.0)
Socio-economic status: Filmer Pritchett Asset Index quintile **(%)**	
1	7 (42)
2	4 (24)
3	4 (24)
4	2 (12)
5	0 (0)
HIV-related characteristics	
HIV RNA load, copies/ml (IQR)	114, 442 (58,390-191,434)
HIV RNA load, log_{10} copies/ml (IQR)	5.1 (4.7-5.3)
Median time to first measurement of HIV RNA <400/copies/ml, months (IQR)	3.0 (2.8-3.2)
Median CD4 count, cells/mm^3 (IQR) at ART initiation	108 (56-167)
Median %CD38+ HLA-DR+ CD8+T-cells (IQR) at ART initiation	70 (54-76)
Dermatological characteristics	
History of any skin disease (%)	6 (35)
History of specific skin disease (%)	
Eczema	2 (12)
Psoriasis	0 (0)
Scabies	6 (35)
Drug reaction	1 (6)
Median Skindex-16 scores at ART initiation (IQR)	
Symptoms	100 (75-100)
Emotions	64 (31-95)
Functioning	17 (0-50)
Median itch severity on 10-cm VAS at ART initiation (IQR)	10 (9-10)
Median sleep impairment severity on 10-cm VAS at ART initiation (IQR)	5 (4-10)
Median effect of dyspigmentation on 10-cm VAS at ART initiation (IQR)	10 (10-10)
Sites affected at onset (%)	
Head and neck	1 (6)
Trunk	4 (24)
Genital areas	2 (12)
Extremities	7 (41)
Generalised	3 (18)
Sites affected at ART initiation (%)	
Head and neck	2 (12)
Trunk	2 (12)

Genital areas	0 (0)
Extremities	8 (47)
Generalised	6 (35)
Environmental Characteristics	
Outdoor work (%)	12 (71)
Indoor work (%)	3 (18)
- missing data	2 (12)
Work in daytime (%)	15 (88)
- missing data	2 (12)
Livestock ownership (%)	6 (35)
Insect repellant use (%)	0 (0)
Bed net use (%)	11 (65)
Reported daily bites (%)	11 (65)
Roof material (%) - metal	16 (94)
Wall material (%)	
Unfinished brick	10 (59)
Mud	5 (29)
Cement	2 (12)
Floor material (%)	
Cement	5 (29)
Uncovered mud	8 (47)
Mud with covering	4 (24)
Toilet type	
Uncovered pit latrine	11 (65)
Covered pit latrine	6 (35)
Shared toilet with other households (%)	9 (53)

ART, antiretroviral therapy. HIV, human immunodeficiency virus. IQR, interquartile range. RNA, ribonucleic acid. VAS, visual analogue scale.

The study participants' median HIV viral load at ART commencement was 114,442 copies/ml and CD4 count was 108 cells/mm^3. The median time taken for virological suppression of HIV RNA to less than 400 copies/ml was three months from ART initiation. Virological failure was not detected in any study participant over the two-year follow-up period. It is defined as plasma HIV RNA >1000 copies/ml in two consecutive measurements within a three-month interval with adherence support between measurements, after at least six months of ART (World Health Organization 2013a). Immunological failure, defined as the fall of CD4 count to baseline levels (or below) or persistent CD4 levels below 100 cells/mm^3 (World Health Organization 2013a), was not detected in any study participants.

Of note, median Skindex-16 scores at ART initiation were highest for the symptoms subscale, followed by emotions subscale and then functioning subscale (100/100, 64/100 and 17/100, respectively). Eleven of 17 (65%) participants reported daily insect bites, 15 of 17 participants worked in the daytime (88%) and twelve of 17 participants (71%) worked outdoors. All study participants had pit latrines at home and nine of 17 participants (53%) shared their pit latrines with other households.

Two participants were lost to follow-up after their first follow-up visit at three months post-initiation of ART; both were female. Median period of follow-up for the other 15 participants was 22 months. Two participants

had persistent PPE throughout the follow-up period. In the other 13 participants, median time to resolution of PPE was 8.5 months but recurred during the follow-up period in seven participants. The time to resolution of PPE is presented using a Kaplan-Meier survival curve in Figure 10.

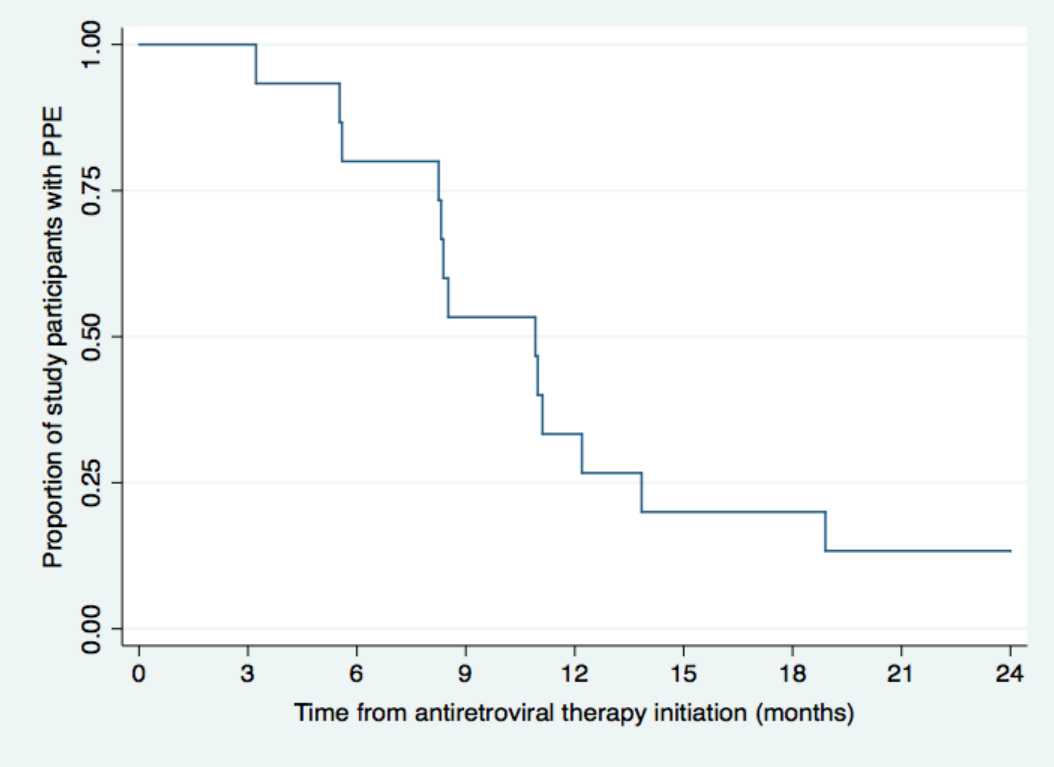


Figure 10 Kaplan-Meier survival curve of time to resolution of papular pruritic eruption of human immunodeficiency virus infection

PPE, papular pruritic eruption of human immunodeficiency virus infection

Characteristics of PPE in study participants during the follow-up period are presented in Table 15. Study participants who reported active PPE had similarly high Skindex-16, itch, sleep impairment and dyspigmentation scores at the end of the follow-up period compared to baseline, although lower scores was observed at six and nine months of follow-up.

CD4 counts measured in study participants with resolution of PPE, recurrent or persistent PPE during the study period are presented in Figure 11, Figure 12 and Figure 13, respectively. Persistent CD4 counts <100 cells/mm^3 is one of the criteria for immunological failure of ART; that level has been marked with a reference line in Figure 11, Figure 12 and Figure 13. The proportion of CD38+ HLA-DR+ CD8+ T-cells, a marker of CD8+ T-cell activation, was measured in study participants only in the first year of follow-up. They are shown in Figure 14 and Figure 15 in participants with PPE resolution and recurrence, respectively, where a trend towards gradual decline of this CD8+ T-cell activation marker was observed in both groups of participants. These levels were measured over the follow-up period in only one of two participants with persistent PPE therefore they have not been presented graphically.

Table 15 Characteristics of papular pruritic eruption of human immunodeficiency virus infection over follow-up period

Follow-up, months	Baseline	3	6	9	12	15	18	21	24
Number of participants who attended study visit	17	16	11	12	11	13	10	10	10
Number of participants who reported active PPE	17	15	7	6	3	5	5	3	3
Characteristics of participants with active PPE									
Median Skindex-16 scores									
Symptoms (range)	100 (25-100)	55 (0-100)	50 (13-100)	48 (25-100)	83 (58-100)	67 (42-100)	100 (100-100)	100 (54-100)	100 (25-100)
Emotions (range)	64 (0-100)	64 (7-100)	31 (0-78)	32 (2-57)	64 (62-69)	64 (31-81)	57 (26-100)	62 (57-67)	71 (38-90)
Functioning (range)	17 (0-100)	7 (0-60)	0 (0-60)	0 (0-50)	13 (0-37)	23 (0-50)	50 (0-73)	0 (0-60)	0 (0-50)
Median itch severity on 10-cm VAS (range)	10 (3-10)	10 (0-10)	5 (0-8)	9 (3-10)	8 (2-10)	8 (7-10)	8 (8-10)	9 (8-9)	10 (2-10)
Median sleep impairment severity on 10-cm VAS (range)	5 (0-10)	5 (0-10)	0 (0-8)	5 (0-10)	3 (2-10)	7 (3-10)	6 (5-10)	8 (0-10)	5 (0-8)
Median dyspigmentation effect on 10-cm VAS (range)	10 (5-10)	10 (2-10)	8 (3-10)	5 (5-10)	5 (4-10)	6 (1-10)	8 (3-10)	6 (5-6)	7 (7-7)
Frequency of reported sites of PPE									
Head and neck	2	3	0	0	0	1	0	0	1
Trunk	2	0	3	2	2	3	1	2	1
Genital areas	0	1	2	2	0	0	1	1	1
Extremities	8	10	1	2	1	2	4	1	0
Generalised	6	2	1	0	0	0	0	0	0

PPE, papular pruritic eruption of human immunodeficiency virus infection. VAS, visual analogue scale.

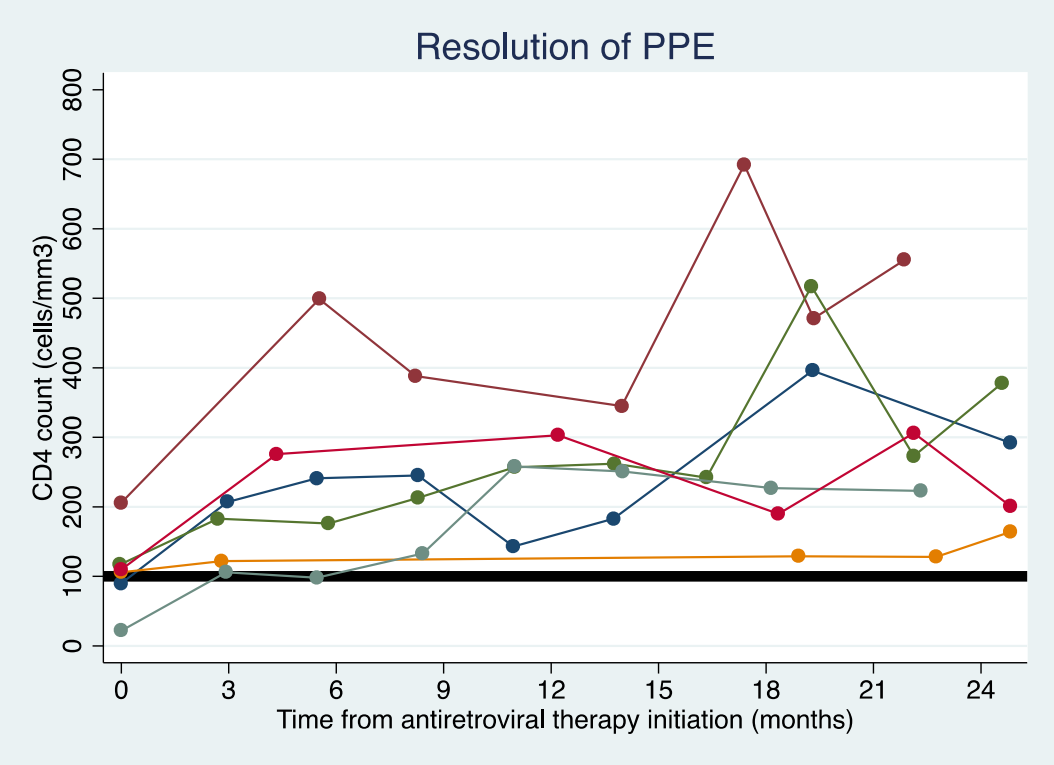


Figure 11 CD4 counts in study participants with resolution of papular pruritic eruption of human immunodeficiency virus infection within 24 months of initiating antiretroviral therapy

Each line presents one study participant. A black line in bold has been drawn at CD4 count of 100 cells/mm^3. Immunological failure of antiretroviral treatment is defined by the World Health Organization as persistent CD4 counts below 100 cells/mm^3 or the decline of CD4 count to the level at baseline or below (World Health Organization 2013a).

