Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults

World Health Organization

WHO Library Cataloguing-in-Publication Data

Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults.

1.HIV Infections – complications. 2.Skin Diseases – therapy. 3.AIDS-Related Opportunistic Infections. 4.Guideline. 5.Child. 6.Adult. I.World Health Organization.

ISBN 978 92 4 154891 5 (NLM classification: WC 503.5)

Printed in Switzerland

Contents

Abbreviations and acronyms

3TC	lamivudine
ABV	vinicristine with bleomycin and doxorubicin
ACTG	AIDS Clinical Trials Group
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BSA	body surface area
BV	bleomycin with vincristine
CI	confidence interval
EFV	efavirenz
FTC	emtricitabine
GDG	Guidelines Development Group
GRADE	grading of recommendations, assessment, development and evaluation
GRC	Guidelines Review Committee
HAART	highly-active antiretroviral therapy
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
HR	hazard ratio
IRIS	immune reconstitution inflammatory syndrome
IV	intravenous fluids
IVIG	intravenous immunoglobulin
kg	kilogram
KOH	potassium hydroxide
KS	Kaposi sarcoma
m2	metre
MC	molluscum contagiosum
MCA	Department of Maternal, Newborn, Child and Adolescent Health
MD	mean difference
µg	microgram
mg	milligram
mm	millimetre
NNRTI	non-nucleoside reverse transcriptase inhibitor
OC	oropharyngeal candidiasis
OI	opportunistic infection
PI	protease inhibitor
PICO	Population, Intervention, Comparator, and Outcomes
PLD	pegylated liposomal doxorubicin
PPE	papular pruritic eruption

PUVA	psoralen combined with ultraviolet A
RCT	randomized controlled trial
RR	relative risk
SD	seborrhoeic dermatitis
SJS	Stevens-Johnson syndrome
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TIS	tumour-immune system-systemic illness
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
UVB	ultraviolet light – B (PUVA) therapy
VZV	varicella zoster virus
WHO	World Health Organization

Definitions of key terms

Kaposi sarcoma (KS): case definition
(**Note:** these case definitions are modified from the original AIDS Clinical Trials Group T0 and T1 definitions, and are intended as a general guide for treatment decision-making)

Mild/moderate Kaposi sarcoma may include the following:	Severe Kaposi sarcoma may include the following:
• Confined to skin and/or lymph nodes; • No symptomatic visceral disease; • No significant oral disease (i.e. does not interfere with chewing or swallowing; • No significant oedema affecting function; • Not functionally disabling or immediately life-threatening.	• Symptomatic visceral disease (pulmonary[a] or gastrointestinal[b]); • Extensive oral KS lesions which interfere with chewing or swallowing; • Painful or disabling tumour-associated facial/genital/peripheral oedema or ulcerated tumours; • Life-threatening or functionally disabling disease; • Progressive[c] or persistent KS despite antiretroviral therapy

[a] Symptomatic pulmonary KS, suggested by shortness of breath, hemoptysis or moderate/severe cough, which cannot be attributed to other pulmonary conditions.
[b] Symptomatic gastrointestinal KS, suggested by bleeding from mouth or rectum, which cannot be attributed to other gastrointestinal conditions.
[c] Progressive disease is defined as: an increase of 25% or more in the size of previously-existing lesions and/or the appearance of new lesions or new sites of disease and/or a change in the character of 25% of more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing symptomatic tumour-associated oedema or effusion is also considered to represent disease progression.

Seborrhoeic dermatitis: mild versus severe

Mild seborrhoeic dermatitis:
Scalp scaling or mild to marked erythema of eyebrows, eyelashes and the nasolabial fold.

Severe seborrhoeic dermatitis:
Seborrhoeic dermatitis involving multiple body sites, including face, chest, mid-back, axillae and groin, presenting with marked erythema and extensive greasy scaling. It may also involve the full body (erythrodermic).

Note: Cradle cap (scalp seborrhoeic dermatitis in newborns) is not included in these guidelines.

Tinea infections
Tinea is dermatophyte infection of keratinized tissue such as skin (*tinea corporis, tinea cruris, tinea faceii, tinea pedis, tinea manuum*), hair (*tinea capitis*) or nail (*tinea unguium*). Extensive tinea refers to infection of the hair or nail, or involving large areas of the body.

Molluscum contagiosum
Extensive: large numbers of lesions (perhaps more than 30) involving more than one body site (such as face and trunk, or trunk and genitalia).

Unusual distribution: extragenital sites in adults and genital involvement in children; also if it involves the mucocutaneous junction.

Herpes zoster

Herpes zoster is an infection caused by varicella zoster virus. It presents as painful cutaneous eruptions of clusters of vesicles over an erythematous base. They are distributed over a single dermatome (or two or more contiguous or non-contiguous dermatomes); they are invariably unilateral and do not cross the midline.

Rarely, the rash of herpes zoster can be more widespread and affect three or more dermatomes or present with scattered vesicles (numbering more than 20) outside the dermatome of primary involvement. This condition is called disseminated zoster. Disseminated zoster can be difficult to distinguish from varicella. It generally occurs only in people with compromised immune systems.

Scabies: mild/moderate versus severe/crusted

Scabies is classified into mild (10 lesions or less), moderate (11–49), severe (50 or more) and crusted forms.

Crusted scabies is an extreme form of scabies due to the profuse proliferation of mites that can occur in some people who have a weakened immune system or are elderly, disabled or debilitated. This variant is highly infectious and typically presents with widespread, scaly patches and crusted lesions. The fingernails can be thickened and discoloured. Itching may be minimal or absent in this form of scabies.

Classification of topical corticosteroids (WHO, 1997)

Corticosteroids, often simply called steroids, are anti-inflammatory drugs. Most are synthetic forms of cortisone, a hormone naturally made in the adrenal glands. Corticosteroids can be given orally or by injection. They may also be applied to the skin as a cream or an ointment (topical corticosteroids). The commonly-used systemic steroids include: prednisone, prednisolone, methylprednisolone, dexamethasone and hydrocortisone.

Topical corticosteroids can be subdivided into seven groups, with group one being the most potent and group seven the least potent (classification used in United States of America):

Group 1	Super high potency	e.g. clobetasol propionate 0.05%
Group 2	High potency	e.g. betamethasone diproprionate 0.05%
Group 3	Upper-mid potency	e.g. mometasone furoate 0.1% ointment
Group 4	Mid potency	e.g. mometasone furoate 0.1% cream
Group 5	Lower-mid potency	e.g. betamethasone valerate 0.1%
Group 6	Mild potency	e.g. flucinolone acetonide 0.01%
Group 7	Least potent	e.g. hydrocortisone 1%

Stevens-Johnson syndrome

Erythema multiforme is an acute, self-limited and sometimes recurring skin condition that is associated with certain infections, medications and other various triggers. Stevens-Johnson syndrome and toxic epidermal necrolysis, however, are more severe, potentially life-threatening disorders, the etiology of which is often attributed to medication.

Controversy exists in the literature with regard to the clinical definitions of these three conditions and whether they are distinct entities or represent a spectrum of one disease process. The consensus classification is as follows (Bastuji-Garin et al., 1993):[1]

- Erythema multiforme: detachment below 10% of the body surface area plus localized typical targets or raised atypical targets.
- Stevens-Johnson syndrome: detachment below 10% of the body surface area plus widespread macules or flat atypical targets.

[1] All of these conditions may have involvement of one or more mucous membranes (oral, genital or conjunctival).

- Overlap Stevens-Johnson syndrome-toxic epidermal necrolysis: detachment between 10% and 30% of the body surface area plus widespread macules or flat atypical targets.
- Toxic epidermal necrolysis with spots (with or without blisters): detachment above 30% of the body surface area plus widespread macules or flat atypical targets.
- Toxic epidermal necrolysis without spots: detachment above 30% of the body surface area with large epidermal sheets and without any macule or target.

Thrush

Candidiasis of the mouth, throat and vagina are often referred to as "thrush".

Acknowledgements

The Departments of Maternal, Newborn, Child and Adolescent Health and HIV/AIDS of the World Health Organization gratefully acknowledge the contributions that many individuals and organizations made to the development of these guidelines.

Guidelines Development Group

Co-chairs: Roderick Hay (International Foundation for Dermatology, United Kingdom) and **Toby Maurer** (University of California, San Francisco, USA).

GRADE methodologist: Robert Dellavalle (Department of Veterans Affairs Eastern Colorado Health Care System, USA).

Members

Anisa Mosam (Nelson Mandela School of Medicine, South Africa), **Anouk Amzel** (United States Agency for International Development, USA), **Dick Chamla** (United Nations Children's Fund, USA), **Ebunoluwa Aderonke Adejuyigbe** (Obafemi Awolowo University, Nigeria), **Elizabeth D. Pienaar** (South African Cochrane Centre, South African Medical Council, South Africa), **Esther Freeman** (Harvard Medical School, USA), **Hilda Angela Mujuru** (University of Zimbabwe College of Health Sciences, Zimbabwe), **Jennifer Cohn** (Médecins Sans Frontières, Switzerland), **John Stephen** (St. John's Medical College, India), **Kevin R. Clarke** (Centers for Disease Control and Prevention, USA), **Lut Lynen** (Institute of Tropical Medicine, Belgium), **Mamadou O. Diallo** (Centers for Disease Control and Prevention, USA), **Mark Bower** (National Centre for HIV Malignancy, Chelsea & Westminster Hospital, United Kingdom), **Piamkamon Vacharotayangul** (Srinakharinwirot University, Thailand), **Rosa Bologna** (Hospital de Pediatría Juan P. Garrahan, Argentina).

Kaposi sarcoma guidelines advisory group

Anisa Mosam (Nelson Mandela School of Medicine, South Africa), **Anurag K. Agrawal** (Children's Hospital and Research Center Oakland, USA), **Arax Bozadjian** (Médecins Sans Frontières, Switzerland), **Esther Freeman** (Harvard Medical School, USA), **Frederick Chite Asirwa** (Moi University, Kenya), **Ian Magrath** (International Network for Cancer Treatment, Belgium), **Jennifer Cohn** (Médecins Sans Frontières, Switzerland), **Margaret Borok** (University of Zimbabwe School of Medicine, Zimbabwe), **Mark Bower** (National Centre for HIV Malignancy, Chelsea & Westminster Hospital, United Kingdom), **Susan Krown** (AIDS Malignancy Consortium, USA), **Toby Maurer** (University of California, San Francisco, USA).

External Peer Reviewers

Ahmed Saadani Hassani (Centers for Disease Control and Prevention, USA), **Ameena Goga** (Medical Research Council, South Africa), **Andrew Mbewe** (World Health Organization, Nigeria), **Andrew Prandergast** (Queen Mary University, United Kingdom), **Assaye Kassie** (United Nations Children's Fund, Zimbabwe), **Christian Pitter** (Elizabeth Glaser Pediatric AIDS Foundation, USA), **Dorothy Mbori-Ngacha** (United Nations Children's Fund, Kenya), **Eihab alli Hassan Abbass** (Sudanese People Living with HIV Federal Association, Sudan), **Emilia H. Koumans** (Centers for Disease Control and Prevention, USA), **Jeff Martin** (University of California, San Francisco, USA) **Mary-Ann Davies** (University of Cape Town, South Africa), **Moses Bateganya** (Centers

for Disease Control and Prevention, USA), **Nandita Sugandhi** (Clinton Health Access Initiative, USA), **Natella Rahhmania** (George Washington University & Elizabeth Glaser Pediatric AIDS Foundation, USA), **Omar Sued** (Fundación Huésped, Argentina), **Rakesh Lodha** (All-India Institute of Medical Sciences, India), **Serge Eholie** (Medical School of the University of Abidjan, Côte d'Ivoire), **Teshome Desta** (World Health Organization, Zimbabwe), **Yibetal Assefa** (Federal HIV/AIDS Prevention and Control Office, Ethiopia).

Contributors to the GRADE systematic reviews and supporting evidence

Kaposi sarcoma

Esther Freeman (Harvard Medical School, USA), **Toby Maurer** (University of California, San Francisco, USA), **Oluwatoyin Gbabe** (Stellenbosch University, South Africa), **Charles L. Okwundu** (Stellenbosch University, South Africa), **Miriam Laker** (University of California, San Francisco, USA), **Philippa J. Easterbrook** (World Health Organization, Switzerland), **Jeffrey Martin** (University of California, San Francisco, USA), **Martin Dedicoat** (Birmingham Heartlands Hospital, United Kingdom).

Treatment of Kaposi sarcoma in children

Andrew Anglemyer (University of California, San Francisco, USA), **Anurag K. Agarwal** (Children's Hospital Research Center Oakland, USA), **George W. Rutherford** (University of California, San Francisco, USA).

Seborrhoeic dermatitis

John Stephen (St. John's Medical College, India), **Tony Raj** (St. John's Medical College, India), **Kedar Radhakrishna** (St. John's Medical College, India), **Tinku Thomas** (St. John's Medical College, India).

Papular pruritic eruption & eosinophilic folliculitis

Ser Ling Chua (University Hospital Birmingham, United Kingdom), **Kedar Radhakrishna** (St. John's Medical College, India), **John Stephen** (St. John's Medical College, India), **Mike Zangenberg** (World Health Organization, Switzerland).

Tinea infections

Mamadou O. Diallo (Centers for Disease Control and Prevention, USA), **Magdy El-Gohary** (University of Southampton, United Kingdom), **Esther J. van Zuuren** (Leiden University, Netherlands), **Hana Burges** (University of Southampton, United Kingdom), **Liz Doney** (University of Nottingham, United Kingdom), **Zbys Fedorowicz** (Cochrane Collaboration Awali, Bahrain), **Michael Moore** (University of Southampton, United Kingdom), **Paul Litle** (University of Southampton, United Kingdom).

Scabies

Dunja Vekic (St. Vincent's Hospital, Australia), **Lisa Abbott** (St. Vincent's Hospital, Australia), **Emily M. Asher** (University of California, San Francisco, USA), **Margot J. Whitfeld** (Skin and Cancer Foundation, Sydney, Australia).

Herpes zoster

Elissa M. McDonald (University of Auckland, New Zealand), **Johannes de Kock** (Wanganui Hospital, New Zealand), **Feliz S.F. Ram** (Massey University, New Zealand), **Cristina C. Chang** (Monash University, Australia), **Vivek Naranbhai** (Doris Duke Medical Research Institute, South Africa), **Allen C. Cheng** (Monash University, Australia), **Monica Slavin** (Peter MacCallum Institute, Australia), **John Stephen** (St. John's Medical College, India), **Kedar Radhakrishna** (St. John's Medical College, India), **Tinku Thomas** (St. John's Medical College, India), **Abijeet Waghmare** (St. John's Medical College, India).

Molluscum contagiosum

Paul Martin (London School of Hygiene & Tropical Medicine, United Kingdom), **Sinead Langan** (London School of Hygiene & Tropical Medicine, United Kingdom).

Oropharyngeal candidiasis

Elizabeth D. Pienaar (South African Cochrane Centre, South African Medical Research Council, South Africa), **Taryn Young** (South African Cochrane Centre, South African Medical Research Council, South Africa), **Haly Holmes** (University of Western Cape, South Africa).

Stevens-Johnson syndrome & toxic epidermal necrolysis

Monica Rani (University of Minnesota, USA), **Toby Maurer** (University of California, San Francisco, USA).

WHO staff and consultants

Lulu Muhe (Department of Maternal, Newborn, Child and Adolescent Health, Switzerland) and **Philippa Easterbrook** (Department of HIV/AIDS, Switzerland) led the development of these guidelines. They were assisted during the initial work by **Mike Zangenberg** (Department of Maternal, Newborn, Child and Adolescent Health, Switzerland). Other WHO staff who participated in the process included: **Elizabeth Mason** (Department of Maternal, Newborn, Child and Adolescent Health, Switzerland), **Frank Lule** (HIV/AIDS, Regional Office for Africa, Brazzaville), **Kasonde Mwinga** (Maternal and Child Health, Regional Office for Africa, Brazzaville), **Meg Doherty** (Department of HIV/AIDS, Switzerland), **Rajiv Bahl** (Department of Maternal, Newborn, Child and Adolescent Health, Switzerland), **Wilson Were** (Department of Maternal, Newborn, Child and Adolescent Health, Switzerland) and **Poul Erik Petersen** (Department of Chronic Diseases and Health Promotion/Oral Health Unit, Switzerland).

Peggy Henderson, consultant, prepared drafts of the guidelines, and did the final editing. **Philippa Easterbrook** wrote the section on Kaposi sarcoma. **John Stephen** provided technical inputs to the draft. **Nadia Pillai**, **Stephanie Sharabianlou** and **Elizabeth Centeno Tablante** supported WHO in the development of the draft as interns and volunteer respectively.

Funders

A grant from the **United States of America Centers for Disease Control and Prevention** supported the development of this publication. In addition, it provided support through releasing **Mamadou O. Diallo** for the technical preparation of the Guidelines Development Group meeting. Dr Diallo acted in his individual capacity while released. The **International Foundation for Dermatology (International League of Dermatological Societies**) also contributed funding.[1]

WHO is thankful to the institutions that contributed staff time and made other in-kind contributions to the guidelines development process.

[1] The International Federation of Dermatology receives some funding from industry, but this is specified funding to support specific projects. Commercial funding did not contribute to the development of this guideline.

Executive summary

Despite the increasing availability of effective antiretroviral therapy (ART) regimens, human immunodeficiency virus (HIV)-associated opportunistic infections (OIs) continue to cause considerable morbidity and mortality, particularly in resource-limited settings, where treatment coverage is still low and diagnoses are frequently made at an advanced stage of disease. The current poorer standards in management of OIs and co-morbidities and limited access to OI drugs contribute to high HIV-related mortality in many resource-limited settings.

Global guidance on the diagnosis, prevention and treatment of the major OIs and co-morbidities in adults and children has been lacking, and has been requested by many countries. To respond to this situation, the World Health Organization's (WHO) Department of Maternal, Newborn, Child and Adolescent Health (MCA), in collaboration with the Department of HIV/Acquired immunodeficiency disease (AIDS), has developed these guidelines on the treatment of common skin and oral conditions associated with HIV.

The objectives of these guidelines are to provide a summary of the key evidence and practice recommendations on the diagnosis and treatment of the main skin and oral conditions in HIV-infected adults and children. The primary audience for these guidelines is health professionals who are responsible for providing care to children, adolescents and adults in settings with HIV, primarily where resources are limited. They are also expected to be used by policy-makers and managers of HIV/AIDS and disease control programmes, health facilities and teaching institutions to set up and maintain care services.

These guidelines describe common HIV-related dermatologic and oral conditions in resource-limited settings and their differential diagnoses, and include treatment strategies that are likely to be available locally. Details are provided about an algorithmic tool being developed by a multi-agency group led by WHO to aid in diagnosis based on expert opinion by clinicians working in HIV dermatology.

The grading of recommendations, assessment, development and evaluation (GRADE) approach was followed throughout the development and review of the recommendations in these guidelines, and the steps involved and methodology are described. A review addressing a population, intervention, comparator and outcomes (PICO) question was carried out for each condition (three reviews were done for Kaposi sarcoma), with the search strategy and flow diagramme for inclusion of papers described in each.

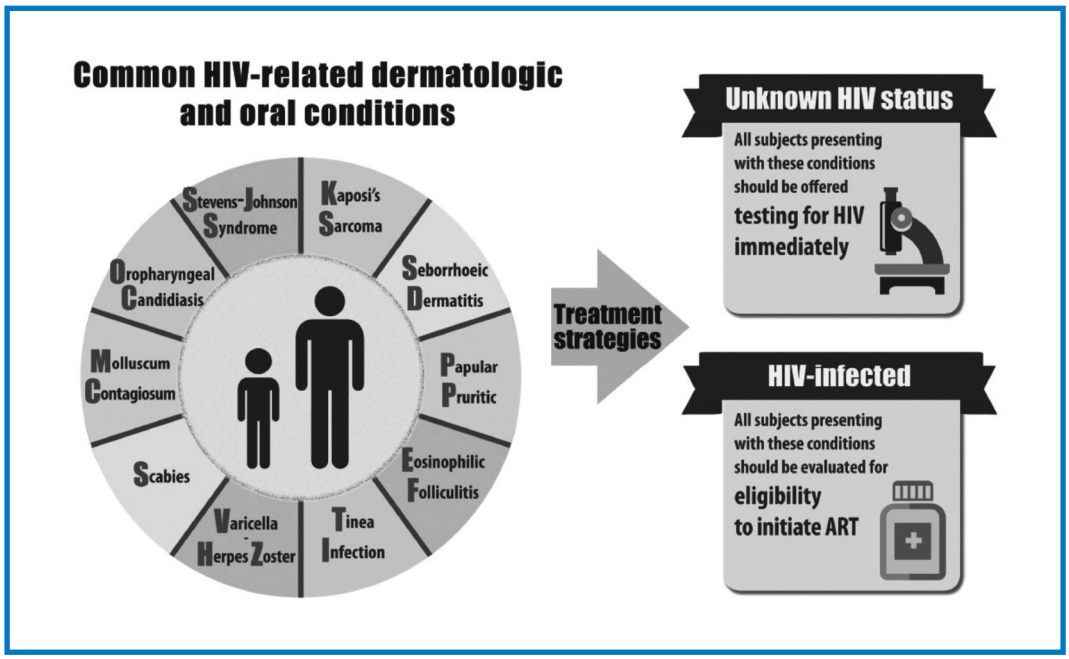
A final consensus meeting, attended by all members of the Guidelines Development Group (GDG), was held in Geneva on 25–27 September 2013. A range of evidence, assessments and evaluations was made available to the GDG in order to review, suggest revisions and approve the final recommendations during the meeting. Some further refinement of the recommendations took place through electronic communications and teleconferences after the meeting, and a peer review group offered comments on a draft document. The final recommendations were submitted for approval by the WHO Guidelines Review Committee. They appear in the **SUMMARY OF RECOMMENDATIONS** below.

General principles underlying the formulation of the recommendations are described. For each condition, specific treatment recommendations and a summary of the evidence are provided, and considerations relevant to implementation are noted. The final recommendations, as shown in the summary table, are meant to complement the *Consolidated guidelines on the use of*

antiretroviral drugs for treating and preventing HIV infection (WHO, 2013). The GDG made a "strong" recommendation after evaluating possible harms and benefits even when there was low quality of evidence.

The guidelines development process also identified key gaps in knowledge for each condition that will guide the future research agenda. These include issues around chemotherapy for Kaposi sarcoma, standardization of outcome measures, and more trials on different treatment regimens for other conditions, especially in the HIV-infected population.

The conditions addressed in these guidelines were selected on the basis of clear criteria, including the burden of disease in HIV-infected adults and children and the availability of evidence and effective interventions. They are Kaposi sarcoma, seborrhoeic dermatitis, papular pruritic eruption, eosinophilic folliculitis, tinea infections, herpes zoster, scabies, molluscum contagiosum, oropharyngeal candidiasis and Stevens-Johnson syndrome and toxic epidermal necrolysis (see **FIGURE**).



All adults (including pregnant women), adolescents and children with unknown HIV status presenting with the conditions included in these guidelines should be offered testing for HIV immediately. All known HIV-infected adults (including pregnant women), adolescents and children presenting with the conditions included in these guidelines should be evaluated (by clinical criteria or CD4 count) for eligibility to initiate antiretroviral therapy (ART). All known HIV-negative adults (including pregnant women), adolescents and children presenting with seborrhoeic dermatitis, tinea infections, herpes zoster, scabies, molluscum contagiosum, oropharyngeal candidiasis and Stevens-Johnson syndrome and toxic epidermal necrolysis should be evaluated and treated according to these guidelines.

The guidelines development process developed a clinical algorithm for recognition of common skin and oral conditions using morphology and typical pictures. A GDG subgroup made up of oncologists made recommendations on the staging and chemotherapy of Kaposi sarcoma in adults and children.

These recommendations will be disseminated through a broad network of international partners, and through updates of other relevant materials.

Summary of recommendations

The following table summarizes the new WHO recommendations formulated for the 2014 guidelines on the treatment of the main skin and oral conditions in HIV-infected adults and children.

These recommendations should be read in the context of **Section 3** Guiding principles for HIV testing, ART initiation and general HIV care.