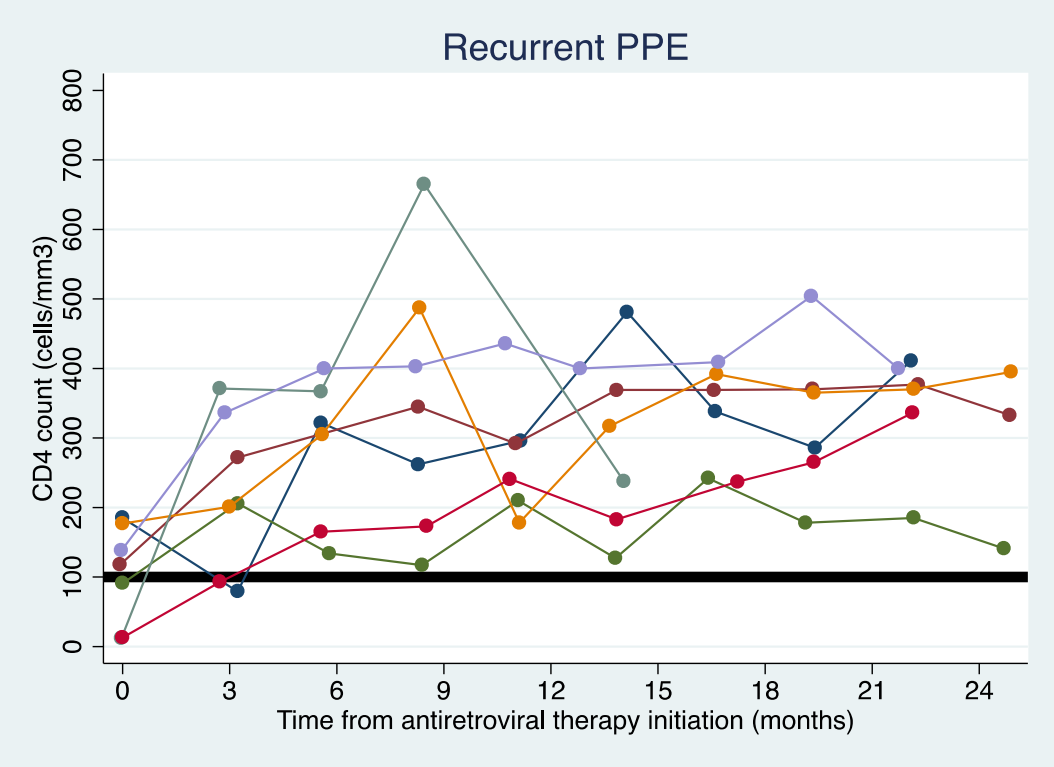


Figure 12 CD4 counts in study participants with recurrent papular pruritic eruption of human immunodeficiency virus infection

Each line represents one study participant. A black line in bold has been drawn at CD4 count of 100 cells/mm^3. Immunological failure of antiretroviral treatment is defined by the World Health Organization as persistent CD4 counts below 100 cells/mm^3 or the decline of CD4 count to the level at baseline or below (World Health Organization 2013a).

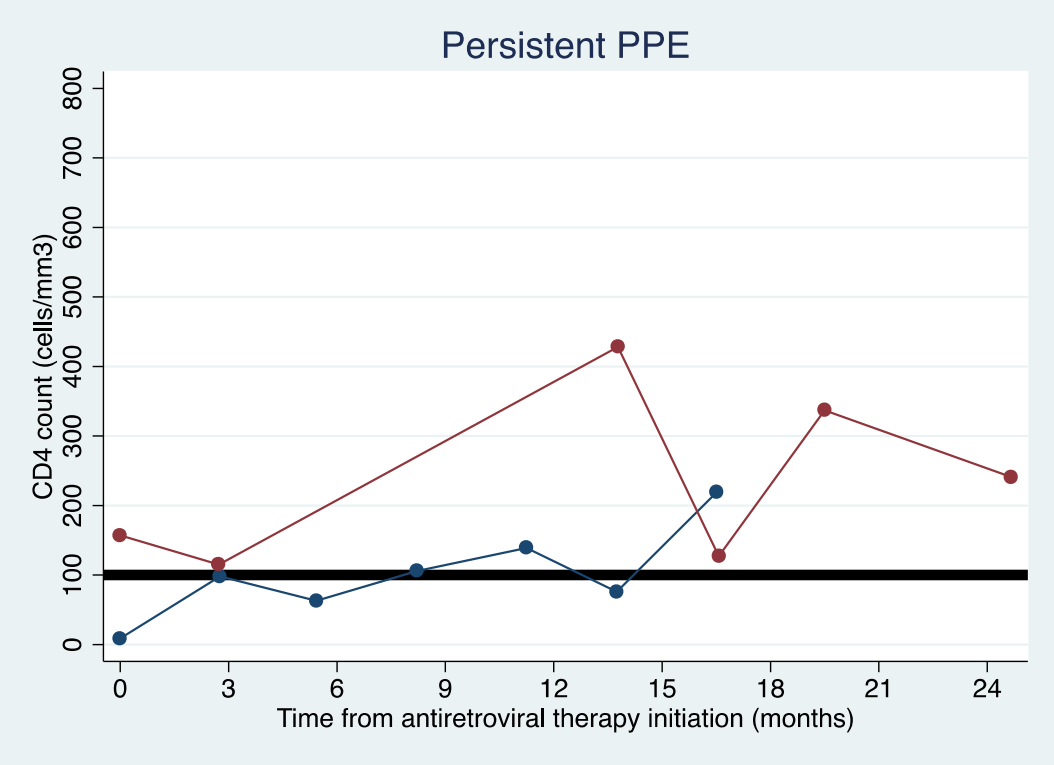


Figure 13 CD4 counts in study participants with persistent papular pruritic eruption of human immunodeficiency virus infection

Each line represents one study participant. A black line in bold has been drawn at CD4 count of 100 cells/mm^3. Immunological failure of antiretroviral treatment is defined by the World Health Organization as persistent CD4 counts below 100 cells/mm^3 or the decline of CD4 count to the level at baseline or below (World Health Organization 2013a).

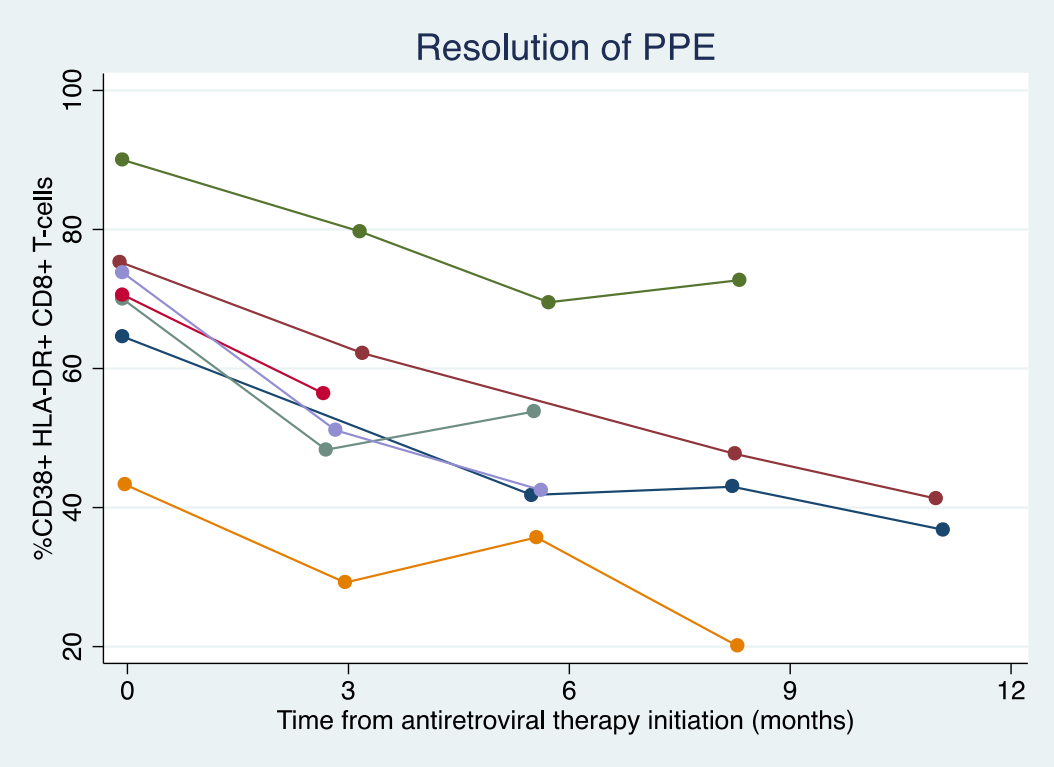


Figure 14 Proportion of CD38+ HLA-DR+ CD8+ T-cells in study participants with resolution of papular pruritic eruption of human immunodeficiency virus infection within 24 months of initiating antiretroviral therapy

Each line represents one study participant. Measurements of the proportion of CD38+ HLA-DR+ CD8+ T-cells were available for up to twelve months after the initiation of antiretroviral therapy in study participants.

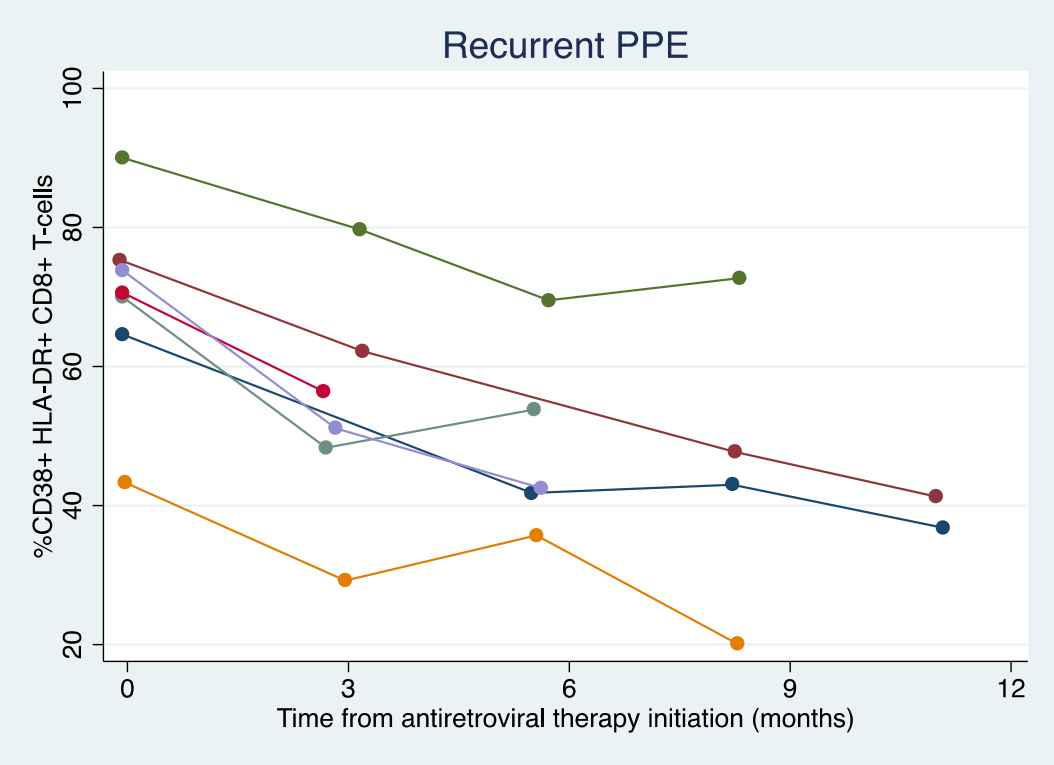


Figure 15 Proportion of CD38+ HLA-DR+ CD8+ T-cells in study participants with recurrent papular pruritic eruption of human immunodeficiency virus infection

Each line represents one study participant. Measurements of the proportion of CD38+ HLA-DR+ CD8+ T-cells were available for up to twelve months after the initiation of antiretroviral therapy in study participants.

5.5 Discussion

The results of this study do not suggest the use of recurrent or persistent PPE after at least six months of ART as one of the clinical indicators of virological failure. None of the study participants experienced virological or immunological failure throughout the study period. HIV RNA was less than 400 copies/ml at a median of three months after ART initiation in all study participants.

Resolution of PPE occurred in 13 of 17 (76%) study participants at a median of 8.5 months after ART initiation. These findings are consistent with anecdotal reports of the improvement of PPE in response to ART (Resneck et al. 2004a; Colebunders et al. 2006). Among the 13 study participants with remission of PPE, seven participants experienced recurrence of PPE within two years from ART commencement even though none of them experienced virological or immunological failure of ART. Detailed ART adherence data was not available on these study participants but excellent ART adherence has been reported in the UARTO cohort (Ware et al. 2009).

The confirmation of clinical diagnoses of PPE with skin biopsies is one of the strengths of this study. This is because it may be difficult to distinguish between PPE and other chronic itchy papular conditions such as papular

eczema clinically, therefore clinical diagnosis alone cannot be regarded as optimal.

Enrolling study participants from a well-established cohort (UARTO 2014) in which study participants had detailed structured interviews and blood draws at three-month intervals and whose participants had high levels of adherence to ART (Ware et al. 2009) was another strength of this study. This enabled coordination of interviewer-administered questionnaires and clinical examination of the skin for this study at the same time as UARTO follow-up visits and facilitated follow-up over a two-year period. In the context of a resource-limited setting and the study of diseases (skin disease and HIV) associated with considerable stigma, following study participants over a two-year period was challenging and in itself, an achievement.

The large proportion of female study participants (15/17, 88%) is a limitation of this study as PPE may behave differently in female compared with male HIV-infected adults. The small number of study participants precluded meaningful analysis of predictors that may have been associated with the resolution, recurrence or persistence of PPE. Screening more potential UARTO participants for PPE could not be considered, as there are a finite number of participants in the UARTO cohort. Enrolment of participants outside the UARTO cohort was not

possible due to the lack of resources for study procedures such as detailed interviews and analysis of blood samples.

The inclusion of UARTO participants with chronic pruritic skin conditions other than PPE was not considered, as it would have fundamentally changed the objective of the study from an exploration of the natural history of PPE to that of any chronic pruritic papular skin condition in HIV-infected Ugandan adults. As study participants had their skin biopsies performed at enrolment to the study and only one lesion was biopsied, it is possible that the lesion biopsied was not representative of the participant's skin eruption and may have led to the inappropriate inclusion or exclusion of participants based on their skin biopsy findings.

In conclusion, recurrent or persistent PPE was not associated with virological failure of antiretroviral treatment in participants of this study and therefore has no utility as a clinical indicator of virological failure. There are large gaps in the understanding of factors associated with the clinical course of PPE in HIV-infected adults receiving ART. Studies that bridge these gaps may inform interventions for PPE and whether it has potential as a clinical indicator for failure of ART.

6. Impact of research and directions for the future

6.1 Introduction

Papular pruritic eruption (PPE) of human immunodeficiency virus (HIV) has been described since the beginning of the HIV epidemic. The introductory chapter of this thesis has highlighted the scale of HIV as a public health problem, especially in sub-Saharan Africa. Despite PPE's prevalence and associated morbidity, little is understood of its natural history, utility as a clinical marker for failure of ART and clinical management. Studies included within this thesis have sought to add to the existing body of knowledge on PPE. My personal reflections on the impact of the work that has contributed to this thesis are outlined below.

6.2 Systematic review of interventions for papular pruritic eruption of human immunodeficiency virus infection

This review has directly contributed to World Health Organization guidelines on the treatment of skin and oral conditions associated with HIV infection published in 2014, which has recommended the initiation of ART for PPE and suggested the use of oral antihistamines and topical corticosteroids to help with associated symptoms. The lack of high quality

evidence of interventions for PPE, as evidenced by the findings of this systematic review, was highlighted.

6.3 Adaptation of a Runyankore version of Skindex-16 for oral administration in Mbarara, Uganda

This study was published in the International Journal of Dermatology in 2011. It has demonstrated the feasibility, reliability and validity of the orally or interviewer administered Runyankore-version of Skindex-16 that was translated and adapted for use in Mbarara, Uganda. Orally administered quality of life instruments are valuable when working with populations who have low literacy levels.

6.4 Factors associated with papular pruritic eruption of human immunodeficiency virus infection in the antiretroviral therapy era - a case control study

This study was published in the British Journal of Dermatology in 2014 and presented at the AIDS and sexually transmitted disease symposium at the 71st annual meeting of the American Academy of Dermatology in 2013. It demonstrated the association between greater HIV viraemia at the time of ART initiation and the presence of PPE in study participants who have received ART for at least 15 months. Virological failure of ART, CD4

cell counts, CD4 gains and CD8+ T-cell activation markers were not found to be associated with PPE in ART-treated study participants. Participant-reported daily insect bites or stings were associated with the presence of PPE as well as any other chronic itchy papular eruptions in ART-treated study participants.

6.5 Cohort study describing the natural history of papular pruritic eruption of human immunodeficiency virus infection over two years of antiretroviral therapy

This study has been presented at the 73rd annual meeting of the American Academy of Dermatology in 2015. It has shown that recurrent or persistent PPE was not associated with virological failure of ART, therefore the utility of PPE as a clinical marker for virological failure of ART was not demonstrated by the findings of this study. The natural history of PPE was described in this study, in particular its resolution at a median of 8.5 months after ART initiation in 13 of 17 (76%) study participants but recurrence seen in seven of these 13 participants.

Both case control and cohort studies of PPE also highlighted the need for clinical diagnoses of PPE to be confirmed by histology, as reliance on the clinical case definition of PPE alone was suboptimal.

6.6 Future direction

As mentioned in the systematic review of interventions for PPE, standardised and validated outcome measures would serve to improve the quality of studies of PPE and enable comparison of outcomes across studies as well as meta-analyses. Well-designed studies that document the effect of ART on PPE, as well as randomised controlled trials of other modalities of treatment would help in bridging the existing research and knowledge gaps. The practicability, cost effectiveness and availability of interventions are important considerations, especially in resource-limited settings.

Better characterization of the clinical course of PPE and the immunological (or other) mechanisms responsible for its onset, recurrence and persistent would be a worthy subject of study as it may inform interventions for PPE, improve care for persons affected by PPE and may have the potential to add to existing knowledge on immune responses in HIV disease

6.7 Personal Reflection

Embarking on this piece of work has been a privilege for me, especially the opportunity to get to know and learn to love the beautiful people and

country of Uganda and the charming city of San Francisco. More importantly, I have the pleasure of having met, worked with, learned from and become friends with wonderful people. Apart from learning the skills and competencies of research work, I have also learnt about myself and have been enriched by this experience.

Figure 16 The end of a day's work....

7. References

Afonso, J.P.J.M. et al., 2012. Pruritic papular eruption and eosinophilic folliculitis associated with human immunodeficiency virus (HIV) infection: A histopathological and immunohistochemical comparative study. *Journal of the American Academy of Dermatology*, 67(2), pp.269–275.

Ahoua, L. et al., 2009. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. *BMC infectious diseases*, 9(1), p.81.

Akinboro, A.O., Onayemi, O. & Mejiuni, A.D., 2014. Frequency, pattern, and extent of skin diseases in relation to CD4+ cell count among adults with human immunodeficiency virus infection or acquired immunodeficiency syndrome in Osogbo, southwestern Nigeria. *International journal of dermatology*, 53(4), pp.416–424.

Aksu, A.E.K. et al., 2007. Turkish version of Skindex-29. *International journal of dermatology*, 46(4), pp.350–355.

Alessi, E., Cusini, M. & Zerboni, R., 1988. Mucocutaneous manifestations in patients infected with human immunodeficiency virus. *Journal of the American Academy of Dermatology*, 19(2), pp.290–297.

AlGhamdi, K.M. & AlShammari, S.A., 2007. Arabic version of Skindex-16: Translation and cultural adaptation, with assessment of reliability and validity. *International journal of dermatology*, 46(3), pp.247–252.

Aquilina, C., 1998. Prurigo et infection VIH: trois observations. *Nouvelles Dermatologiques*, 17, pp.105–106.

Ash, S. & Hewitt, C., 1994. HIV-associated cutaneous disorders. *Current Opinion in Infectious Diseases*, 7(2), pp.195–201.

Asiimwe-Okiror, G. et al., 1997. Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda. *AIDS*, 11(14). Available at: http://journals.lww.com/aidsonline/Fulltext/1997/14000/Change_in_sexual_behaviour_and_decline_in_HIV.13.aspx.

Bañuls, J. et al., 1991. Papular pruritic eruption with human immunodeficiency virus infection. *International journal of dermatology*, 30(11), pp.801–803.

Barré-Sinoussi, F. et al., 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*, 220(4599), pp.868–871.

Barth, R.E. et al., 2010. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a

systematic review. *The Lancet infectious diseases*, 10(3), pp.155–166.

Basavaraj, K., Navya, M. & Rashmi, R., 2010. Quality of life in HIV/AIDS. *Indian journal of sexually transmitted diseases*, 31(2), p.75.

Bason, M.M., Berger, T.G. & Nesbitt, L.T., 1993. Pruritic papular eruption of HIV disease. *International Journal of Dermatology*, 32(11), pp.784–789.

Bellavista, S. et al., 2013. Pruritic papular eruption in HIV: a case successfully treated with NB-UVB. *Dermatologic Therapy*, 26(2), pp.173–175.

Berman, B., Flores, F. & Burke, G., 3rd, 1998. Efficacy of pentoxifylline in the treatment of pruritic papular eruption of HIV-infected persons. *Journal of the American Academy of Dermatology*, 38(6 Pt 1), pp.955–959.

Bernstein, J., 1998. Runyankitara. *Journal of multilingual and multicultural development*, 19(2), pp.93 – 107.

Binet, O. et al., 1987. Papular eruption associated with HIV infection. In Annales de Dermatologie et de Venereologie. Masson Editeur 120 Blvd Saint-Germain, 75280 Paris 06, France, pp. 1348–1349.