TOPIC	RECOMMENDATIONS
Kaposi sarcoma	**Mild/moderate disease:** In HIV-infected adults, adolescents and children diagnosed with mild/moderate Kaposi sarcoma, immediate ART initiation is recommended. *(Strong recommendation, low quality evidence)* **Severe/symptomatic disease:** In HIV-infected adults, adolescents and children diagnosed with severe symptomatic Kaposi sarcoma, immediate ART initiation in combination with systemic chemotherapy is recommended. *(Strong recommendation, low quality evidence)* Recommended chemotherapy regimens in adults, adolescents and children may include vincristine with bleomycin and doxorubicin (ABV), bleomycin with vincristine (BV), and when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care. *(Conditional recommendation, low quality evidence)*
Seborrhoeic dermatitis	**Mild seborrhoeic dermatitis:** HIV-infected children and adults with mild seborrhoeic dermatitis (including on the scalp) should be treated with topical ketoconazole 2% two to three times per week for four weeks, with a maintenance treatment once per week as needed. *(Conditional recommendation, low quality evidence)* **Severe seborrhoeic dermatitis and seborrhoeic dermatitis unresponsive to first line therapy:** HIV-infected children and adults with severe seborrhoeic dermatitis and those patients with mild seborrhoeic dermatitis unresponsive to first-line therapy should be treated with a combination therapy of topical antifungals (e.g. ketoconazole 2%) and topical corticosteroids. *(Strong recommendation, very low quality evidence)* Patients with severe seborrhoeic dermatitis whose HIV status is unknown should be tested for HIV, and if positive, should be assessed for ART initiation according to WHO *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection*.
Papular pruritic eruption	In HIV-infected children, adolescents, pregnant women and adults with papular pruritic eruption, ART should be considered as the primary treatment. *(Strong recommendation, low quality evidence)* Additional symptomatic therapy with antihistamines and topical corticosteroids (class 3, 4, 5 or 6, e.g. betamethasone valearate) is also recommended for the duration of persistent symptoms. *(Conditional recommendation, very low quality evidence)*

TOPIC	RECOMMENDATIONS
Eosinophilic folliculitis	ART should be considered as the primary treatment of eosinophilic folliculitis in eligible patients. *(Strong recommendation, low quality evidence)* All HIV-infected adults (including pregnant women), adolescents and children who have been initiated on ART and who subsequently develop HIV-associated eosinophilic folliculitis should not discontinue the ART. *(Conditional recommendation, very low quality evidence)* Additional symptomatic therapy is recommended for the duration of the persistent symptoms with, depending on severity: • oral antihistamine; if no adequate response, add • topical corticosteroids (class 3, 4, 5 or 6, e.g. betamethasone valearate); if no adequate response, add • oral itraconazole; if no adequate response, add • permethrin 5% cream (applied above the waist). *(Conditional recommendation, very low quality evidence)*
Tinea infections	In children and adults (including pregnant women) with tinea infections that are not extensive, topical treatment with terbinafine 1% cream/gel (for two weeks) or miconazole (for three to four weeks) should be initiated. *(Strong recommendation, low quality evidence)* In children and adults with extensive tinea infections or hair/nail involvement, oral griseofulvin should be considered.[a] *(Conditional recommendation, very low quality evidence)* If there is no response, then oral terbinafine or itraconazole should be used. *(Conditional recommendation, very low quality evidence)* In children and adults having tinea infections with unknown HIV status, an HIV test should be offered. *(Strong recommendation, low quality evidence)*
Herpes zoster	For all HIV-infected children, adolescents and adults (including pregnant women) with herpes zoster, acyclovir is recommended to prevent dissemination and for resolution of disease (at any time in the course of the disease). *(Strong recommendation, low quality evidence)* All children, adolescents and adults presenting with herpes zoster with unknown HIV status should be offered an HIV test and, if positive, assessed for ART eligibility. *(Strong recommendation, low quality evidence)*
Scabies	**Mild/moderate scabies:** • For scabies in HIV-infected children and adults (including pregnant women) topical application of permethrin 5% (two applications) is recommended. If permethrin is not available, benzyl benzoate (at least two applications) should be used. • If there is poor response to treatment, or permethrin treatment is not feasible, then oral ivermectin at 200 µg/kg is recommended. *(Strong recommendation, low quality evidence)* **Severe/crusted scabies:** For severe or crusted scabies in HIV-infected children ≥15 kg and adults: • two doses (with one to two weeks in-between) of oral ivermectin; • if ivermectin is not available, then treat with topical permethrin 5% (or alternatively benzyl benzoate) until clinically clear, as longer treatments may be required. *(Conditional recommendation, very low quality evidence)* For severe or crusted scabies in HIV-infected children <15 kg, • topical permethrin 5% (or alternatively benzyl benzoate) until clinically clear, as longer treatments may be required. *(Conditional recommendation, very low quality evidence)* • In addition, a keratolytic, such as 5% salicylic acid, can be used to remove scale bulk. *(Conditional recommendation, very low quality evidence)*

[a] See **SECTION 8.2** for concerns regarding pregnant women.

TOPIC	RECOMMENDATIONS
Molluscum contagiosum	ART should be considered as the primary treatment of extensive and/or unusually distributed molluscum contagiosum in HIV-infected patients. No additional specific treatment is recommended. *(Conditional recommendation, very low quality evidence)* All adults presenting with new-onset molluscum contagiosum in high HIV-prevalence settings with unknown HIV status should be offered an HIV test and, if positive, assessed for ART eligibility. *(Strong recommendation, low quality evidence)*
Oropharyngeal candidiasis	**Specific therapy:** In adults: • Oral fluconazole 100–150 mg for seven to 14 days is recommended as the preferred treatment. • When fluconazole is not available or contraindicated, alternatives include topical therapy with nystatin suspension or pastilles, or clotrimazole troches. *(Strong recommendation, moderate quality evidence)* In children: • Oral fluconazole 3 mg/kg for children for seven to 14 days is recommended as the preferred treatment. • When fluconazole is not available or contraindicated, alternatives include topical therapy with nystatin suspension or pastilles, or clotrimazole troches. • In children with mild oropharyngeal candidiasis, topical therapy with nystatin suspension or pastilles (alternatively clotrimazole troches) is recommended. *(Strong recommendation, low quality evidence)* **ART eligibility:** • Prompt ART initiation is recommended in all HIV-infected adults (including pregnant and breastfeeding women), adolescents and children with orophyaryngeal candidiasis. *(Strong recommendation, high quality evidence)*
Stevens- Johnson syndrome & toxic epidermal necrolysis	In HIV-infected children and adults with Stevens-Johnson syndrome or toxic epidermal necrolysis, the suspected causative drug should be promptly discontinued and supportive therapies should be offered. *(Strong recommendation, very low quality evidence)* The use of systemic corticosteroids is not recommended. *(Conditional recommendation, very low quality evidence)*

1. Introduction

1.1 Background and context

Despite the increasing availability of effective antiretroviral therapy (ART) regimens, human immunodeficiency virus (HIV)-associated opportunistic infections (OIs) and related conditions continue to cause considerable morbidity and mortality, particularly in resource-limited settings. Global guidance on the diagnosis, prevention and treatment of the major OIs and co-morbidities in adults and children are lacking, and has been requested by many countries. The current poor standards in management of OIs and co-morbidities and limited access to OI drugs contribute to high HIV-related mortality in many resource-limited settings.

The World Health Organization's (WHO) Department of HIV/Acquired immunodeficiency virus (AIDS) recently released *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection* (WHO, 2013). To complement this guidance, the Department of Maternal, Newborn, Child and Adolescent Health (MCA), in collaboration with the Department of HIV/AIDS, has developed these guidelines on common skin and oral conditions associated with HIV.

1.2 Rationale for new guidelines

Despite increasing ART coverage and improvement of overall survival of HIV-infected patients in resource-limited settings (WHO et al., 2013), treatment coverage remains relatively low (e.g. 34% for children) and HIV presentation and diagnosis often occur at a late stage. As a result, HIV-associated conditions continue to cause considerable morbidity and mortality, particularly in resource-limited settings. Even in high-income settings, such conditions represent a problem due to late presentation with severe immunosuppression and ART failure.

The existing Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO guidelines on this topic were published in 1998, which was prior to the global "3 by 5" ART roll-out initiative in 2003. Since then, considerable new scientific evidence and programmatic experience has become available.

Although national OIs guidelines exist in some countries, they are frequently neither widely available nor regularly updated, and none have used graded evidence to support their recommendations.

Given this situation, there was a need for a standardized evidence-based grading of recommendations, assessment, development and evaluation (GRADE) approach on treatment and care of conditions that: includes HIV-related conditions; incorporates newer scientific evidence, programmatic experience and data relevant to resource-limited and middle-income settings; and includes overall benefits and harms, feasibility and cost implications of any interventions being recommended.

1.3 Why guidelines are needed

1.3.1 Major burden of HIV-related skin and oral diseases

Skin and mucosal conditions are extremely common in HIV-infected adults and children, particularly in resource-limited settings, affecting 90% of individuals during the course of their illness. They are one of the most common management problems faced by health care workers caring for patients with HIV infection. As the CD4 count declines below 200 cells/mm^3, the

prevalence, spectrum and severity of skin and oral conditions further increases (Goh et al., 2007).

Certain systemic diseases may be initially noted on the skin, such as Kaposi sarcoma, and can cause significant mortality. Other cutaneous conditions, while not always a major cause of mortality, can be a source of severe morbidity through, for example, intractable pruritus that provokes scratching, secondary infections, disfigurement, sleep disturbance and psychological stress, and oropharyngeal candidiasis that causes pain on swallowing. Many of the treatments used are also burdensome and costly.

HIV infection can also be a source of stigma in many societies. Physical signs in the form of skin diseases, such as papular pruritic eruption, that suggest the possibility of HIV infection may subject the affected person to discrimination. The desire to conceal the skin disease and avoid social contact may affect health-seeking behaviour (Muyinda et al., 1997). Concealment of skin disease at some sites, especially the head and neck, might be difficult. The ensuing embarrassment and stigma is likely to have a negative impact on self-esteem and quality of life (Schmid-Ott et al., 1996). Therefore, prompt resolution of the skin manifestations is a priority to the patients and their families.

1.3.2 Different manifestations of skin and oral conditions in the presence of HIV infection

HIV infection is associated with an increased risk for many common as well as uncommon skin and oral diseases. In addition, with HIV infection, some of these conditions (e.g. molluscum contagiosum, scabies, tinea infections and oropharyngeal candidiasis) tend to be more severe, have atypical presentations, respond less well to therapy and relapse more frequently (requiring multiple courses of therapy) than in the uninfected population (Aftergut & Cockerell, 1999; Dlova & Mosam, 2006a; Dlova & Mosam, 2005 & 2009). Drug eruptions are also 100 times more common in HIV-infected persons compared to the general population, and their prevalence rises as immunodeficiency increases in severity (Dlova & Mosam, 2006b; Battegay et al., 1989). Diagnosing and managing skin and oral conditions in the context of advanced immunosuppression is therefore challenging, and warrants specific guidance.

Mucocutaneous findings occur throughout the course of HIV infection. Some of the infectious dermatoses (such as mucocutaneous candidiasis, molluscum contagiosum, herpes zoster, persistent herpes simplex infection, Kaposi sarcoma and tinea infections) and some inflammatory disorders (including eosinophilic folliculitis, papular pruritic eruption and seborrhoeic dermatitis) show an inverse relation with CD4 cell count. These dermatoses can be used as a proxy indicator of advanced immunosuppression to start ART in the absence of facilities to carry out CD4 cell counts. The presentations of mucocutaneous manifestations in HIV-infected patients may be atypical and less responsive to treatment. Given the relative ease of examination of skin, and because most skin diseases are amenable to diagnosis by inspection and biopsy, evaluation of skin remains an important tool in the diagnosis of HIV infection.

1.3.3 Better recognition of indicator skin and oral conditions offers potential for earlier HIV diagnosis and ART initiation

Several infectious, inflammatory and neoplastic skin and oral conditions are pathognomonic of HIV/AIDS. For example, in Africa, Kaposi sarcoma, herpes zoster and oropharyngeal candidiasis have positive predictive values of more than 80% for the presence of HIV infection (Lim et al., 1990). Other skin problems that are suggestive of HIV infection include extensive seborrhoeic dermatitis and extensive molloscum contagiosum. In addition, some skin and oral conditions are often the first manifestation of HIV infection and serve as a sentinel diagnosis in at least 37% of individuals (Lim et al., 1990).

Early and correct diagnosis of skin and oral diseases in HIV-infected individuals allows for prompt management and improved quality of life. On the other hand, because dermatological and oral manifestations may be the first sign of HIV infection (and a surrogate marker of the severity of disease), offering HIV testing to affected individuals can lead to early diagnosis and early treatment with ART, and so in turn a decrease in disease progression and onward transmission.

1.3.4 *Changing profile of skin conditions with ART and impact of immune reconstitution inflammatory syndrome (IRIS)*

Although the advent of ART has decreased the incidence of HIV-related skin and oral problems, HIV treatment is associated with a range of other skin-related problems, such as adverse effects, an increased risk of drug reactions and IRIS skin diseases (unmasking of new skin disease or paradoxical worsening of existing dermatologic conditions). Cutaneous IRIS has been described in association with a range of infectious, inflammatory, neoplastic and autoimmune disorders, but now also with certain tropical skin diseases, such as leishmaniasis and leprosy.

1.3.5 *Limited diagnostic facilities and access to specialist dermatologists*

Scarce access to dermatological specialty care and limited educational resources can make diagnosing and treating skin diseases a challenge in resource-limited settings. Pathologists to confirm diagnosis of certain dermatologic conditions, such as Kaposi sarcoma, may also not be available in resource-limited settings, thus further complicating the prompt and appropriate diagnosis and care of HIV patients with these conditions. As front-line HIV care is increasingly delivered by a variety of providers with variable levels of training, there is a particular need for clear guidance on diagnosis and management of skin and oral diseases in the HIV clinic.

1.3.6 *Lack of existing evidence-based international and national guidelines*

Despite the importance of HIV-related skin conditions, there has been a striking lack of any international guidelines on their diagnosis and management. Few national authorities have addressed this issue, although the United States of America (USA) has recently issued guidance (Siberry et al., 2013; Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2014). Some national guidelines include algorithms on diagnosis and treatment of skin conditions, but they vary widely in their approach and recommendations, and none are specific for HIV.