Bland, J.M. & Altman, D.G., 1997. Statistics notes: Cronbach's alpha. *Bmj*, 314(7080), p.572.

Boasso, A., Shearer, G. & Chougnet, C., 2009. Immune dysregulation in human immunodeficiency virus infection: know it, fix it, prevent it? *Journal of internal medicine*, 265(1), pp.78–96.

Boonchai, W. et al., 1999a. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *International journal of dermatology*, 38(5), pp.348–350.

Boonchai, W. et al., 1999b. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *International journal of dermatology*, 38(5), pp.348–350.

Boonchai, W. et al., 1999c. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *International Journal of Dermatology*, 38(5), pp.348–350.

Bor, J. et al., 2013. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science*, 339(6122), pp.961–965.

Both, H. et al., 2007. Critical review of generic and dermatology-specific health-related quality of life instruments. *Journal of Investigative Dermatology*, 127(12), pp.2726–2739.

Budavari, J.M. & Grayson, W., 2007. Papular follicular eruptions in human immunodeficiency virus-positive patients in South Africa. *International Journal of Dermatology*, 46(7), pp.706–710.

Buvé, A., Bishikwabo-Nsarhaza, K. & Mutangadura, G., 2002. The spread and effect of HIV-1 infection in sub-Saharan Africa. *The Lancet*, 359(9322), pp.2011–2017.

Calista, D. et al., 2002. Changing morbidity of cutaneous diseases in patients with HIV after the introduction of highly active antiretroviral therapy including a protease inhibitor. *American journal of clinical dermatology*, 3(1), pp.59–62.

Carswell, J.W., Lloyd, G. & Howells, J., 1989. Prevalence of HIV-1 in east African lorry drivers. *AiDS*, 3(11), pp.759–762.

Castelnuovo, B. et al., 2008a. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? *AIDS (London, England)*, 22(2), pp.269–273.

Castelnuovo, B. et al., 2008b. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? *AIDS*, 22(2), pp.269–73.

Chaturvedi, S.K., Singh, G. & Gupta, N., 2005. Stigma experience in skin disorders: an Indian perspective. *Dermatologic clinics*, 23(4), pp.635–642.

Chren, M.-M. et al., 1997. Improved Discriminative and Evaluative Capability of Quality-of-Life. *Arch Dermatol*, 133, pp.1433–1440.

Chren, M.-M. et al., 2001. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. *Journal of cutaneous medicine and surgery*, 5(2), pp.105–110.

Chren, M.-M. et al., 1996. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *Journal of Investigative Dermatology*, 107(5), pp.707–713.

Chren, M.-M. & Weinstock, M.A., 2004. In That Issue: The Burden of Skin Disease. *J Investig Dermatol*, 122(3), pp.viii–viii.

Chua, S. & Maurer, T., 2009. Recurrence of the pruritic papular eruption of HIV with immunologic failure of antiretroviral therapy. *Journal of the American Academy of Dermatology*, 60, pp.AB121–AB121.

Clerici, M. & Shearer, G.M., 1993. A Th1→ Th2 switch is a critical step in the etiology of HIV infection. *Immunology today*, 14(3), pp.107–111.

Clumeck, N. et al., 1984. Acquired immunodeficiency syndrome in African patients. *New England Journal of Medicine*, 310(8), pp.492–497.

Coffin, J. et al., 1986. Human immunodeficiency viruses [letter]. *Science*, 232(4751), p.697.

Coldiron, B.M. & Bergstresser, P.R., 1989. Prevalence and clinical spectrum of skin disease in patients infected with human immunodeficiency virus. *Archives of dermatology*, 125(3), pp.357–361.

Colebunders, R. et al., 2006. A new model to monitor the virological efficacy of antiretroviral treatment in resource-poor countries. *The Lancet Infectious Diseases*, 6(1), pp.53–59.

Colebunders, R. et al., 1987. Generalized Papular Pruritic Eruption in African Patients with Human Immunodeficiency Virus Infection. *AIDS*, 1, pp.117–121.

Colvin, M. & Sharp, B., 2000. Sexually transmitted infections and HIV in a rural community in the Lesotho highlands. *Sexually transmitted infections*, 76(1), pp.39–42.

Coopman, S.A. et al., 1993. Cutaneous disease and drug reactions in HIV infection. *New England journal of medicine*, 328(23), pp.1670–1674.

Creagh-Kirk, T. et al., 1988. Survival experience among patients with AIDS receiving zidovudine: follow-up of patients in a compassionate plea program. *JAMA*, 260(20), pp.3009–3015.

Cronbach, L.J., 1951. Coefficient alpha and the internal structure of tests. *Psychometrika*, 16(3), pp.297–334.

Dagatti, M.S. et al., 2000. Erupción papulosa y pruriginosa en pacientes HIV (+): a propósito de ocho casos; Papular pruritic eruption in HIV (+) patients: report of 8 cases. *Arch Argent Dermatol*, 50(5), pp.227–30.

Deeks, S.G. et al., 2004. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. *Blood*, 104(4), pp.942 –947.

Department of Dermatology, University of California, San Francisco, 2015. Dermatology Glossary. Available at: http://missinglink.ucsf.edu/lm/DermatologyGlossary/secondarylesions1a.html.

Dixon, S., McDonald, S. & Roberts, J., 2002. The impact of HIV and AIDS on Africa's economic development. *BMJ: British Medical Journal*, 324(7331), p.232.

Dournon, E. et al., 1988. Effects of zidovudine in 365 consecutive patients with AIDS or AIDS-related complex. *The Lancet*, 332(8623), pp.1297–1302.

Edwards, S.L. et al., 2007. Development and use of touch-screen audio computer-assisted self-interviewing in a study of American Indians. *American Journal of Epidemiology*, 165(11), pp.1336–1342.

Egger, M. et al., 2002. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *The Lancet*, 360(9327), pp.119–129.

Elm, E. Von et al., 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Preventive medicine*, 45(4), pp.247–251.

Farsani, T.T. et al., 2013. Etiology and risk factors associated with a pruritic papular eruption in people living with HIV in India. *Journal of the International AIDS Society; Vol 16 (2013)*. Available at: http://www.jiasociety.org/index.php/jias/article/view/17325/3168.

Fearfield, L.A. et al., 1999. Itchy folliculitis and human immunodeficiency virus infection: clinicopathological and immunological features, pathogenesis and treatment. *The British Journal of Dermatology*, 141(1), pp.3–11.

Filmer, D. & Pritchett, L., 2001. Estimating Wealth Effects Without Expenditure Data—Or Tears: An Application To Educational Enrollments In States Of India*. *Demography*, 38(1), pp.115–132.

Finlay, A.Y. & Khan, G.K., 1994. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology*, 19(3), pp.210–216.

Fischl, M.A. et al., 1987. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *New England Journal of Medicine*, 317(4), pp.185–191.

Fleischer, A.B., Jr, Gallagher, P.N. & van der Horst, C., 1992. Mucocutaneous abnormalities predicted by lymphocyte counts in patients infected with the human immunodeficiency virus. *Southern Medical Journal*, 85(7), pp.687–690.

Force, T. et al., 1997. Guidelines of care for dermatologic conditions in patients infected with HIV. *Journal of the American Academy of Dermatology*, 37(3), pp.450–472.

French, M.A., Price, P. & Stone, S.F., 2004. Immune restoration disease after antiretroviral therapy. *Aids*, 18(12), pp.1615–1627.

Friedman-Kien, A. et al., 1981. Kaposis sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. *MMWR. Morbidity and mortality weekly report*, 30(25), pp.305–8.

Fylkesnes, K. et al., 1997. The HIV epidemic in Zambia: socio-demographic prevalence patterns and indications of trends among childbearing women. *Aids*, 11(3), pp.339–345.

Gabriel, S.E. & Normand, S.-L.T., 2012. Getting the methods right—the foundation of patient-centered outcomes research. *New England Journal of Medicine*, 367(9), pp.787–790.

Gallo, R.C. et al., 1984. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*, 224(4648), pp.500–503.

Geier, S. et al., 1992. [Differences in detectability of human immunodeficiency virus type 1 in tears and blood lymphocytes]. *Klinische Monatsblatter fur Augenheilkunde*, 201(3), pp.164–168.

Gill, T.M. & Feinstein, A.R., 1994. A critical appraisal of the quality of quality-of-life measurements. *Jama*, 272(8), pp.619–626.

Ginsburg, I.H. & Link, B.G., 1993. Psychsocial consequences of rejection and stigma feelings in psoriasis patients. *International Journal of Dermatology*, 32(8), pp.587–591.

Giorgi, J.V. et al., 1993. Elevated Levels of CD38+ CD8+ T Cells in HIV Infection Add to the Prognostic Value of Low CD4+ T Cell Levels: Results of 6 Years of Follow-Up. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 6(8).

Giorgi, J.V. et al., 1999. Shorter Survival in Advanced Human Immunodeficiency Virus Type 1 Infection Is More Closely Associated with T Lymphocyte Activation than with Plasma Virus Burden or Virus Chemokine Coreceptor Usage. *Journal of Infectious Diseases*, 179(4), pp.859 –870.

Gisselquist, D. & Potterat, J.J., 2003. Heterosexual transmission of HIV in Africa: an empiric estimate. *International journal of STD & AIDS*, 14(3), pp.162–173.

Goh, B.-K. et al., 2007. Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. *International Journal of Dermatology*, 46(7), pp.695–699.

Goldstein, B. et al., 1997. Correlation of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. *Journal of the American Academy of Dermatology*, 36(2), pp.262–264.

Goodman, D.S. et al., 1987. Prevalence of cutaneous disease in patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. *Journal of the American Academy of Dermatology*, 17(2), pp.210–220.

Google Maps, 2014. Google Maps. *Google Maps*. Available at: https://www.google.co.uk/maps/dir/Kampala,+Uganda/Mbarara+University+of+Science+%26+Technology,+Mbarara%2FP.O.Box+1410+University+Rd,+Mbarara,+Uganda/@-0.1512995,31.0290216,9z/data=!3m1!4b1!4m13!4m12!1m5!1m1!1s0x177dbc0f9d74b39b:0x4538903dd96b6fec!2m2!1d32.581111!2d0.313611!1m5!1m1!1s0x19d91a52e5dc9b19:0xebd6b4ebbf17bf68!2

m2!1d30.657228!2d-0.616226?hl=en [Accessed November 10, 2014].

Gottlieb, M.S. et al., 1981. Pneumocystis pneumonia--Los Angeles. *MMWR. Morbidity and Mortality Weekly Report*, 30(21), pp.250–2.

GRADE Working Group, 2004. Grading quality of evidence and strength of recommendations. *BMJ*, 328(7454), p.1490.

Guillemin, F., Bombardier, C. & Beaton, D., 1993. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *Journal of clinical epidemiology*, 46(12), pp.1417–1432.

Haddow, L.J. et al., 2012. Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. *PloS one*, 7(11), p.e40623.

Hahn, E.A. et al., 2004. The talking touchscreen: a new approach to outcomes assessment in low literacy. *Psycho-Oncology*, 13(2), pp.86–95.

Harindra, V. & Roy, R.B., 1992. Papulo-pruritic eruption and giant ulceration of the mouth: a difficult clinical feature to treat in the patient infected with human immunodeficiency virus. *Archives of Internal Medicine*, 152(9), p.1924.

Hay, R.J. et al., 2014. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *Journal of Investigative Dermatology*, 134(6), pp.1527–1534.

Health Statistics and Information Systems, World Health Organization, 2013. Adult HIV prevalence (15-49 years), 2013 by WHO region. Available at: http://www.who.int/gho/hiv/hiv_013.jpg?ua=1 [Accessed November 30, 2014].

Hevia, O. et al., 1991. Pruritic papular eruption of the acquired immunodeficiency syndrome: A clinicopathologic study. *Journal of the American Academy of Dermatology*, 24(2), pp.231–235.

Higgins, J. & Green, S., 2011. *Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]*, Available at: http://www.cochrane-handbook.org.

Ho, D.D. et al., 1985. Infrequency of isolation of HTLV-III virus from saliva in AIDS [letter]. *New England Journal of Medicine*, 313(25), p.1606.

Hollander, H. & Levy, J., 1987. Neurologic abnormalities and recovery of human immunodeficiency virus from cerebrospinal fluid. *Annals of internal medicine*, 106(5), pp.692–695.

Howe, L.D. et al., 2009. Is the wealth index a proxy for consumption expenditure? A systematic review. *Journal of Epidemiology and Community Health*, 63(11), pp.871–877.

Hunt, P.W. et al., 2003. T Cell Activation Is Associated with Lower CD4+ T Cell Gains in Human Immunodeficiency Virus-Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy. *Journal of Infectious Diseases*, 187(10), pp.1534 –1543.

Ishii, N. et al., 1994. Pruritic papular eruption of the acquired immunodeficiency syndrome. *Acta dermato-venereologica*, 74(3), p.219.

Jaffar, S. et al., 2009. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. *The Lancet*, 374(9707), pp.2080–2089.

Jensen, B.L. et al., 2000. Incidence and prognostic significance of skin disease in patients with HIV/AIDS: a 5-year observational study. *Acta Derm Venereol*, 80, pp.140–143.

Jing, W., 2000. A retrospective survey of mucocutaneous manifestations of HIV infection in Malaysia: analysis of 182 cases. *The Journal of Dermatology*, 27(4), pp.225–232.

Jones-Caballero, M. et al., 2000. The Spanish version of Skindex-29. *International journal of dermatology*, 39(12), pp.907–912.

Keiser, O. et al., 2009. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and

without viral load monitoring. *AIDS (London, England)*, 23(14), p.1867.

Kilmarx, P.H., 2009. Global epidemiology of HIV. *Current Opinion in HIV and AIDS*, 4(4), pp.240–246.

Kim, T.-G., Lee, K.-H. & Oh, S.-H., 2010. Skin disorders in Korean patients infected with human immunodeficiency virus and their association with a CD4 lymphocyte count: a preliminary study. *Journal of the European Academy of Dermatology and Venereology: JEADV*, 24(12), pp.1476–1480.

Kini, S. et al., 2011. The impact of pruritus on quality of life: The skin equivalent of pain. *Archives of Dermatology*, 147(10), pp.1153–1156.

Kirunga, C.T. & Ntozi, J.P., 1997. Socio-economic determinants of HIV serostatus: a study of Rakai District, Uganda. *Health Transition Review*, pp.175–188.

Koek, M.B. et al., 2010. Cost effectiveness of home ultraviolet B phototherapy for psoriasis: economic evaluation of a randomised controlled trial (PLUTO study). *BMJ*, 340.

De Korte, J. et al., 2004. Quality of life in patients with psoriasis: a systematic literature review. In Journal of Investigative Dermatology Symposium Proceedings. Nature Publishing Group, pp. 140–147.

Kumarasamy, N. et al., 2000. Dermatologic manifestations among human immunodeficiency virus patients in south India. *International Journal of Dermatology*, 39(3), pp.192–195.

Labhardt, N.D. et al., 2012. A Clinical Prediction Score in Addition to WHO Criteria for Anti-Retroviral Treatment Failure in Resource-Limited Settings - Experience from Lesotho. *PLoS ONE*, 7(10), p.e47937.

Lakshmi, S.J. et al., 2008a. Pruritic papular eruptions of HIV: a clinicopathologic and therapeutic study. *Indian Journal of Dermatology, Venereology and Leprology*, 74(5), pp.501–503.

Lakshmi, S.J. et al., 2008b. Pruritic papular eruptions of HIV: a clinicopathologic and therapeutic study. *Indian Journal of Dermatology, Venereology and Leprology*, 74(5), pp.501–503.

Levy, J.A. et al., 1984. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science*, 225(4664), pp.840–842.

Liautaud, B. et al., 1989. Pruritic skin lesions. A common initial presentation of acquired immunodeficiency syndrome. *Arch Dermatol*, 125(5), pp.629–32.

Liautaud B, P.J., 1989. Pruritic skin lesions: A common initial presentation of acquired immunodeficiency syndrome. *Archives of Dermatology*, 125(5), pp.629–632.

Link, B.G. & Phelan, J.C., 2006. Stigma and its public health implications. *The Lancet*, 367(9509), pp.528–529.

Liu, Z. et al., 1998. CD8+ T-Lymphocyte Activation in HIV-1 Disease Reflects an Aspect of Pathogenesis Distinct From Viral Burden and Immunodeficiency. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 18(4).

Magadi, M.A., 2013. The disproportionate high risk of HIV infection among the urban poor in sub-Saharan Africa. *AIDS and Behavior*, 17(5), pp.1645–1654.

Mahajan, A.P. et al., 2008. Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. *AIDS (London, England)*, 22(Suppl 2), p.S67.

Matis, W.L. et al., 1987. Dermatologic findings associated with human immunodeficiency virus infection. *Journal of the American Academy of Dermatology*, 17(5), pp.746–751.

Maurer, T. et al., 2004. The effect of highly active antiretroviral therapy on dermatologic disease in a longitudinal study of HIV type 1-infected women. *Clinical infectious diseases*, 38(4), pp.579–584.

Mbuagbaw, J. et al., 2006. Patterns of skin manifestations and their relationships with CD4 counts among HIV/AIDS patients in

Cameroon. *International Journal of Dermatology*, 45(3), pp.280–284.

McCalmont, T.H. et al., 1995. Eosinophilic folliculitis: the histologic spectrum. *The American journal of dermatopathology*, 17(5), pp.439–446.

Mermin, J. et al., 2011. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. *Bmj*, 343, p.d6792.

Ministry of Health, Republic of Uganda, 2008. National Antiretroviral Treatment and Care Guidelines for Adults, Adolescents, and Children. Available at: http://www.who.int/hiv/amds/uganda_moh_treatment_guidelines.pdf.

Munoz-Perez, M. et al., 1998. Dermatological findings correlated with CD4 lymphocyte counts in a prospective 3 year study of 1161 patients with human immunodeficiency virus disease predominantly acquired through intravenous drug abuse. *British Journal of Dermatology*, 139(1), pp.33–39.

Naswa, S., Khambhati, R. & Marfatia, Y.S., 2011. Pruritic papular eruptions as presenting illness of HIV. *Indian Journal of Sexually Transmitted Diseases*, 32(2), pp.118–120.

Navarini, A.A. et al., 2010. Antihistamines are superior to topical steroids in managing human immunodeficiency virus (HIV)-associated papular pruritic eruption. *International Journal of Dermatology*, 49(1), pp.83–86.

N'Galy, B. & Ryder, R.W., 1988. Epidemiology of HIV infection in Africa. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 1(6), pp.551–558.

Nnoruka, E.N., 2004. Current epidemiology of atopic dermatitis in south-eastern Nigeria. *International Journal of Dermatology*, 43(10), pp.739–744.

Nnoruka, E.N., Chukwuka, J.C. & Anisuiba, B., 2007. Correlation of mucocutaneous manifestations of HIV/AIDS infection with CD4 counts and disease progression. *International Journal of Dermatology*, 46 Suppl 2, pp.14–18.

Ortblad, K.F., Lozano, R. & Murray, C.J.L., 2013. The burden of HIV: insights from the Global Burden of Disease Study 2010. *AIDS*, 27(13). Available at: http://journals.lww.com/aidsonline/Fulltext/2013/08240/The_burden_of_HIV___insights_from_the_Global.1.aspx.

Palella, F.J. et al., 1998. Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection. *New England Journal of Medicine*, 338(13), pp.853–860.

Pantaleo, G., Graziosi, C. & Fauci, A.S., 1993. The Immunopathogenesis of Human Immunodeficiency Virus Infection. *New England Journal of Medicine*, 328(5), pp.327–335.

Pardo, R.J. et al., 1992. UVB phototherapy of the pruritic papular eruption of the acquired immunodeficiency syndrome. *Journal of the American Academy of Dermatology*, 26(3 Pt 2), pp.423–428.

Parkhurst, J.O., 2002. The Ugandan success story? Evidence and claims of HIV-1 prevention. *The Lancet*, 360(9326), pp.78–80.

Patel, P. et al., 2014. Estimating per-act HIV transmission risk: a systematic review. *AIDS*, 28(10). Available at: http://journals.lww.com/aidsonline/Fulltext/2014/06190/Estimating_per_act_HIV_transmission_risk__a.14.aspx.

Peng, Z. et al., 2004. Evidence for natural desensitization to mosquito salivary allergens: mosquito saliva specific IgE and IgG levels in children. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*, 93(6), pp.553–556.

Peng, Z. & Simons, F.R., 1998. A prospective study of naturally acquired sensitization and subsequent desensitization to mosquito bites and concurrent antibody responses. *The Journal of allergy and clinical immunology*, 101(2), pp.284–286.

Penneys, N.S. et al., 1989. Chronic pruritic eruption in patients with acquired immunodeficiency syndrome associated with increased antibody titers to mosquito salivary gland antigens. *Journal of the American Academy of Dermatology*, 21(2), pp.421–425.

Van de Perre, P. et al., 1984. Acquired immunodeficiency syndrome in Rwanda. *The Lancet*, 324(8394), pp.62–65.

Piot, P. et al., 1984. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. *The Lancet*, 324(8394), pp.65–69.

Piot, P. et al., 2009. AIDS: lessons learnt and myths dispelled. *The Lancet*, 374(9685), pp.260–263.

Piot, P. & Carael, M., 1988. Epidemiological and sociological aspects of HIV-infection in developing countries. *British medical bulletin*, 44(1), pp.68–88.

Pirmohamed, M. & Park, B.K., 2001. HIV and drug allergy. *Current opinion in allergy and clinical immunology*, 1(4), pp.311–316.

del Pozo, L.J. et al., 1992. [Itchy rash in an HIV-positive patient]. *Enfermedades Infecciosas Y Microbiología Clínica*, 10(3), pp.173–175.

Pujades-Rodríguez, M. et al., 2008. Second-line antiretroviral therapy in resource-limited settings: the experience of Medecins Sans Frontieres. *Aids*, 22(11), pp.1305–1312.

Quinn, T.C. et al., 1986. AIDS in Africa: an epidemiologic paradigm. *Science*, 234(4779), pp.955–963.

Raju, P., Rao, G.R. & Ramani, T., 2005. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *International journal of dermatology*, 44(8), pp.646–649.

Ramos, H. et al., 2005. Pruritic papular eruption associated with HIV-etiopathogenesis evaluated by clinical, immunohistochemical, and ultrastructural analysis. *The Journal of Dermatology*, 32(7), pp.549–556.

Ratnam, I. et al., 2006. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1–infected cohort. *Clinical Infectious Diseases*, 42(3), pp.418–427.

Resch, S. et al., 2011. Economic returns to investment in AIDS treatment in low and middle income countries. *PloS one*, 6(10), p.e25310.

Resneck, J.S., Jr et al., 2004a. Etiology of pruritic papular eruption with HIV infection in Uganda. *JAMA: The Journal of the American Medical Association*, 292(21), pp.2614–2621.

Resneck, J.S., Jr et al., 2004b. Etiology of pruritic papular eruption with HIV infection in Uganda. *JAMA: The Journal of the American Medical Association*, 292(21), pp.2614–2621.