1.3.7 *Need for guidance in ethnically diverse populations*

Medical research and literature regarding HIV- and AIDS-associated dermatologic disease have until recently focused on patterns of skin disease observed in caucasians in higher-income environments. Differences in skin pigmentation, climate, hygiene and other genetic, environmental, demographic and behavioural variables contribute to unique clinical presentations and epidemiologic patterns of HIV-associated skin disease in Africa and Asia compared with North America and Europe. Examples of such diseases with divergent characteristics in different populations include the papular pruritic eruption associated with HIV, Kaposi sarcoma and photodermatitis. There is a need for specific evidence-based guidance in ethnically diverse populations.

1.4 Objectives

The objectives of these guidelines are to provide a summary of the key evidence and practice recommendations on the diagnosis and treatment of the main skin and oral conditions in HIV-infected adults and children. These guidelines describe common HIV-related dermatologic and oral conditions in resource-limited settings and their differential diagnoses, and include treatment strategies that are likely to be available locally. While focusing on the treatment of HIV-infected individuals, they also note where the same treatment would be recommended for non HIV-infected populations.

1.5 Target audience

The primary audience for these guidelines is health professionals who are responsible for providing care to children, adolescents and adults in settings with HIV infection, primarily where resources are limited. These health professionals include physicians, nurses and auxiliary personnel providing primary health care. The guidelines are also expected to be used by policy-makers and managers of HIV/AIDS control programmes, health facilities and teaching institutions to set up and maintain care services. The information in these guidelines will be included in

job aids and tools for both pre- and in-service training of health professionals to improve their knowledge, skills and performance in HIV/AIDS care.

1.6 Scope of guidelines: which skin conditions to address?

The following criteria were used by the Steering Group for the guideline development process for selecting skin and oral HIV-associated conditions for prioritization in these guidelines:

- burden of disease in HIV-infected children and adults;
- severity of cutaneous disease or risk of progression of severe cutaneous disease;
- impact on prognosis of HIV infection;
- cutaneous conditions that would serve as markers of low CD4 count which would therefore lead to early initiation of ART;
- availability of prior/established evidence;
- applicability for primary health care in resource-limited settings;
- conditions for which effective interventions are available;
- lack of guidance in existing national/international guidelines.

The scope of the guidelines was somewhat modified after approval of the planning clearance form by the GRC. The two phases envisioned for the work were collapsed into one. A clinical algorithm (see **SECTION 2**) was developed on the basis of expert opinion and clinical experience, so that less emphasis was given to diagnosis in the reviews and recommendations. The list of conditions to be addressed was modified because some of them were found to be covered elsewhere, e.g. tuberculosis (TB), and only one oral condition was included.

Based on the agreed criteria, the following nine skin and one oral conditions affecting people living with HIV, including children, were selected to be addressed in these guidelines:

1. Kaposi sarcoma
2. Seborrhoeic dermatitis
3. Papular pruritic eruption
4. Eosinophilic folliculitis
5. Tinea infections
6. Herpes zoster
7. Scabies
8. Molluscum contagiosum
9. Oropharyngeal candidiasis
10. Stevens-Johnson syndrome and toxic epidermal necrolysis

The Steering Group recognizes that other common important skin conditions are not included, such as genital herpes, planar warts, impetigo, necrotizing ulcerative gingivitis and necrotizing (ulcerative) periodontitis.

1.7 Methodology

WHO follows the GRADE approach described below for the development and review of recommendations (Guyatt et al., 2008). The procedure outlined in the following sections was followed for the preparation of the guidelines. The GRADE tables produced as a result of this process are in **WEB APPENDIX 1**.

Quality of evidence was defined as the extent to which one could be confident that an estimate of effect or association was correct. The quality of the set of included studies reporting results for an outcome was graded as high, moderate, low or very low. The implications of these categories are detailled in **TABLE 1**.

TABLE 1. CATEGORIES OF EVIDENCE

LEVEL OF EVIDENCE	RATIONALE
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the effect.
Low	Further research is very likely to have an important impact on estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

The assessment of quality of studies was based on the following criteria:

- *Study design:* randomized controlled trials (RCTs) – individual or cluster RCTs; non-randomized experimental studies; or observational studies.
- *Risk of bias:* risk of selection bias – allocation concealment in RCTs and comparability of groups in observational studies; risk of measurement bias – blinding or objective outcomes; extent of loss to follow-up; appropriateness of analysis – intention-to-treat, adjustment for cluster randomization in cluster RCTs, adjustment for confounding in observational studies.
- *Consistency:* similarity of results across the set of available studies – direction of effect estimates, most studies showing meaningful benefit or unacceptable harm.
- *Precision:* based on the width of confidence intervals (CIs) of the pooled effects across studies.
- *Directness:* whether the majority of included studies evaluated interventions relevant to the identified questions.

Additional considerations included the magnitude of the effect, presence or absence of a dose-response gradient, and direction of plausible biases. GRADE tables from systematic reviews were cross-checked, and a discussion on benefits and harms, values and preferences of health care providers and policy-makers, and whether costs are qualitatively justifiable compared to the benefits in low and middle-income countries was drafted. No efforts were made to collate the values and preferences of the persons addressed by the guidelines. Data from observational studies were considered to have a risk of bias, thereby resulting in moderate quality of evidence, if there was no very serious risk of bias due to methodological issues, imprecision, consistency or directness. Thus, the highest possible quality of evidence when data were from observational studies was "moderate".

Recommendations were formulated and drafted in accordance with procedures outlined in the WHO *Handbook for guideline development* (WHO, 2012), and guided by the quality of evidence using the GRADE methodology.

1.7.1 Establish a Steering Group

A Steering Group, with members from different relevant WHO departments, has overseen the guidelines review process. WHO staff are listed in the **ACKNOWLEDGEMENTS**.

1.7.2 Establish a Guideline Development Group (GDG)

The duties of the GDG were to elaborate and agree upon the scoping questions, review evidence and other complementary assessments, reach consensus and update or establish new recommendations. The list of members with their specific function and affiliation is in the **ACKNOWLEDGEMENTS**. The group contained a balanced mix of scientists, researchers, programme managers, health care providers and implementing partners, with gender and geographic representation respected.

1.7.3 Establish a Peer Review Group

The duties of the Peer Review Group were to review the recommendations developed by the GDG. The list of members, from various countries and disciplines, with their affiliation is in the **ACKNOWLEDGEMENTS**.

1.7.4 Scope of the document and relevant outcomes

The Steering Group defined the scope of the recommendations based on programme experience and review of existing guidelines on this topic.

1.7.5 Formulate Population, Intervention, Comparator and Outcome (PICO) Questions

Major PICO questions and relevant outcomes were drafted and are listed under each condition in the recommendations section.

1.7.6 Conflict of interests

All GDG members were required to sign and submit a Declaration of Interests prior to participation in meetings. WHO staff assessed the Declarations prior to the GDG meeting to determine whether a conflict existed that might have precluded or limited anyone's participation. All members of the GDG declared no conflict of interest except one, a university professor who has provided consulting services to pharmaceutical companies.[1] After discussion and considering his expertise, he was allowed to participate.

1.7.7 Evidence retrieval, assessment and synthesis, and recommendation formulation process

The Steering Group oversaw the conduct and completion of the systematic reviews and GRADE tables for the PICO questions according to the following process:

- The PICO questions were reviewed and agreed upon by the Steering Group and, upon approval to proceed from the Guidelines Review Committee (GRC), were discussed via teleconference, email or in a meeting with the GDG.
- The evidence retrieval process for the PICO questions followed the standard outlined in the WHO *Handbook for Guideline Development* (WHO, 2012).
- A protocol for each systematic review was developed and included the search terms and strategy, and the populations, interventions, comparators and outcomes used to define the inclusion and exclusion criteria. The detailed search strategy for each PICO question was agreed upon after a series of discussions with the Steering Group and lead investigators. Each review includes a flow diagramme showing the numbers of studies excluded and included.
- Medline and Embase databases were used for identifying peer-reviewed publications. The WHO International Clinical Trials Registry Platform, the Cochrane Central Register of Controlled Trials, the International Standard Randomised Controlled Trial Number Register, and ClinicalTrials.gov were searched for future and on-going studies. Each step was presented and discussed during planned teleconferences with the GDG.
- The quality of the evidence for each PICO question was assessed using the GRADE methodology (www.gradeworkinggroup.org). The quality of the evidence for treatment interventions was graded as high, moderate, low or very low based on the definitions in the GRADE handbook (WHO, 2012). The GRADE tables in **WEB APPENDIX 1** were prepared using the GRADE profiler software, where appropriate.[2]

[1] Consulting services performed by Mark Bower were speaking engagements (fees of less than US$ 1000 each from GlaxoSmithKline, Bristol-Myers Squibb, Janssen, Abbott and Gallen); and research collaboration (with GlaxoSmith-Kline and the Medical Research Council, no income). He is also a trustee of St. Stephens AIDS Trust; guidelines committee chair/advisor (British HIV Association, European AIDS Clinical Society); and Medicus Regulatory Committee member (Medical and Healthcare Products Regulatory Agency).

[2] GRADE tables were not prepared for Stevens-Johnson syndrome or toxic epidermic necrolysis because of the nature of the studies.

- The systematic reviews and GRADE tables were shared with the GDG for identification of any missing evidence, additional comments and suggestions. The reviews (except for those in preparation at the time of publication of the guidelines) are available as published documents or web appendices.
- The decision-making tables were drafted including:
  - benefits and risks of interventions from a public health perspective;
  - cost and feasibility of implementing the recommended interventions (focusing on national programmes in resource-limited or other settings);
  - values, preferences and acceptability to programme managers and policy-makers, health care providers and people living with HIV.

1.7.8 GDG meeting

The final consensus meeting, attended by all members of the GDG, was held in Geneva on 25-27 September 2013. A range of evidence, assessments and evaluations was made available to the GDG in order to review, suggest revisions and approve the final recommendations during the meeting. The Department of HIV/AIDS oversaw the production of these materials. The objectives of the meeting were to:

- review the evidence summaries, GRADE reviews, evaluations of the risk-benefit analyses, the feasibility, costs and acceptability of the proposed recommendations;
- review the draft recommendations;
- develop consensus on and rank the strength of the final recommendations;
- identify implementation steps and tools required; and
- make recommendations for future research.

Decisions were made by consensus, that is, agreement on the general wording of a recommendation with no major dissent. Comments from the GDG and the Steering Group were recorded and summarized, and changes were incorporated prior to finalizing recommendations. Opposing views were resolved through discussion. Based on the quality of the evidence and the risk/benefit analyses, a guideline panel decided whether to make a strong recommendation, a conditional recommendation or no recommendation. When there was no consensus on a particular recommendation, a decision was made by a vote.

Following the meeting, draft guidelines were circulated to the GDG and the Peer Review Group, and their comments incorporated as appropriate. An advisory group on Kaposi sarcoma participated in teleconferences and commented on various drafts of that section. The group reached consensus on the recommendations through focusing on the public health approach to the problem considering the resources available in middle- and low-income situations.

The GDG identified important knowledge gaps that need to be addressed through primary research. In this guideline, recommendations based on evidence quality that was rated as 'very low' or 'low' require further research. Conversely, further research is not a priority for those recommendations based on evidence of 'moderate' or 'high' quality.

The identified knowledge gaps were prioritized by considering whether such research would be feasible, innovative, original, likely to promote equity and contribute to the improvement of management of the conditions included in these guidelines. The research gaps are listed under each condition.

1.8 Review and update of recommendations

These recommendations will be regularly updated as more evidence is collated and analysed on a continuous basis, with major reviews and updates at least every five years. The next major update will be considered in 2019 under the oversight of the WHO GRC.

2. Tool to aid in diagnosis of skin conditions

Simultaneous with the development of these guidelines, a multi-agency group, led by WHO, has been developing a tool to aid in the diagnosis of HIV/AIDS skin conditions. While the emphasis in these guidelines is on treatment, the tool focuses in addition on diagnosis, and therefore serves as a useful complement to these recommendations. It is described here as an additional resource for the target audience set out above.[1]

The development of this tool initially involved three steps:

1. PubMed review and ranking of prevalence of HIV-associated diseases in adults and children;
2. Identification of all existing algorithms and guidelines for diagnosis of HIV-associated skin conditions which included 17 national documents (seven from Asia, six from Africa, four from the Caribbean/Latin America), WHO guidelines and three textbooks; and
3. Development of an algorithmic tool.

The algorithmic tool was developed through expert opinion by clinical dermatologists working in HIV dermatology in India, South Africa, the United Kingdom and USA.

There were two iterations in the development of the algorithmic tool. The first iteration was developed using three different approaches that diagnosed 45 diseases (oral and genital diseases excluded). The three approaches included a topography map (disease by distribution on the body), a decision-making tree and a picture atlas (see **WEB APPENDIX 2**). Practitioners use the tool by first identifying basic morphology and then using one of the above approaches or a combination of them.

After input from dermatologists in the field, the tool was refined to include better diagnostic criteria, additional diagnoses of relevance and additional pictures of children and of skin diseases in diverse subjects.

This tool was designed to include the three approaches mentioned above and was formatted into large laminated cards that hang on a ring. These cards may either be distributed to individual practitioners or hang from the wall in a clinic setting.

To test the utility of this tool, field surveys were conducted in clinics in Moshi, United Republic of Tanzania; Durban, South Africa; Kampala, Uganda; and Eldoret, Kenya. Patients on whom the tool was used included HIV-infected children and adults, both on ART and not yet taking it. Practitioners completed both a global and an individual survey to determine user-friendliness, the overall approach and the usefulness of the tool to reach a diagnosis. The diagnoses by field practitioners were compared to a dermatologist's diagnosis in a small pilot study in which surveys and pictures were sent electronically through a smartphone device.

The decision-making tree and picture atlas were considered the most helpful and useful parts of the tool, while the topography maps were less frequently used. There was 90% agreement between field practitioners and the dermatologist in the pilot study.

The tool was presented for discussion at the GDG meeting in Geneva in September 2013. The next iteration of the tool will include skin diseases that are seen worldwide and need to be differentiated from HIV-related skin diseases. In addition, conditions which alert the practitioner that HIV testing is necessary and those in which there is special consideration for biopsy will be highlighted. This tool will be produced more widely, with plans for further field testing for ease of use and diagnostic validity.

[1] Note that some of the conditions in the algorithm could be severe enough to require hospitalization. Referral should be considered if there is no response after treatment is initiated.

3. Guiding principles for HIV testing, ART initiation and general care

Two guiding principles underpin the recommendations in this document:

- *All adults (including pregnant women), adolescents and children with unknown HIV status presenting with the conditions included in these guidelines should be offered testing for HIV immediately.*
- *All known HIV-infected adults (including pregnant women), adolescents and children presenting with the conditions included in these guidelines should be evaluated (by clinical criteria or CD4 count) for eligibility to initiate ART.*

These guiding principles are consistent with the recommendations included in WHO's *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection* (WHO, 2013). In generalized epidemics, provider-initiated testing and counselling should be recommended to everyone attending all health facilities, including medical and surgical services; sexually transmitted infection, hepatitis and TB clinics; public and private facilities; inpatient and outpatient settings; mobile or outreach medical services; services for pregnant women (antenatal care, family planning, and maternal and child health settings); services for key populations; services for infants and children; and reproductive health services. In concentrated and low-level epidemics, provider-initiated testing and counselling should be recommended in all health facilities for specific populations, including adults, adolescents or children who present with signs and symptoms or medical conditions that could indicate HIV infection.

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. Current guidance (WHO, 2013) recommends that national HIV programmes provide ART to all people with HIV with a CD4 count of 500 cells/mm^3 or less, giving priority to initiating ART among those with severe/advanced HIV disease or a CD4 count of 350 cells/mm^3 or less. It also recommends initiating ART in people with active TB or hepatitis B coinfection with severe liver disease, all pregnant and breastfeeding women with HIV, children below 5 years and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count. (See **ANNEX 1** for more details.)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Ideally, once-daily regimens are maintained as the preferred choices in adults, adolescents and children older than 3 years. For children younger than 3 years, this possibility may not be there as yet.

Another consideration in managing these opportunistic conditions is the WHO *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults* (WHO, 2006), which are currently being updated to indicate that individuals with any of the conditions mentioned in this document should be taking this drug long-term.

In some of these conditions, personal hygiene is an important preventive and care measure. Basic skin hygiene practices should be observed, and patients should be advised of the measures they can take themselves and for their families, especially infants.

When any of the conditions referred to in these guidelines do not respond to the recommended treatment, referral to a higher-level health facility should be considered.

4. Evidence and recommendations on Kaposi sarcoma (KS)

4.1 Background

KS, a tumour of endothelial cell origin, is an AIDS-defining illness caused by the human herpesvirus-8 (HHV-8). KS lesions are characterized by abnormal angiogenesis, inflammation and proliferation of spindled tumour cells infected with HHV-8. It remains the most common malignancy in people living with HIV, especially in sub-Saharan Africa (International Agency for Research on Cancer, 2012). Reported rates of HHV-8 infection in East and Central Africa are as high as 90% in adults, and between 25% and 60% in children (Sarmati, 2004; Kasolo et al., 2007). The roll-out of ART has had a profound influence on the epidemiology of HIV-associated KS, particularly in developed countries, and has been associated with a substantial reduction in KS incidence (Biggar et al., 2007; Franceschi et al., 2010; Msyamboza et al., 2012; Pipkin et al., 2011; Semeere et al., 2012; Simard et al., 2011; Polesel et al., 2010) and improved survival (Holkova et al., 2001). ART can also lead to KS lesion regression (Paparizos et al., 2002; Gill et al., 2002; Cattelan et al., 1999). However, despite the continued scale-up of ART, incidence of AIDS-related KS remains high in many countries in sub-Saharan Africa and is still associated with poor survival (Engels et al., 2006; Asiimwe et al., 2012).

4.1.1 Clinical features

Adults

The diagnosis is usually suggested by the characteristic appearance of skin lesions, which can present as macules, papules, nodules or plaques, ranging in colour from faint pink to purple to brown. These characteristic lesions may also be present on the oral and genital mucosa, with or without accompanying internal organ involvement. Associated dissemination to lymphatics may occur, with or without painful lymphoedema and/or lymphadenopathy. Visceral disease is present in a significant proportion of cases at presentation, but occurs at much higher rates in sub-Saharan Africa (Di Lorenzo et al., 2007). It may be symptomatic or an incidental finding, and typically involves the lungs, gastrointestinal tract and liver.

Children

The presentation and outcome of KS in children may differ from that in adults. For example, children often present without characteristic skin lesions. A distinct presentation with lymphadenopathic KS in young Ugandan children with higher CD4 counts has also been observed (Gantt et al., 2010) – an uncommon presentation in adults. This has implications regarding staging and treatment of paediatric KS, and use of adult staging criteria as the basis for selecting treatment may not be applicable in all cases.

4.1.2 Staging criteria

Adults

The AIDS Clinical Trials Group (ACTG) staging classification was developed in the pre-ART era to establish a common language to use in describing AIDS-associated KS (Krown et al., 1989) and was later shown to be associated with survival (Krown et al., 1997). The classification is based on three criteria: tumour extent (T), the status of the patient's immune system as measured by CD4 cell count (I) and presence of systemic symptoms (S). Each factor is further grouped into good risk (0) or poor risk (1). T0 disease is defined as KS that is limited to the skin but without oedema or ulceration, lymph node disease or minimal oral disease (e.g. flat palatal lesions). T1

disease is defined as the presence of tumour-associated oedema or ulceration, or extensive oral or gastrointestinal disease or other non-nodal visceral lesions (**TABLE 2**) (Krown et al., 1989; Krown et al., 1997).

TABLE 2. TUMOUR-IMMUNE SYSTEM–SYSTEMIC ILLNESS (TIS) STAGING SYSTEM FOR AIDS-RELATED KS AND PROGNOSIS

	GOOD PROGNOSIS (ALL OF THE FOLLOWING)	POOR PROGNOSIS (ANY OF THE FOLLOWING)
Tumour (T)	(T0) Tumour confined to skin and/or lymph nodes and/or minimal oral diseasea	(T1) Tumour-associated oedema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
Immune system (I)	(I0) CD4 cells ≥150/µl	(I1) CD4 cells <150/µl
Systemic illness (S)	(S0) No history of opportunistic Infections and/or thrush Absence of 'B' symptomsb Performance status: Karnofsky score ≥70	(S1) History of OIs and/or thrush Presence of 'B' symptoms[b] Performance status: Karnofsky score <70 Other HIV-related illness (e.g. neurological disease, lymphoma)

Adapted from Krown and colleagues (1989 & 1997).

[a] 'Minimal oral disease' defined as non-nodular KS confined to the palate.

[b] 'B' symptoms: unexplained fever, drenching night sweats, >10% involuntary weight loss, or diarrhoea persisting more than two weeks.

The TIS criteria were developed prior to the availability of ART. A subsequent study performed early in the ART era showed the validity of these criteria with respect to survival, but with different weighting of the TIS factors (Nasti et al., 2003), However, they may not sufficiently reflect the significant impact of ART on the prognostic importance of these three criteria and do not include other factors that may affect prognosis and treatment decisions (Krown, 2005).

Children

No uniform paediatric staging criteria or treatment regimen has been prospectively evaluated or validated. In some cases, treatment selection has been based on experience with adult patients, utilizing the TIS system cited above (Krown et al., 1989). However, the following staging classification system modified from Mitsuyasu (1987) and utilized by Stefan and colleagues (2011) has been used for paediatric KS, although it has not yet been validated:

- Stage I: <10 KS lesions isolated to the skin without significant associated oedema;
- Stage II: ≥10 KS lesions isolated to the skin, or lesions involving the palate/oral mucosa, subcutaneous nodules, lymph nodes and/or bone marrow (i.e., two cytopoenias not otherwise explained);
- Stage III: Disseminated KS involving the lymphatics resulting in lymphoedema (i.e., "woody" oedema) in the extremities and/or groin;
- Stage IV: Systemic KS, defined as pulmonary KS with noted infiltrates/effusions on chest radiography, abdominal involvement with intra-abdominal nodes, hepatomegaly and/or ascites and/or cardiac involvement with cardiomegaly and associated pericardial effusion.

4.1.3 Treatment strategies

In the pre-ART era, chemotherapy was frequently used alone to treat patients with KS. Currently, however, ART initiation is recommended for all patients with KS, but there are no universally agreed criteria for identifying those patients with KS who also require chemotherapy, and practices vary widely. While the presence of symptomatic visceral KS would be considered an indication for systemic chemotherapy in most settings, patients with widespread or ulcerated cutaneous disease, symptomatic oedema or oral-cavity disease may also be considered

suitable candidates for treatment with chemotherapy in many settings. Regimens commonly used in high-resource settings are single-agent liposomal anthracyclines (doxorubicin and daunorubicin) and single-agent paclitaxel. Other options, which are more widely used in lower-resource settings, include combination chemotherapy with BV, with or without non-liposomal doxorubicin. For those with less extensive skin involvement, ART alone may be sufficient to cause lesion regression. Localized therapies used both in the pre-ART era and together with ART for patients with symptomatic local disease or for cosmesis include radiotherapy, topical therapy and intralesional chemotherapy.

KS IRIS

A significant proportion (7% to 30%) of adult patients with KS may experience IRIS, characterized by an abrupt clinical worsening of KS, often with a prominent inflammatory component to the lesions and/or increase in oedema, in the initial weeks after ART initiation or change in ART regimen following treatment failure (Letang et al., 2013), accompanied by evidence of HIV suppression and/or improved immunocompetence. KS IRIS can be associated with significant mortality (Letang et al., 2013). In KS patients on ART, distinguishing KS IRIS from KS progression may be clinically challenging, and requires exclusion of ART non-adherence or failure of ART to achieve viral suppression. There is no standarized case definition of KS IRIS, which makes comparison of reported incidence rates challenging. Data on paediatric KS IRIS remain limited.

4.2 Recommendations

Mild/moderate disease
In HIV-infected adults, adolescents and children diagnosed with mild/moderate KS, immediate ART initiation is recommended.
(Strong recommendation, low quality evidence)

Severe/symptomatic disease
In HIV-infected adults, adolescents and children diagnosed with severe symptomatic KS, immediate ART initiation in combination with systemic chemotherapy is recommended.
(Strong recommendation, low quality evidence)

Recommended chemotherapy regimens in adults, adolescents and children may include vincristine with bleomycin and doxorubicin (ABV), bleomycin with vincristine (BV), and when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide, at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care.
(Conditional recommendation, low quality evidence)

Remarks

- *Chemotherapy can also be considered if KS is progressive despite ART.*
- *Whenever feasible, suspected KS lesions should be biopsied and diagnosis confirmed, especially before administration of chemotherapy.*
- *All patients should be evaluated for supportive and palliative care at diagnosis.*
- *All patients should be monitored for potential development of KS IRIS after ART initiation.*
- *Chemotherapy drugs, especially those administered during the first trimester of pregnancy, may cause serious adverse fetal effects.*

Kaposi sarcoma – classification/case definitions

(**Note:** these case definitions are modified from the original ACTG T0 and T1 definitions, and are intended as a general guide for treatment decision-making)

1. Mild/moderate KS disease may include the following:	2. Severe symptomatic KS disease may include the following:
• Confined to skin and/or lymph nodes; • No symptomatic visceral disease; • No significant oral disease (i.e. does not interfere with chewing or swallowing; • No significant oedema affecting function; • Not functionally disabling or immediately life-threatening.	• Symptomatic visceral disease (pulmonary[a] or gastrointestinal[b]); • Extensive oral KS lesions which interfere with chewing or swallowing; • Painful or disabling tumour-associated facial/genital/peripheral oedema or ulcerated tumours; • Life-threatening or functionally disabling disease; • Progressive[c] or persistent KS despite ART

[a] Symptomatic pulmonary KS, suggested by shortness of breath, hemoptysis or moderate/severe cough, which cannot be attributed to other pulmonary conditions.

[b] Symptomatic gastrointestinal KS, suggested by bleeding from mouth or rectum, which cannot be attributed to other gastrointestinal conditions.