Reynolds, S.J. et al., 2009. Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS (London, England)*, 23(6), pp.697–700.

Rigopoulos, D., Paparizos, V. & Katsambas, A., 2004. Cutaneous markers of HIV infection. *Clinics in Dermatology*, 22(6), pp.487–498.

Roosta, N. et al., 2010. Skin Disease and Stigma in Emerging Adulthood: Impact on Healthy Development. *Journal of Cutaneous Medicine and Surgery*, 14(6), pp.285–290.

Rosatelli, J.B., Machado, A.A. & Roselino, A.M.F., 1997. Dermatoses among Brazilian HIV-positive patients: correlation with the evolutionary phases of AIDS. *International Journal of Dermatology*, 36(10), pp.729–734.

Rosatelli, J.B. & Roselino, A.M., 2001. Hyper-IgE, eosinophilia, and immediate cutaneous hypersensitivity to insect antigens in the

pruritic papular eruption of human immunodeficiency virus. *Archives of Dermatology*, 137(5), pp.672–673.

Satimia F, McBride SR & Leppard B, 1998. Prevalence of skin disease in rural tanzania and factors influencing the choice of health care, modern or traditional. *Archives of Dermatology*, 134(11), pp.1363–1366.

Sears, A., Wee, J. & Natkunarajah, J., 2014. A persistent itchy eruption. *Clinical and experimental dermatology*, 39(1), pp.94–96.

Selik, R. et al., 2014. CDC. 2014 Revised surveillance case definition for HIV infection—United States. *MMWR. Morbidity and Mortality Weekly Report*, 63(3), pp.1 – 10.

Serwadda, D. et al., 1985. Slim disease: a new disease in Uganda and its association with HTLV-III infection. *The Lancet*, 326(8460), pp.849–852.

Simpson-Dent, S., Fearfield, L.A. & Staughton, R.C., 1999. HIV associated eosinophilic folliculitis--differential diagnosis and management. *Sexually Transmitted Infections*, 75(5), pp.291–293.

Singh, H. et al., 2009. Dermatological manifestations in HIV-infected patients at a tertiary care hospital in a tribal (Bastar) region of Chhattisgarh, India. *Indian Journal of Dermatology*, 54(4), pp.338–341.

Sivayathorn, A., Srihra, B. & Leesanguankul, W., 1995. Prevalence of skin disease in patients infected with human immunodeficiency virus in Bangkok, Thailand. *Annals of the Academy of Medicine, Singapore*, 24, pp.528–33.

Smith, K.J. et al., 1994. Cutaneous findings in HIV-1-positive patients: a 42-month prospective study. *Journal of the American Academy of Dermatology*, 31(5), pp.746–754.

Spira, R. et al., 1998. Prevalence of cutaneous disorders in a population of HIV-infected patients: southwestern France, 1996. *Archives of dermatology*, 134(10), pp.1208–1212.

Sud, N. et al., 2009. Mucocutaneous manifestations in 150 HIV-infected Indian patients and their relationship with CD4 lymphocyte counts. *International journal of STD & AIDS*, 20(11), pp.771–774.

Tanser, F. et al., 2000. HIV heterogeneity and proximity of homestead to roads in rural South Africa: an exploration using a geographical information system. *Tropical Medicine & International Health*, 5(1), pp.40–46.

Tanser, F. et al., 2009. Localized spatial clustering of HIV infections in a widely disseminated rural South African epidemic. *International Journal of Epidemiology*, 38(4), pp.1008–16.

Testa, M.A. & Simonson, D.C., 1996. Assessment of quality-of-life outcomes. *New England Journal of Medicine*, 334(13), pp.835–840.

UARTO, 2014. Uganda AIDS Rural Treatment Outcomes (UARTO). Available at: http://cfar.ucsf.edu/cfar?page=cores-03-uarto [Accessed October 28, 2014].

Uchigasaki, S. et al., 1996. Pruritic papular eruptions and candidiasis due to HIV infection. *The Journal of Dermatology*, 23(8), pp.572–576.

Uganda Bureau of Statistics, 2010. *Uganda National Household Survey Report 2009/2010*, Kampala, Uganda: Uganda Bureau of Statistics. Available at: http://www.ubos.org/UNHS0910/home.html [Accessed November 6, 2014].

UNAIDS, 2010. *Getting to zero: 2011-2015 strategy*, Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS.

UNAIDS, 2014a. *HIV and AIDS Uganda Country Progress Report 2013*, Joint United Nations Programme on HIV/AIDS. Available at: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2014countries/UGA_narrative_report_2014.pdf [Accessed October 21, 2014].

UNAIDS, 2007. *Reducing HIV stigma and discrimination: a critical part of national AIDS programmes*, Geneva: Joint United Nations Programme on HIV/AIDS. Available at:

http://data.unaids.org/pub/Report/2008/JC1521_stigmatisation_en.pdf.

UNAIDS, 2014b. *The Gap Report*, Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf [Accessed October 20, 2014].

UNAIDS, 2013. *Treatment 2015*, Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/JC2484_treatment-2015_en.pdf.

UNAIDS, 2014c. *UNAIDS Fact Sheet 2014*, Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS.

UNAIDS, 2003. UNAIDS Fact sheet on stigma.

UNICEF, 2013. Uganda Statistics. *UNICEF*. Available at: http://www.unicef.org/infobycountry/uganda_statistics.html [Accessed November 6, 2014].

Uthayakumar, S. et al., 1997. The prevalence of skin disease in HIV infection and its relationship to the degree of immunosuppression. *The British Journal of Dermatology*, 137(4), pp.595–598.

Valle, S.-L., 1987. Dermatologic findings related to human immunodeficiency virus infection in high-risk individuals. *Journal of the American Academy of Dermatology*, 17(6), pp.951–961.

Ware, N.C. et al., 2009. Explaining Adherence Success in Sub-Saharan Africa: An Ethnographic Study. *PLoS Med*, 6(1), p.e1000011.

Weiss, M.G., 2008. Stigma and the Social Burden of Neglected Tropical Diseases. *PLoS Negl Trop Dis*, 2(5), p.e237.

Wells, G. et al., 2000. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

Wernham, A. & Chua, S.-L., 2014. Papular pruritic eruption of HIV responsive to oral thalidomide. In BRITISH JOURNAL OF DERMATOLOGY. WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, pp. 103–104.

Wiwanitkit, V., 2004a. Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases. *International Journal of Dermatology*, 43(4), pp.265–268.

Wiwanitkit, V., 2004b. Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases. *International Journal of Dermatology*, 43(4), pp.265–268.

Wofsy, C. et al., 1986. Isolation of AIDS-associated retrovirus from genital secretions of women with antibodies to the virus. *The Lancet*, 327(8480), pp.527–529.

World Health Organization, 2006a. *Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. – 2006 revision*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2014a. *Consolidated Guidelines on HIV Diagnosis, Prevention, Treatment and Care for Key Populations*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2013a. *Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2013b. *Global update on HIV treatment 2013: results, impact and oportunities*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2014b. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach APPROACH. Available at:

http://apps.who.int/iris/bitstream/10665/145719/1/9789241508193_eng.pdf?ua=1.

World Health Organization, 2014c. *Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults*, Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/maternal_child_adolescent/documents/skin-mucosal-and-hiv/en/ [Accessed November 3, 2014].

World Health Organization, 2002. *Scaling up antiretroviral therapy in resource-limited settings: treatment gudelines for a public health approach*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2012. *The strategic use of antiretrovirals to help end the HIV epidemic*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2006b. *Towards universal access by 2010: How WHO is working with countries to scale-up HIV prevention, treatment, care and support*, Geneva, Switzerland: World Health Organization.

World Health Organization, 2007. *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*, Geneva, Switzerland: World Health Organization. Available at:

http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf [Accessed October 24, 2014].

World Health Organization, 2014d. WHO HIV/AIDS Fact sheet No. 360. *WHO*. Available at: http://who.int/mediacentre/factsheets/fs360/en/ [Accessed October 20, 2014].

World Health Organization, 2013c. *WHO Model List of Essential Medicines: 18th List*, Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/index.html [Accessed November 3, 2014].

World Health Organization, 1997. WHOQOL: Measuring quality of life.

Zachariae, R. et al., 2004. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. *Acta dermato-venereologica*, 84(3), pp.205–212.

Zancanaro, P.C.Q. et al., 2006. Cutaneous manifestations of HIV in the era of highly active antiretroviral therapy: an institutional urban clinic experience. *Journal of the American Academy of Dermatology*, 54(4), pp.581–588.

8. Appendices

Appendix 1 World Health Organization clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

(From: World Health Organization, 2007. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children, Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf [Accessed October 24, 2014].

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)[I] Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections

Clinical stage 3
Unexplained[i] severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)
Clinical stage 4[ii]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

Appendix 2 World Health Organization definitions of clinical, immunological and virological failure of antiretroviral therapy

(From: World Health Organization, 2013. Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection. Geneva, Switzerland. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/en/ [Accessed 24 October 2014])

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome[b] occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm³ **Children** Younger than 5 years Persistent CD4 levels below 200 cells/mm³ or <10% Older than 5 years Persistent CD4 levels below 100 cells/mm³	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (*182*). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

Appendix 3 Data abstraction form for systematic review of interventions for papular pruritic eruption of human immunodeficiency virus infection

Data Collection Form

1. General Information

Reviewer	
Date of form completion	
First author and Year of publication	
Title of publication	
Type of publication *(eg. full report, abstract, letter)*	
Study funding source	

2. Methods

Aim(s) of study	
Design (eg. parallel crossover RCT, etc)	If it was a clinical trial, Randomised ☐ Yes ☐ No Controlled ☐ Yes ☐ No Parallel group ☐ Yes ☐ No Crossover ☐ Yes ☐ No Open trial ☐ Yes ☐ No If it was an observational study, ☐ Prospective ☐ Retrospective ☐ Not specified/Unclear If it was a case series/report, number of patients: _____

3. Population and setting

Population description and setting *(eg. Teaching hospital outpatient dermatology clinic, Kampala, Uganda)*	
Were the participants receiving ART at the time of the intervention? *(specify if ART initiated simultaneously or during intervention)*	
Ascertainment of diagnosis *(clinical case definition and/or consistent biopsy findings)*	
Inclusion criteria	
Exclusion criteria	

4. Participants

	Description (as stated in paper)
Total number randomised *(or number at start of study)*	
Withdrawals and exclusions	
Age	
Sex	
Race/Ethnicity	
Co-morbidities	
Previous unsuccessful treatments	

5. Intervention groups

	Description (as stated in paper)
Intervention group 1	
Number randomised to group *(specify number of participants/clusters)*	
Description *(eg. content, dose, frequency, topical/oral, duration of treatment, etc)*	
Co-interventions	
Intervention group 2	
Number randomised to group *(specify number of participants/clusters)*	
Description *(eg. content, dose, frequency, topical/oral, duration of treatment, etc)*	
Co-interventions	

6. Outcomes

	Description (as stated in paper)
Outcome 1 (specify definition, scales [with upper and lower limit] if relevant)	
Time points reported (specify from start or end of intervention)	
Outcome assessor	
Is outcome / tool validated?	
Outcome 2 (specify definition, scales [with upper and lower limit] if relevant)	
Time points reported (specify from start or end of intervention)	
Outcome assessor	
Is outcome / tool validated?	
Any other details	

7. Results

	Description (as stated in paper)
Results for each group *(specify sample size, outcome, time point, summary data)*	
Number of missing participants and reasons	
Any other results reported	
Statistical methods used *(appropriateness, adjustment for confounders, etc)*	

8. Applicability

	Description (as stated in paper)
Key conclusions of study	

Continue to the relevant section if this is a randomised controlled trial, cohort study or case control study