[c] Progressive disease is defined as: an increase of 25% or more in the size of previously existing lesions and/or the appearance of new lesions or new sites of disease and/or a change in the character of 25% of more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing symptomatic tumour-associated oedema or effusion is also considered to represent disease progression.

4.3 Review question and summary of evidence

Three systematic reviews were undertaken: two linked reviews on treatment in adults with mild/moderate disease and adults with severe KS, and one in children.

Mild/moderate disease

The systematic review was based on the PICO question: in HIV-infected ART-naïve adults diagnosed with mild/moderate KS, not requiring immediate anti-KS therapy (P), does the use of ART alone (I) compared to ART plus any additional therapy (chemotherapy, radiation, intralesional injections or topical therapy) (C), improve survival or clinical response (includes complete, partial, stable or progressive disease) (O). Secondary outcomes were time to response, KS IRIS, adverse events (including toxicity and/or worsening of co-existent disease), adherence and quality of life (Freeman et al., in press).

Chemotherapy with ART versus ART alone: No RCTs or observational studies have been specifically designed or powered to address the value of adding chemotherapy to ART compared to ART alone, in patients with mild to moderate KS. Two studies, one RCT in South Africa (Mosam et al., 2012) and one cohort from France (Dupin et al., 1999), compared ABV with ART versus ART alone, and a further two – one Spanish RCT (Martin-Carbonero et al., 2004) and one United Kingdom cohort (Bower et al., 2014) compared liposomal anthracyclines plus ART to ART alone. However, all these studies included patients at different stages of KS disease, and the number of participants with mild/moderate disease ranged from three to 213. None identified a significant mortality or treatment response benefit to the addition of either ABV or liposomal anthracyclines to ART in patients with mild to moderate ART-naïve KS.

Two studies (Letang et al., 2013; Mosam et al., 2012) examined the development of KS IRIS as an endpoint. Among patients with mild to moderate KS, none developed KS IRIS in either treatment arm in the trial from South Africa (Mosam et al., 2012). In the United Kingdom cohort within the multisite cohort study (Letang et al., 2013), six of the 77 patients with mild to moderate disease who received ART alone did so, in comparison to none of the seven observed in the chemotherapy plus ART arm (additional non-published data from authors). There were limited data on adverse events among those with mild to moderate KS, with no Grade III-V adverse events reported in the RCT (Mosam et al., 2012), and in only three patients out of 28 receiving chemotherapy in one cohort study (Martin-Carbonero et al., 2004; Freeman et al., in press).

Protease inhibitor (PI)-based ART versus non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART: A large RCT from Uganda compared PI versus NNRTI-based ART regimens in treatment-naïve patients with mild to moderate KS, and found no difference in overall survival or KS progression-free survival (Martin et al., 2013).

Radiation therapy, use of locally-injectable agents and topical therapy: Although there are many studies from the pre-ART era comparing different radiation dosages or examining the use of intralesional injections of chemotherapeutic agents (such as bleomycin, vincristine or vinblastine), none compared ART alone to ART plus radiotherapy, or intralesional chemotherapy. Similarly, none of three studies of topical retinoids met the criteria for inclusion in the review, because of a mix of different KS stages and/or lack of uniform receipt of ART (Bodsworth et al., 2001; Duvic et al., 2000; Walmsley et al., 1999).

Severe disease

The systematic review was based on the PICO question: in HIV-infected adults (receiving and not receiving ART) diagnosed with severe KS (defined as ACTG T1 disease, or when ACTG staging not available, as visceral KS, oedema affecting function, oral KS interfering with chewing or swallowing, tumours with ulceration, or life-threatening KS) (P), the interventions (I) and comparisons (C) were as follows: any chemotherapy regimen in combination with ART (I) compared with ART alone (C); any chemotherapy regimen alone (I) compared to ART alone (C); one chemotherapy regimen, e.g. liposomal anthracyclines (I), compared to another chemotherapy regimen (C), e.g. ABV, with or without the presence of ART. Outcome measures (O) were survival or clinical response (includes complete, partial, stable or progressive disease). Secondary outcomes were time to response, KS IRIS, adverse events (including toxicity and/or worsening of co-existent disease), adherence and quality of life (Gbabe et al., in press).

The review included six RCTs conducted in the USA (Cianfrocca et al., 2010; Cooley et al., 2007; Gill et al., 1996), Spain (Martin-Carbonero et al., 2004), South Africa (Mosam et al., 2012) and Zimbabwe (Olweny, et al., 2005); and three observational studies from the United Kingdom (Bower et al., 2009), Germany (Grünaug et al., 1998) and Venezuela (Hernández & Pérez, 1997). The number of patients with T1 stage disease ranged from 29 to 227 (Grünaug et al., 1998; Hernández & Pérez, 1997; Cianfrocca et al., 2010; Bower et al., 2009; Cooley et al., 2007; Gill et al., 1996). None of the studies had the same interventions, and therefore pooled analyses were not possible.

ART plus chemotherapy versus ART alone was compared in two trials. *ABV plus ART versus ART alone* was compared in an RCT from South Africa (Mosam et al., 2012) which excluded patients requiring urgent chemotherapy. No survival benefit was observed, but the overall clinical response (complete plus partial) favoured ABV plus ART (RR 1.78; 95% CI 1.16 to 2.72), and there was also less disease progression in this arm (RR 0.1; 95% CI 0.01 to 0.75). There were similar rates of adverse events. *Pegylated liposomal doxorubicin (PLD) plus ART versus ART alone* was examined in one very small RCT with five patients with severe disease in each arm, which appeared to favour liposomal anthracyclines in terms of treatment response but did not reach statistical significance (Martin-Carbonero et al., 2004)

ART plus chemotherapy versus ART plus a different chemotherapy regimen was examined in two RCTs. Cianfrocca and colleagues (2010) compared ART plus paclitaxel to ART plus liposomal anthracyclines, and found no difference in treatment response or survival between the two arms. Cooley and colleagues (2007) compared ART plus PLD to ART plus liposomal daunorubicin and similarly found no difference.

Chemotherapy versus a different chemotherapy regimen in the pre-ART era was compared in one RCT (Gill et al., 1996) of liposomal daunorubicin versus ABV in patients not on ART. The overall response and progression were similar in both arms. In one cohort study (Grünaug et al., 1998), mortality was three times higher in those patients who received either ABV or no chemotherapy, in comparison to PLD (survival time 11.8 months versus 4.4 months, $p<0.01$).

Two large RCTs that were part of a previous Cochrane review (Dedicoat et al., 2009) were excluded from this review because of a mix of KS stages. They compared PLD with ABV (Northfelt et al., 1998) or PLD with BV (Stewart et al., 1998) without ART (total 499 patients). Mortality was similar across the treatment arms (RR 1.26; 95% CI 0.83 to 1.91), but PLD had a superior clinical response rate (complete plus partial) (RR 2.16; 95% CI 1.68 to 2.78) without an increase in toxic side effects. Additionally, there were fewer withdrawals in the PLD arm (RR 0.57; 95% CI 0.48 to 0.68), but more OIs (RR 1.42; 95% CI 1.12 to 1.80).

No studies were identified that evaluated the optimal timing of ART in relation to chemotherapy (i.e. whether chemotherapy should be initiated prior to ART, and duration prior to ART initiation).

Children

In a systematic review of studies in children based on the same PICO questions (Anglemyer et al., 2013), four cohort studies from Malawi (Cox et al., 2013), Mozambique (Vaz et al., 2011), South Africa (Stefan et al., 2011) and Uganda (Gantt et al., 2010) were identified that involved retrospective analysis of chart review data in hospitalized children. These studies included a mix of KS severities. The regimens examined included ABV, BV, vincristine alone, and paclitaxel. No RCT was identified, and in general the data were not adequately adjusted for stage of disease or co-morbidities. Overall the quality of evidence was rated as very low.

Chemotherapy plus ART versus ART alone

The use of ART together with a chemotherapy regimen (ABV/BV/V) compared to ART alone increased the likelihood of partial or complete KS remission in one cohort (88.5% of 26 children versus 15.4% of 13 children; RR 5.75; 95% CI 1.59-20.73), although there was no significant difference in risk of death (Gantt et al., 2010). A pooled analysis of two cohorts showed no difference in complete response to chemotherapy (Cox et al., 2013; Gantt et al., 2010).

Chemotherapy plus ART versus chemotherapy alone

Data are again limited to two cohorts, and quality of evidence rated as very low. The use of ART together with a chemotherapy regimen compared with chemotherapy alone increased the likelihood of complete KS remission and reduced the risk of death. Analysis of two cohorts (Cox et al., 2013; Stefan et al., 2011) showed the addition of ART over chemotherapy alone provided survival benefits (pooled RR=0.46; 95% CI 0.29-0.72). In a further cohort (Gantt et al., 2010) there was no difference in overall (complete plus partial) clinical response or complete clinical response in patients with known outcomes.

Type of chemotherapy

There are limited data on the relative benefits of ABV versus BV or paclitaxel regimens in children. No studies were identified on liposomal doxorubicin, although it is being used for the treatment of KS in children in higher-income settings. Given the small sample size in these studies, it was not possible to determine whether there was a difference in the proportion with complete or partial remission between use of ART plus vincristine versus ART plus BV (Gantt et al., 2010). The use of paclitaxel specifically in paediatric KS patients was reported in one study (Vaz et al., 2011). Cox and colleagues (2013) reported mortality among children treated with combination chemotherapy and ART versus children treated with single agent chemotherapy and ART. Of 36 children treated with combination chemotherapy and ART, 13 died by 12 months of follow-up; all 14 children treated with single agent chemotherapy and ART died (RR 0.38; 95% CI 0.24 to 0.58).

4.4 Rationale for recommendations

The GDG identified improvement in survival, regression of KS lesions and avoidance of treatment-limiting adverse events as the most critical outcomes to consider in the evaluation of evidence and formulation of recommendations. They also considered the overall benefits and harms, feasibility and cost of ART and additional chemotherapy.

ART initiation

The GDG endorsed the prompt initiation of ART as the most important intervention in all patients with KS regardless of stage of disease, in order to improve survival and reduce morbidity through immune recovery and reduction in OIs. It was recognized that ART may result in KS lesion regression in some cases. Since 2006, WHO has recommended ART initiation in patients with KS or other WHO stage 3 or 4 disease in successive guidelines (WHO, 2013), and it has been associated with a marked improvement in survival and morbidity. ART is also widely available in HIV programmes at low cost (US$ 120 per patient per year), is well tolerated and requires minimal monitoring. This recommendation can therefore be readily implemented at all levels of service delivery, including at primary health care centres. However, where possible, patients with KS should first be evaluated at a site that has familiarity with KS and KS treatment.

PI and NNRTI regimens were equally effective in those with KS (Martin et al., 2013). Therefore the current preferred WHO recommended regimen of tenofovir disoproxil fumarate (TDF)+ lamivudine (3TC)/emtricitabine (FTC)+efavirenz, which is available as a fixed dose combination of one pill once a day, can be used.

Use of chemotherapy

Although ART by itself may induce regression of KS lesions, the resolution of KS with ART may be a slow process over several months, as it usually follows the recovery of cell-mediated immunity in the host. It may also have little effect on severe disseminated disease. Furthermore, use of ART alone may be complicated by IRIS, especially in those with severe KS (Letang et al., 2013).

In contrast to the major impact of ART on mortality, the evidence review demonstrated that the main added contribution of chemotherapy in KS patients who will initiate ART is to achieve more rapid regression and remission of significant KS lesions, and in turn provide potential relief of symptoms (such as lymphoedema), and improvement in quality of life. Studies have not yet shown a mortality benefit, although many were of limited sample size and were not powered to detect survival differences. An additional benefit may be to reduce the risk of developing life-threatening ART-associated KS IRIS. Potential harms of chemotherapy include significant toxicities in some cases. Other challenges include the limited access and relatively high cost of chemotherapy drugs in resource-limited settings, where there are also few specialist sites with the infrastructure to safely administer and monitor chemotherapy drugs.

Selection of patients for chemotherapy

There are currently no standardized or universally accepted criteria to guide which HIV-infected adults or children with KS would benefit most from concomitant chemotherapy in addition to receiving ART. Some practitioners (Bower et al., 2014) have advocated using T staging as the primary criterion for treatment planning. Using this approach, patients with T1 stage disease were treated with ART plus systemic chemotherapy, and those with T0 disease with ART alone. In other settings, symptomatic or functionally disabling KS has been used as the main indication for systemic chemotherapy in addition to ART. For example, in one study (Mosam et al., 2012), functionally disabling KS was considered an exclusion to participation in a randomized trial that compared ART alone to ART plus chemotherapy, since patients so affected were considered to require immediate treatment with combined chemotherapy and ART.

The GDG recognized the need for easily-recognized and objective clinical criteria that can be used by all levels of health care workers to guide which patients need prompt referral and assessment for chemotherapy, in addition to use of ART. Extent of tumour alone (based on the

ACTG criteria) may be insufficient to guide who should be prioritized for urgent chemotherapy, as some patients with T1 disease may lack significant KS-related symptoms, whereas others with T0 disease may have extensive skin involvement that adversely affects quality of life and social functioning. Other factors to be considered include presence of distressing or functionally-disabling symptoms (Krown, 2004 & 2005). A simple categorization of KS into mild/moderate KS and severe symptomatic KS based in part on the original ACTG tumour extent criteria was used, with some additional clinical criteria to capture functionally-disabling complications of KS. These two categories do not capture all clinical scenarios, and, for example, do not consider asymptomatic visceral disease. Additional factors noted by the GDG that may help determine priority for immediate chemotherapy include rate of progression, quality of life, presence of other co-morbidities, contraindications to chemotherapy and the wishes of the patients and their families. The GDG recommended that those with severe KS and functionally-disabling symptoms merit urgent referral for chemotherapy in addition to ART. For those with less-extensive skin involvement, ART alone may be sufficient to cause lesion regression; if this fails, chemotherapy remains a future option. The GDG noted that the definitions of mild to moderate KS that may be managed by ART alone, and of severe KS requiring prompt chemotherapy, is a research gap that needs to be addressed, as are the potential benefits of earlier institution of chemotherapy in selected patients with mild to moderate KS.

Other treatments

No specific recommendations were made for the use of local therapies. Local therapies are limited by their inability to treat large areas or to affect the development of lesions in other areas, although they may sometimes be useful for managing localized or symptomatic KS lesions, or for cosmesis. Similarly, although radiotherapy was used in the past for the management of localized cutaneous KS, this was not felt to be a generally feasible intervention for resource-limited settings, as it was costly, as well as being less convenient for patients.

4.5 Other considerations for implementation and in choice of chemotherapy regimen

See **TABLE 3** for commonly-used chemotherapy regimens.

TABLE 3. COMMONLY-USED CHEMOTHERAPY REGIMENS FOR HIV-ASSOCIATED KS IN ADULTS

REGIMEN	DOSE PER CYCLE	ROUTE	FREQUENCY OF CYCLES
Doxorubicin/bleomycin/vincristine (ABV)	A: 15–20 mg/m^2 B: 10–15 mg/m^2 V: 1 mg–1.4 mg/m^2 (max 2 mg)	IV IV IV	Every 3–4 weeks
Bleomycin/vincristine (BV)	B: 15 U/ m^2 V: 1.4 mg/m^2 (max 2 mg)	IV IV	Every 3 weeks
Pegylated liposomal doxorubicin (PLD)	20 mg/m^2	IV	Every 3 weeks
Liposomal daunorubicin	40 mg/m^2	IV	Every 2 weeks
Paclitaxel	100 mg/m^2	IV	Every 2–3 weeks
Etoposide	100–200 mg daily x 7 days	Oral	Every 2–3 weeks

Note: This list is not intended to be comprehensive; alternative drug doses and schedules have been used. Drug doses and schedules may need to be modified for pre-existing organ dysfunction and/or treatment-associated adverse events. Maximum cumulative dose of doxorubicin is 450 mg/m^2 and maximum cumulative dose of bleomycin is 400 U/m^2 body surface area. Maximum cumulative doses of liposomal anthracyclines (i.e. PLD and liposomal daunorubicin) have not been systematically studied.

4.5.1 *Drug availability and cost*

There remains limited access to chemotherapeutic drugs in many parts of Africa, and access is generally limited to tertiary care facilities. The choice of drug regimen will be influenced by drug availability. Vincristine and bleomycin, and to a lesser extent doxorubicin, are available in major specialist tertiary care centres in sub-Saharan Africa. Liposomal preparations are not generally available in those settings at present, and are expensive. However, the entry of generic producers is likely to decrease costs and potentially allow for greater access. Problems with stock-outs of medications may occur, often due to forecasting rather than difficulty obtaining the drugs.

The number of treatment courses required will vary according to regimen type, and rapidity and completeness of treatment response. The total cost for six treatment cycles (given about every two to four weeks) of ABV is around US$ 400 (US$ 66 for vincristine, US$ 375 for bleomycin and US$ 33, US$ 125 and US$ 111 respectively for an ABV combination). The costs of liposomal doxorubicin treatment are high, ranging from US$ 150 per vial for the generic product to US$ 1000 for a branded one, or US$ 1800 to US$ 14 000 respectively for six treatment cycles.

4.5.2 *Toxicities*

Most data on toxicity of different KS chemotherapy regimens are based on studies conducted in the pre-ART era. In general, most regimens are relatively well tolerated, but serious toxicities may occur. For example, vincristine is associated with neuropathy which may be irreversible. This is of particular significance in children where administration of vincristine may be associated with the development of gastric ileus. Differences in monitoring requirements exist between various regimens depending on the toxicities associated with different chemotherapeutic agents (see **TABLE 4**).

TABLE 4. MAJOR TOXICITIES OF CHEMOTHERAPY DRUGS

DRUG	COMMON TOXICITIES	LESS COMMON BUT SERIOUS
Etoposide	Neutropenia, thrombocytopenia, anaemia, alopecia	Leukemia, myelodysplastic syndromes
	Nausea, vomiting	
Liposomal anthracyclines (doxorubicin, daunorubicin)	Neutropenia, thrombocytopenia, anaemia, myelosuppresion, drug may turn urine red	Hand-foot syndrome
		Acute infusional reactions
		Cardiac toxicity
Paclitaxel	Neutropenia, thrombocytopenia, anaemia, peripheral neuropathy, tiredness, alopecia	Serious allergic reactions (anaphylaxis)
Vincristine	Peripheral neuropathy	Vesicant → skin ulcers if extravasated
	Constipation, ileus	
Bleomycin	Pulmonary fibrosis (late)	Skin changes, including distal digital necrosis
	Fever, chills, myalgias (infusional reactions)	
Doxorubicin (non-liposomal)	Neutropenia, thrombocytopenia, anaemia, myelosuppresion, nausea and vomiting, alopecia, mucositis, radiation recall, photosensitivity, hyperuricaemia, drug may turn urine red	Cardiac toxicity

Liposomal anthracycline (PLD and non-pegylated liposomal daunorubicin) treatment is the standard of care for adults in the USA and Western Europe. These regimens are of comparable efficacy and are better tolerated with less toxicity, and improvements in several domains of health-related quality of life, compared with BV or ABV. These include less alopecia and fewer gastrointestinal and neurological side effects, while Grade 3/4 myelosuppression, stomatitis and infusion reactions are more common with PLD. However, liposomal preparations are expensive, not widely available, remain under patent, and require cold storage. No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted among contemporary ART agents and those used for the treatment of KS, whereas the PK of each agent has been evaluated. The data presently available are sparse and largely based on case reports. Yet there are reasons for potential concern, as many of the chemotherapeutic agents currently in use (i.e. liposomal and non-liposomal anthracyclines, paclitaxel, vincristine, etoposide) undergo metabolism in the liver by enzymes that have the potential to be inhibited or induced by various ART drugs (Rudek et al., 2011).

4.5.3 Site infrastructure and staff training

Site infrastructure: Provision of chemotherapy drugs requires adequate infrastructure (e.g. pharmacy, laminar flow) for preparation of the drugs, as well as a level of expertise with trained staff to ensure that the drugs are administered correctly and monitored appropriately to minimize potential side effects and ensure that serious toxicities are identified and managed. Since the drugs are largely available as liquid vials, they need to be reconstituted with calculation for a specific dose for each patient, which requires access to a laminar flow hood and appropriate training. In the absence of such facilities, reconstitution may result in aerosolization, exposure of staff to toxic drugs, and for pregnant women the risk of associated teratogenicity. In addition, most drugs can only be kept for a short time after reconstitution.

Staff training: Although treatment protocols are relatively straightforward to follow, they still require a level of expertise, infrastructure and follow-up to ensure that the drugs are given correctly and reliably in order to minimize potential side effects. Simplified treatment regimens and monitoring protocols are needed to optimize access.

4.5.4 KS diagnosis

Although definitive diagnosis of KS requires histological confirmation, in practice in many resource-limited settings, diagnosis is often based on clinical criteria alone, which carries with it the risk of both over- and underdiagnosis. There was overall support from the GDG for the importance of biopsy confirmation, especially in those patients being considered for chemotherapy (Amerson et al., 2012). Cutaneous biopsies using punch biopsy technique have been successfully performed by a range of health care providers in low-resource settings in Kenya and Uganda (Laker-Oketta et al., 2013). However, it was recognized that this will require clinical judgement; biopsy of pulmonary KS, for example, is associated with risk of haemorrhage. There is still very limited access to histopathology services, and most of these are in research settings. The requirement for biopsy should not significantly delay therapy.

4.5.5 Second-line chemotherapy

There is a need to address availability of second-line agents (as with ART) for patients that fail first-line therapy, although a formal evidence review on this topic was not considered for these guidelines. Possible second-line agents include paclitaxel, which has been used with some success in patients who have failed therapy with doxorubicin, bleomycin and vincristine, or doxorubicin in patients failing bleomycin/vincristine.

4.5.6 Need to optimize other aspects of general HIV care

Prompt access to ART and initiation of appropriate prophylaxis is critical, since the mortality of patients with KS appears to remain much higher in resource-limited settings than in high-income countries.

4.6 Research gaps

Further research is needed in the following areas:

- Identification of the subgroup of individuals with initially non functionally-disabling mild/moderate KS who may benefit from initial chemotherapy in addition to ART;
- Identification of the subgroup of individuals meeting the criteria for T1 KS who may respond to ART alone;
- Optimal timing of chemotherapy in relation to ART initiation, i.e. whether chemotherapy should be given prior to ART, and optimal duration before ART initiation;
- Optimal duration of chemotherapy;
- Cost-effectiveness of different chemotherapy regimens;
- Use of oral etoposide for chemotherapy in decentralized settings without facilities for administering infusions;
- In children: development and validation of a paediatric staging system to guide treatment strategies, and in particular the use of chemotherapy; evaluation of benefit of liposomal anthracyclines, and relative benefit of ABV compared to treatment with BV or a single agent.
- Identification of potential biomarkers to distinguish between KS IRIS and KS progression, and evaluation of optimal management strategies for KS IRIS, including chemotherapy.

5. Evidence and recommendations on seborrhoeic dermatitis

5.1 Background

5.1.1 Epidemiology

Seborrhoeic dermatitis is a common chronic condition that can affect people from infancy to old age; it tends to flare and remit spontaneously and is prone to recurrence after treatment. Seborrhoeic dermatitis has been reported to be associated with several conditions, including HIV (Gupta & Bluhm, 2004; Mastrolonardo et al., 2003; Maietta et al., 1990). In HIV-infected patients the prevalence is much higher and occurs early in the course of HIV disease (Wiwanitkit, 2004), with a mean CD4 count at presentation of higher than 400. The presentation can also be much more severe and/or diffuse.

5.1.2 Clinical features

Seborrhoeic dermatitis occurs in areas of the skin with a rich supply of sebaceous glands and manifests as erythematous, sharply marginated lesions with greasy scales.

Adults: Seborrhoeic dermatitis on the scalp manifests as dry, flaking desquamation (dandruff) or yellow, greasy scaling with erythema. In adolescence and adulthood it usually begins as mild greasy scaling of the scalp with erythema and scaling of the nasolabial folds or the postauricular skin. The rash morphology varies from mild scaling to an inflamed red rash. The rash often appears in areas of increased sebaceous gland activity (e.g. auricles, beard, eyebrows, trunk and flexural areas such as axilla, groin and inframammary regions). The central face may sometimes be involved. The rash rarely produces an eruption so generalized that it causes erythroderma (Janniger, 1993).

Children: In infants, seborrhoeic dermatitis may present as thick, greasy scales on the vertex of the scalp. This is commonly called cradle cap seborrhoeic dermatitis and is not included in these guidelines. As in adults, it manifests on the scalp in children as dry, flaking desquamation (dandruff) or yellow, greasy scaling with erythema. Common differential diagnoses for seborrhoeic dermatitis of the scalp are psoriasis, eczema and *tinea capitis*. The scales may vary in colour, appearing white, off-white or yellow. This presentation often is the only sign of seborrhoeic dermatitis in infants. However, widespread fine scaling may be seen over the scalp, face, forehead, ears and flexures and may even become generalized. Generalized seborrhoeic dermatitis is uncommon in otherwise healthy children and usually is associated with immune deficiencies. When the condition occurs in the neonatal period, it usually disappears by 6 to 12 months of age (Janniger, 1993; Janniger and Schwartz, 1995).

HIV: In HIV-infected patients, seborrhoeic dermatitis is not only more common but also more severe, sometimes with extensive spread, even covering the whole body (Chatzikokkinou et al., 2008; Marino et al., 1991). It also appears to be more refractory to conventional treatment, with more frequent relapses (Thiers, 1995). ART decreases the prevalence of seborrhoeic dermatitis (Berrey et al., 2001); in the individual patient with the condition, ART initiation may result in resolution (Dunic et al., 2004). Although ART may not cure seborrhoeic dermatitis, individuals receiving it may have less frequent and less severe occurrences (Hengge et al., 2000).