9. Risk of bias assessment

For randomised controlled trials

Domain	Risk of bias (Low-High-Unclear)	Support for judgment	Location in text
Random sequence generation (selection bias)			
Allocation concealment (selection bias)			
Blinding of participants and personnel (performance bias)			
Blinding of outcome (detection bias)			
Incomplete outcome data (attrition bias)			
Selective outcome reporting? (reporting bias)			
Other bias			

For case control studies

Domain	Location in text
Selection	
1. Is the case definition adequate? ☐ Yes, with independent validation (more than one person, reference to primary record source eg. biopsy report, chart, etc) ★ ☐ Yes, linked to record (eg. ICD code in database) or self-report but with no reference to primary record ☐ No description	
2. Representativeness of cases ☐ Consecutive of representative series of cases (eg. all eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organization, or an appropriate sample of those cases) ★ ☐ Not stated or not as above	
3. Selection of controls ☐ Community controls (i.e. same community as cases and would be cases if had outcome) ★ ☐ Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population ☐ No description	
4. Definition of controls ☐ If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded ★ ☐ No mention of history of outcome	
Comparability	
1. Comparability of cases and controls on the basis of the design or analysis a. Are cases and controls matched in the design eg. by age and sex? ☐ Yes ★ ☐ No b. Are confounders adjusted for in the analysis? Which ones? ☐ Yes ★ ☐ No	

Statements of no differences between groups or that differences are not statistically significant are not sufficient for establishing comparability. Age ★ Other confounders ★	
Exposure	
1. Ascertainment of exposure ☐ Secure record (eg surgical records) ★ ☐ Structured interview where blind to case/control status ★ ☐ Interview not blinded to case/control status ☐ Written self report or medical record only ☐ No description	
2. Same method of ascertainment for cases and controls ☐ Yes ★ ☐ No	
3. Non response rate ☐ Same rate for both groups ★ ☐ Non respondents described Rate different and no designation	

For cohort studies

Domain	Location in text
Selection	
1. Representativeness of exposed cohort ☐ Truly representative of the average of the community ★ ☐ Somewhat representative of the average of the community ★ ☐ Selected group of users eg. nurses, volunteers ☐ No description of derivation of cohort	
2. Selection of non-exposed cohort ☐ Drawn from the same community as the exposed cohort ★ ☐ Drawn from a different source ☐ No description of the derivation of the non exposed cohort	
3. Ascertainment of exposure ☐ Secure record (eg surgical records, pathology reports) ★ ☐ Structured interview ★ ☐ Written self report ☐ No description	
4. Demonstration that outcome of interest was not present at start of study ☐ Yes ★ ☐ No	
Comparability	
1. Comparability of cohorts on the basis of the design or analysis a. Are exposed and non-exposed matched in the design eg. by age and sex? ☐ Yes ★ ☐ No b. Were relative risks for exposure(s) of interest adjusted for confounders in the analysis? Which ones? ☐ Yes ★ ☐ No Statements of no differences between groups or that differences are not statistically significant are not sufficient for establishing comparability. Age ★ Other confounders ★	
Outcome	
1. Assessment of outcome ☐ independent blind assessment ★	

☐ record linkage ★ ☐ self report ☐ no description	
2. Was follow-up long enough for outcomes to occur? ☐ Yes ★ ☐ No	
3. Adequacy of follow-up of cohorts ☐ Complete follow up - all subjects accounted for ★ ☐ Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % follow up, or description provided of those lost) ★ ☐ Follow up rate < ____% and no description of those lost ☐ No statement	

Appendix 4 Runyankore-version of Skindex-16

PARTICIPANT STUDY ID	☐☐☐☐☐☐☐	Record Visit Date	☐☐/☐☐/☐☐
			DAY / MONTH / YEAR
Record Interviewer's Initials	☐☐☐	Record Visit Type	☐☐.☐

EBIBUBUZO BIKUKWATA AHA MBERA YOMUBIIRI EKUTEGANISE MUNOGA OMUSANDE EHWIRE

Omusande ehwire, nemirundi engahi eyoteganisibwe:	Tinteganisibwe ↓			.			Obwire bwona Nteganisibwe ↓
1. Omubiri gwawe kukurya	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Omubiri gwawe kukwotsya nings kukutonera	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Omubiri kukushasha	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Omubiri kuburwa obusingye	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. Okugumizamu ninga kugarukwamu oburwire bwomubiri	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. Okwerarikirira ahabwe embera yomubiri. Ekyokureberaho: okujanjara,okweyongera kubakubi, enkojo,obutatebereza embera nebinidi	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. Endebuka yomubiri gwawe	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. Okweyanga ahabwomubiri gwawe	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. Okushwara ahabwomubiri gwawe	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. Okunyiga ahabwomubiri gwawe	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. Okugira enaku ahabwomubiri gwawe	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. Omubiri gwawe kuteganisa okukwatanisa nabandi, ekyokureberaho: Okukwatanisa nabeka yawe, banywani bawe, nabandi abanyabuzare abakuhikire, nabandi	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. Ekyomubiri gwawe giresire obutenda kuba nabantu	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Omubiri gwewe kukuremesa kworeka okukunda	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. Ahabwomubiri gwawe gukozire aha mirimo yaburijo	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Omubiri gwawe kukugumiza okukora ninga kukoraekyorikukunda	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Appendix 5 English version of Skindex-16

PARTICIPANT STUDY ID	☐☐☐☐☐☐☐	Record Visit Date	☐☐/☐☐/☐☐
			DAY / MONTH / YEAR
Record Interviewer's Initials	☐☐☐	Record Visit Type	☐☐.☐

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓			•			Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Appendix 8 Study instrument for case control study - cases

(Chapter 4)

PARTICIPANT STUDY ID	☐☐☐☐☐☐☐
Record Interviewer's Initials	☐☐☐
Record Visit Date	☐☐/☐☐/☐☐ DAY MONTH YEAR
Record Visit Type	☐☐.☐

Reviewed By	☐☐☐ INITIALS ☐☐/☐☐/☐☐ DAY MONTH YEAR

A STUDY EXAMINING THE UTILITY OF THE PRESENCE OF ACTIVE SKIN DISEASE AFTER AT LEAST 15 MONTHS OF ANTI-RETROVIRAL THERAPY AS A PREDICTOR FOR TREATMENT FAILURE (PARTICIPANTS WITH SKIN DISEASE)

Eligibility Requirements

1. Are you experiencing a skin problem of greater than one month duration?
   O Yes O No

Environment

1. Do you have any animals?
   O Yes O No
   If yes, what type? _____
   If yes, do you they come inside the house? O Yes O No
2. Do you use mosquito netting?
   O Yes O No
3. Do you use any insect repellants on your skin?
   O Yes O No
4. What is your main job?_____
5. Do you work mostly indoors or outdoors?
   O Indoors O Outdoors
6. At what time of day do you work?
   O Day O Night
7. Do you see insect bites on your skin every day?
   O Yes O No

PARTICIPANT STUDY ID		Record Visit Date	/ /		
			DAY	MONTH	YEAR

8. What do you think normally bites you?_____
9. Have you ever had any skin problems in the past?

   O Yes O No

   If yes, have you ever had

   - Eczema? O Yes O No
   - Psoriasis? O Yes O No
   - Asthma? O Yes O No
   - Scabies? O Yes O No
   - skin reaction to medicines or drugs? O Yes O No

HIV related

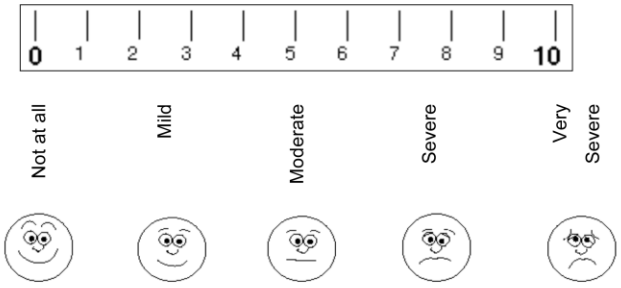
1. Have you ever been given trimethoprim-sulfamethoxazole (Septrin) prophylaxis (to prevent, not to treat illness)? O Yes O No

Questions regarding rash

1. When did your rash first appear?_____
2. Where did it first appear?_____
3. Where is the rash mostly located currently?_____
4. How itchy is it? (0 being no itch and 10 being very severe itch)

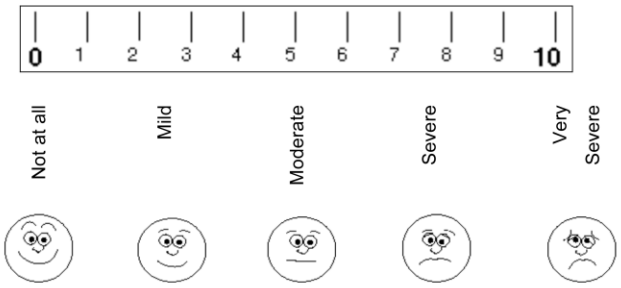
   Please mark with an "X" on the numbered scale below.

   Currently,



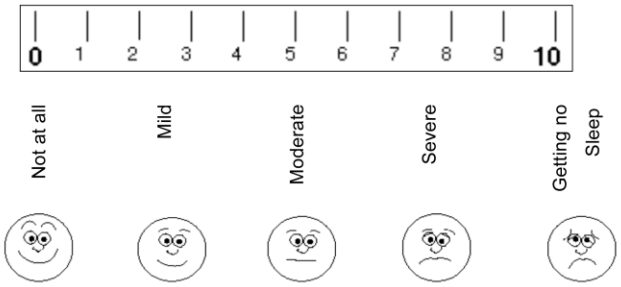
PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

At your last visit,



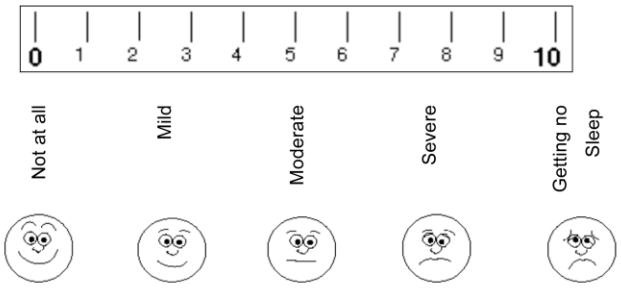
5. How much does the rash affect your sleep? (0 = not at all and 10 = getting no sleep)
   Please mark with an "X" on the numbered scale below.

   Currently,



PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

At your last visit,

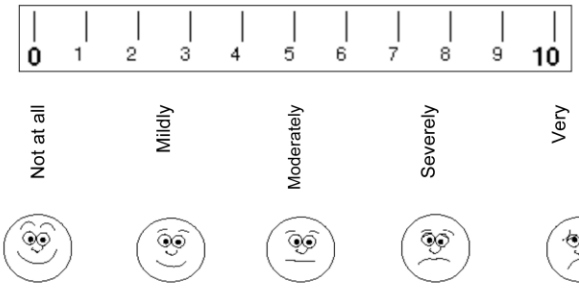


6. Do you scratch your skin till it bleeds?
   O Yes O No
7. Is it better or worse in the sun?
   O Better O Worse O No change O Don't know
8. How long does each spot usually stay itchy?
   O Less than 1 day
   O 1-7days
   O 1-2 weeks
   O 2-4 weeks
   O 1-3 months
   O More than 3 months
9. Has the rash caused your skin to change colour?
   O Yes O No

PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

If yes, how much does it affect you?

Please mark with an "X" on the numbered scale below.



10. Do you feel you have been discriminated against because of your rash?

O Yes O No

11. Does anyone else in your family have a similar rash?

O Yes O No

If yes, how are they related to you? _____

If yes, do you live together?

O Yes O No

12. Have you received treatment for this skin condition?

O Yes O No

If yes, what was the treatment? _____

Appendix 9 Study instrument for case control study - controls (Chapter 4)

PARTICIPANT STUDY ID ☐☐☐☐☐☐☐

Record Interviewer's Initials ☐☐☐

Record Visit Date ☐☐/☐☐/☐☐
DAY MONTH YEAR

Record Visit Type ☐☐.☐

Reviewed By ☐☐☐ INITIALS
☐☐/☐☐/☐☐
DAY MONTH YEAR

A STUDY EXAMINING THE UTILITY OF THE PRESENCE OF ACTIVE SKIN DISEASE AFTER 15 MONTHS OF ANTI-RETROVIRAL THERAPY AS A PREDICTOR FOR TREATMENT FAILURE (PARTICIPANTS WITHOUT SKIN DISEASE)

Eligibility Requirements

1. Are you experiencing a skin problem of greater than one month duration?
   O Yes O No

Environment

1. Do you have any animals?
   O Yes O No
   If yes, what type? _____
   If yes, do you they come inside the house? O Yes O No
2. Do you use mosquito netting?
   O Yes O No
3. Do you use any insect repellants on your skin?
   O Yes O No
4. What is your main job? _____
5. Do you work mostly indoors or outdoors?
   O Indoors O Outdoors
6. At what time of day do you work?
   O Day O Night

PARTICIPANT STUDY ID		Record Visit Date	/ /		
			DAY	MONTH	YEAR

7. Do you see insect bites on your skin every day?

   O Yes O No

8. What do you think normally bites you?_____

9. Have you ever had any skin problems in the past?

   O Yes O No

   If yes, have you ever had

   - Eczema? O Yes O No
   - Psoriasis? O Yes O No
   - Asthma? O Yes O No
   - Scabies? O Yes O No
   - skin reaction to medicines or drugs? O Yes O No

HIV related

1. Have you ever been given trimethoprim-sulfamethoxazole (septrin) prophylaxis (to prevent, not to treat illness)? O Yes O No

Appendix 10 Study instrument for cohort study - baseline (Chapter 5)

PARTICIPANT STUDY ID ☐☐☐☐☐☐☐

Record Interviewer's Initials ☐☐☐

Record Visit Date ☐☐/☐☐/☐☐
DAY MONTH YEAR

Record Visit Type ☐☐.☐

Reviewed By ☐☐☐ INITIALS
☐☐/☐☐/☐☐
DAY MONTH YEAR

A PROSPECTIVE STUDY TO EVALUATE THE CLINICAL RESPONSE OF SKIN DISEASE TO ANTI-RETROVIRAL THERAPY OVER A 2-YEAR PERIOD IN UGANDA
BASELINE FORM

Eligibility Requirements

1. Are you experiencing a skin problem of greater than one month duration?
   O Yes O No

Environment

1. Do you have any animals?
   O Yes O No
   If yes, what type? _____
   If yes, do you they come inside the house? O Yes O No
2. Do you use mosquito netting?
   O Yes O No
3. Do you use any insect repellants on your skin?
   O Yes O No
4. What is your main job? _____
5. Do you work mostly indoors or outdoors?
   O Indoors O Outdoors
6. At what time of day do you work?
   O Day O Night
7. Do you see insect bites on your skin every day?
   O Yes O No

PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

8. What do you think normally bites you?_____
9. Have you ever had any skin problems in the past?

   O Yes O No

   If yes, have you ever had

   - Eczema? O Yes O No
   - Psoriasis? O Yes O No
   - Asthma? O Yes O No
   - Scabies? O Yes O No
   - skin reaction to medicines or drugs? O Yes O No

HIV related

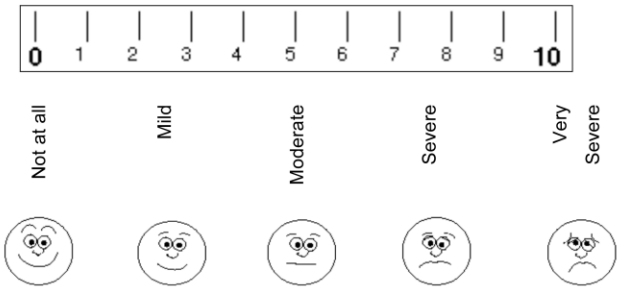
1. Have you ever been given trimethoprim-sulfamethoxazole (Septrin) prophylaxis (to prevent, not to treat illness)? O Yes O No

Questions regarding rash

1. When did your rash first appear?_____
2. Where did it first appear?_____
3. Where is the rash mostly located currently?_____
4. How itchy is it? (0 being no itch and 10 being very severe itch)

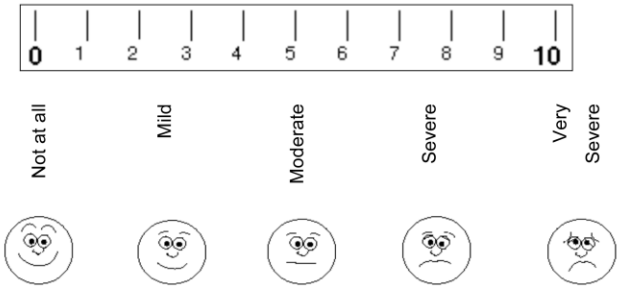
   Please mark with an "X" on the numbered scale below.

   Currently,



PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

5. How much does the rash affect your sleep? (0 = not at all and 10 = getting no sleep)
   Please mark with an "X" on the numbered scale below.



6. Do you scratch your skin till it bleeds?
   O Yes O No
7. Is it better or worse in the sun?
   O Better O Worse O No change O Don't know
8. How long does each spot usually stay itchy?
   O Less than 1 day
   O 1-7days
   O 1-2 weeks
   O 2-4 weeks
   O 1-3 months
   O More than 3 months

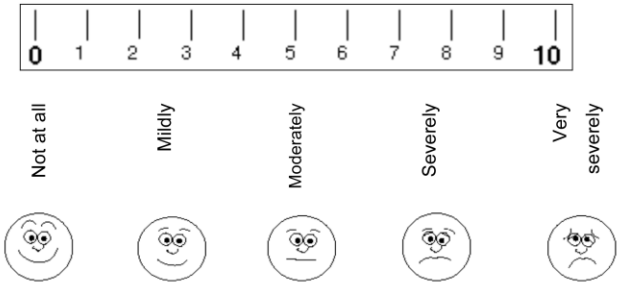
PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

9. Has the rash caused your skin to change colour?

O Yes O No

If yes, how much does it affect you?

Please mark with an "X" on the numbered scale below.



10. Do you feel you have been discriminated against because of your rash?

O Yes O No

11. Does anyone else in your family have a similar rash?

O Yes O No

If yes, how are they related to you? _____

If yes, do you live together?

O Yes O No

12. Have you received treatment for this skin condition?

O Yes O No

If yes, what was the treatment? _____

Appendix 11 Study instrument for cohort study - follow-up

(Chapter 5)

PARTICIPANT STUDY ID ☐☐☐☐☐☐☐

Record Interviewer's Initials ☐☐☐

Record Visit Date ☐☐/☐☐/☐☐ (DAY MONTH YEAR)

Record Visit Type ☐☐.☐

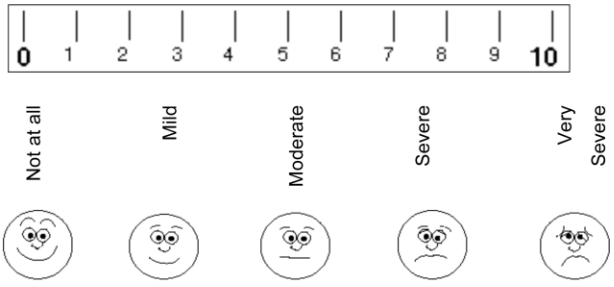
Reviewed By ☐☐☐ (INITIALS) ☐☐/☐☐/☐☐ (DAY MONTH YEAR)

Record the Date of the Last Time this Form was Completed ☐☐/☐☐/☐☐

A PROSPECTIVE STUDY TO EVALUATE THE CLINICAL RESPONSE OF SKIN DISEASE TO ANTI-RETROVIRAL THERAPY OVER A 2 YEAR PERIOD IN UGANDA
FOLLOW-UP FORM

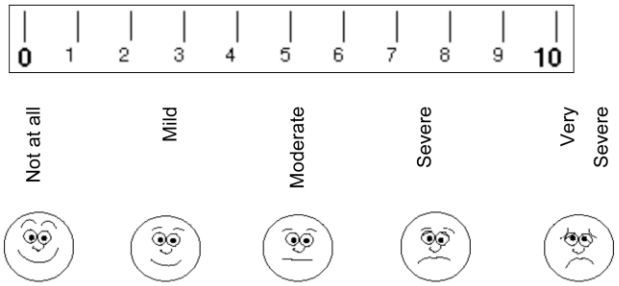
Questions regarding rash

1. Have you still got a rash?
   O Yes O No
2. Is this rash similar to what you had at the last visit?
   O Yes O No
3. Where is the rash mostly located currently?_____
4. How itchy is it? (0 being no itch and 10 being very severe itch)
   Please mark with an "X" on the numbered scale below.
   Currently,



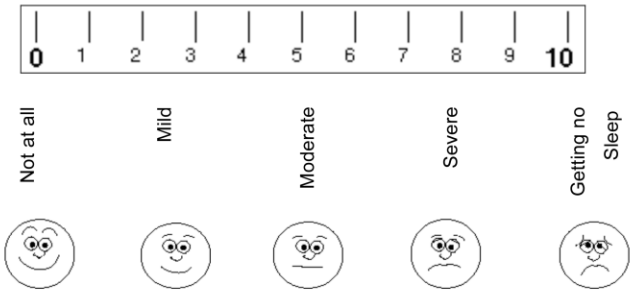
PARTICIPANT STUDY ID		Record Visit Date	/ /		
			DAY	MONTH	YEAR

At your last visit,

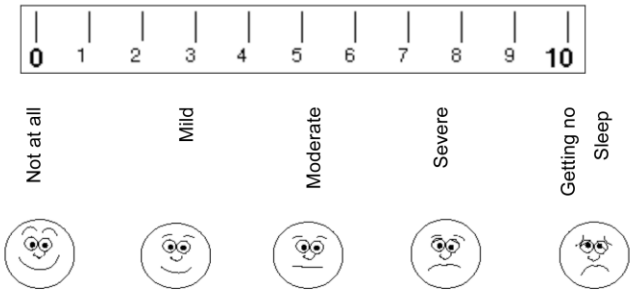


5. How much does the rash affect your sleep? (0 = not at all and 10 = getting no sleep)
   Please mark with an "X" on the numbered scale below.

   Currently,



   At your last visit,



PARTICIPANT STUDY ID		Record Visit Date	/ /
			DAY MONTH YEAR

6. Do you scratch your skin till it bleeds?

   O Yes O No

7. Is it better or worse in the sun?

   O Better O Worse O No change O Don't know

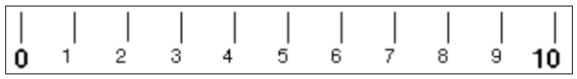
8. How long does each spot usually stay itchy?

   O Less than 1 day
   O 1-7days
   O 1-2 weeks
   O 2-4 weeks
   O 1-3 months
   O More than 3 months

9. Has the rash caused your skin to change colour?

   O Yes O No

   If yes, how much does it affect you?



Not at all Mildly Moderately Severely Very severely

10. Do you feel you have been discriminated against because of your rash?

    O Yes O No

11. Does anyone else in your family have a similar rash?

    O Yes O No

    If yes, how are they related to you? _____

    If yes, do you live together?

    O Yes O No

12. Have you received treatment for this skin condition?

    O Yes O No

    If yes, what was the treatment?_____