5.2 Recommendations

Mild seborrhoeic dermatitis
(scaling and mild erythema with or without itching involving either scalp alone [dandruff] or other body sites)

- HIV-infected children and adults with mild seborrhoeic dermatitis (including on the scalp) should be treated with topical ketoconazole 2% two to three times per week for four weeks, with a maintenance treatment once per week as needed.
  (Conditional recommendation, low quality evidence)

Severe seborrhoeic dermatitis
(severe scaling, erythema and itching involving either scalp alone (dandruff) and /or other body sites)

and seborrhoeic dermatitis unresponsive to first line therapy

- HIV-infected children and adults with severe seborrhoeic dermatitis and those patients with mild seborrhoeic dermatitis unresponsive to first-line therapy should be treated with a combination therapy of topical antifungals (e.g. ketoconazole 2%) and topical corticosteroids.
  (Strong recommendation, very low quality evidence)
- Patients with severe seborrhoeic dermatitis whose HIV status is unknown should be tested for HIV, and if positive, should be assessed for ART initiation according to WHO *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection* (WHO, 2013) (see **SECTION 3**).

Remarks

- *Mid- to high-potency topical corticosteroids can be used in combination with other medications (antifungals such as ketoconazole) but should be reserved for short-term therapy in severe seborrhoeic dermatitis or flare. Treatment of seborrhoeic dermatitis on sensitive areas such as the face should be limited to low-potency agents, whenever possible.*
- *Relevant drug interactions are described in* **ANNEX 2**.

5.3 Review question and summary of evidence

The systematic review (Stephen et al., in preparation) was based on the PICO question: in children and adults living with HIV infection (receiving and not receiving ART) (P) do antifungals (ketoconazole, itraconazole, fluconazolem, bifonazole, terbinafine), calcineurin inhibitors (pimecrolimus), ART, corticosteroids or other drugs (zinc pyrithione, selinium sulphide, lithium succinate) (I) compared to each other or to no treatment (C) achieve complete resolution of the disease, or achieve remission which mainly includes symptom improvement (decrease in pruritus and rash), or a decrease in prevalence of seborrhoeic dermatitis when ART is used (O) less than or up to four weeks following commencement of treatment for short term, or greater than four weeks of treatment for medium to long term, or greater than three months of treatment for ART interventions?

Therapy for seborrhoeic dermatitis in the HIV-infected population

The number of available studies of antifungals on seborrhoeic dermatitis in the HIV-infected population is not only limited, but also the quality is poor with a serious risk of bias in almost all the studies. Only one of the nine papers identified is based on a RCT which examined the effect of lithium succinate in treatment (Langtry et al., 1997). The grade of evidence was moderate because of considerable drop out, and no evidence demonstrates the presence or absence of effect at the end of follow-up. There were no studies in children.

Impact of ART

Three prospective studies show reduced incidence of seborrhoeic dermatitis in individuals on ART. However, the studies are heterogeneous, as one study examined the effect of ART (Dunic et al., 2004), another examined recent ART (Maurer et al., 2004) and the third compared the effect of early and delayed ART (Berrey et al., 2001). Thus, the comparison groups are different. Although the quality of evidence of these studies is low, there appears to be a beneficial effect of reduced incidence of seborrhoeic dermatitis in patients on ART.

Topical therapy for seborrhoeic dermatitis in the non HIV-infected population

A systematic review by Naldi (2010) assessing topical therapies for seborrhoeic dermatitis found 12 publications (systematic reviews, RCTs or observational studies) covering topical ketoconazole 2%, bifonazole 1%, selenium sulphide 2.5%, coal tar 4% and corticosteroid clobetasol proprionate 0.05%.

All antifungal agents were more effective than the ointment they were in. The main topical antifungal agent studied was ketoconazole with moderate quality evidence of its efficacy in treatment of seborrhoeic dermatitis. The adverse effect profile was excellent, as most studies did not report any significant adverse effects with this treatment.

Although no RCTs were found for topical corticosteroids in adults with seborrhoeic dermatitis, the consensus view is that their use is effective. Current practice is to use topical corticosteroids. Affected areas of the body are treated with short courses of potent topical corticosteroids (betamethasone valerate [0.1%], mometasone furoate [0.1%]) while the face is treated with short courses of moderate potency (clobetasone butyrate [0.05%]) or low potency (hydrocortisone [1%]) corticosteroids.

Oral treatments for seborrhoeic dermatitis in the non HIV-infected population

A systematic review (Gupta et al., 2013) assessed the quantity and quality of published reports on oral therapies for seborrhoeic dermatitis. It included 21 publications (RCTs, open trials and case reports) covering itraconazole, terbinafine, fluconazole, ketoconazole, pramiconazole, prednisone, isotretinoin and homeopathic mineral therapy. For itraconazole, six open non-comparative trials and three case studies were included. All except one assessed initial treatment at 200 mg/day for seven days typically followed by varying lengths of pulse therapy for two to 11 months. The clinical improvement rate and mycological cure rate varied from 58.6% to 93.0% and 40.0% to 86% respectively. Terbinafine had higher quality trials (including two RCTs) which showed significant improvement (but not for exposed skin regions), and there was one RCT on fluconazole which showed significant effect. Although there were 21 publications for review, the quality of the evidence was low due to the absence of blinding and control groups in these studies.

5.4 Rationale for recommendations

The review by Stephen and colleagues (in preparation) focused specifically on studies in the HIV-infected population. The number of available studies of interventions for seborrhoeic dermatitis in children and adults living with HIV infection was not only limited, but also the quality was poor with a serious risk of bias in almost all of them. They therefore provided insufficient evidence on which to base a recommendation.

Because the evidence in children and adults with HIV infection was insufficient, data from studies in non HIV-infected populations were considered. The quality of this evidence was necessarily graded one level lower because of indirectness.

Although there are no studies for topical ketoconazole in seborrhoeic dermatitis specifically in HIV-infected individuals, this is the main drug that has been subject to research in the non HIV-infected population. Thise research provides strong evidence of its efficacy (Naldi, 2009; Apasrawirote et al., 2011). Although several drugs have been shown to be effective in treatment of seborrhoeic dermatitis (topical antifungal drugs and topical pimecrolimus in particular), ketoconazole is the most studied and has the strongest evidence for its effectiveness.

Almost all of the studies of antifungals (and other treatments) that provide strong evidence of their efficacy used the medication either twice or three times weekly. Although there is no clear evidence for the role of maintenance therapy in seborrhoeic dermatitis, the general consensus among the GDG was that maintenance therapy of a once-a-week application for three to four months reduced relapse rates.

Although only limited, low quality evidence is available concerning mid- to high-potency topical corticosteroids, alone or in combination with antifungals (Reygagne et al., 2007; Elewski, 2009; Shin et al,. 2009; Ortonne et al., 1992; Faergemann et al., 2007; Milani et al., 2003), there is consensus that topical corticosteroids either alone or in combination with antifungals are effective in treating seborrhoeic dermatitis of the scalp in adults. These are not recommended as first-line therapy because of low quality evidence and also because of the potential for side effects, such as striae, telangiectasia and rebound, especially with long-term use; even low-potency corticosteroids may cause adverse effects when used for long periods or on thin skin.

Data on the use of oral antifungals are limited and the evidence is very low quality even for HIV-negative individuals. No recommendation could be made because of insufficient evidence. Oral ketoconazole is no longer recommended for treatment of seborrhoeic dermatitis due to toxicity.

Only low quality evidence is available to show that ART may result in resolution of seborrhoeic dermatitis (Dunic et al., 2004). If the condition is mild and the only manifestation of HIV, the earlier initiation of lifelong ART for a condition that may respond readily to topical therapy may be less acceptable than in patients with severe and recurrent seborrhoeic dermatitis.

Although studies provided strong evidence for topical ketoconazole and moderate evidence for topical corticosteroids in seborrhoeic dermatitis, all of them were conducted in non HIV-infected populations and therefore could be considered only as indirect evidence. Therefore the quality of evidence is graded as low for topical ketoconazole and very low for topical corticosteroids.

Adverse effects

Topical ketoconazole is safe with an excellent benefit-side effect profile. Topical corticosteroids, although very effective, do have the potential for side effects, such as striae, telangiectasia and rebound, especially with long-term use. Therefore, topical ketoconazole 2% was graded as a strong recommendation for mild seborrhoeic dermatitis, and topical corticosteroids graded as a strong recommendation for severe seborrhoeic dermatitis.

Costs, availability and other implementation considerations

The data show that topical ketoconazole and topical corticosteroids are effective, easily available in all formulations (lotions, shampoos, gels, ointments, cream), affordable and acceptable to all health care providers as they have been in use for many years. Therefore, the recommendation for topical ketoconazole 2% and topical corticosteroids for the treatment of seborrhoeic dermatitis is graded as strong.

Topical ketoconazole is generally more available than other antifungals. It is easier and more feasible to use in low- and middle-income settings and less expensive compared to other treatments. Although selenium sulphide shampoo, tar shampoo, zinc pyrithione and/or mineral oil are also less expensive and easily available, all of these had lower quality evidence.

5.5 Research gaps

The areas of additional research for seborrhoeic dermatitis identified include:

- Well-designed, prospective, blinded RCTs in HIV-infected adults and children to provide high quality evidence upon which to base clinical decision-making;
- Establishment of a standardized outcome measure (e.g. time to resolution of the lesions or resolution after three months) to ensure studies are easier to compare.
- Evaluation of the effect of ART on seborrhoeic dermatitis.

6. Evidence and recommendations on papular pruritic eruption

6.1 Background

6.1.1 Epidemiology

Papular pruritic eruption is one of the most common skin conditions associated with HIV disease in tropical and subtropical regions, with reported prevalence of 11% to 46% (Bason et al., 1993; Boonchai et al., 1999; Rosatelli et al., 1997; Sivayathorn et al., 1995; Smith et al., 1991). The prevalence in HIV-infected children ranges from 38% to 42% (Panya et al., 2009; Lowe et al., 2010). It is more common with lower CD4 counts (Resneck et al., 2004; Wiwanitkit, 2004) and advanced HIV disease (WHO clinical stages 3 and 4) (Castelnuovo et al., 2008). More than half of HIV-infected patients in some countries report the eruption as the initial manifestation of their disease (Colebunders et al., 1987).

6.1.2 Etiology

The pathophysiology of papular pruritic eruption is not completely understood. Hypersensitivity to arthropod bites and a form of chronic recall reaction to arthropod antigens in the setting of HIV-associated immune dysregulation has been suggested (Penneys et al., 1989).

6.1.3 Clinical features

Papular pruritic eruption is characterized by symmetrically distributed itchy papular eruptions on the extremities, face and trunk with sparing of the mucous membranes, palms, soles and digital web spaces. On the arms, lesions are specifically localized on the extensor surface and on the dorsum of the hands. Postinflammatory pigmentation and even prurigo-like nodules and scarring may develop secondary to extensive excoriations because of severe pruritus. Scabies, eosinophilic folliculitis and drug eruptions should always be considered in the differential diagnosis.

Papular pruritic eruption can adversely impact health-related quality of life (Yosipovitch et al., 2000; Zachariae et al., 2004 & 2008). Depression, distress and sleep impairment have been reported as a consequence of chronic pruritus in this condition (Zachariae et al., 2008).

6.2 Recommendations

- In HIV-infected children, adolescents, pregnant women and adults with papular pruritic eruption, ART should be considered as the primary treatment (see **SECTION 3**).
  (Strong recommendation, low quality evidence)
- Additional symptomatic therapy with antihistamines and topical corticosteroids (class 3, 4, 5 or 6, e.g. betamethasone valearate) is also recommended for the duration of persistent symptoms.
  (Conditional recommendation, very low quality evidence)

Remarks

- *Drugs: If betamethasone is not available other potent topical steroids, class III or above, may be used instead.*
- *If there is no response or a failure in response, evaluate for other causes of papular eruptions of HIV.*
- *Caution should be exercised in the use of oral antihistamines in infants under one year of age. Dosage needs to be adjusted in children by weight. Caution should also be exercised in the use of sedating antihistamines in children attending school.*
- *Relevant drug interactions are described in* **ANNEX 2**.

6.3 Review question and summary of evidence

The systematic review (Chua et al., in preparation) was based on the PICO question: in children and adults living with HIV infection (receiving and not receiving ART) (P) does ART alone or ART with pentoxifylline, or antihistamines plus topical cortisteroids, or pentoxifylline alone, or dapsone (I) compared to no treatment (C) result in resolution of skin lesions or resolution of pruritus (O).

Participants in all included studies were adults. There were no studies of interventions for papular pruritic eruption in children, and no RCTs were identified in this review. However, two relevant prospective studies that compared at least two interventions were identified. Other relevant publications identified included three prospective studies investigating one intervention without comparison group(s), one case series and four case reports.

Use of ART

Resolution of papular pruritic eruption has been reported with ART initiation. Colebunders and colleagues (2006) found that mean papular pruritic eruption score declined from 3.9 at enrollment to 0.1 at 24 months. The condition disappeared and never returned in 37 (86%) of the 43 patients with at least six months of follow-up data. However, ART initiation was associated with an exacerbation of the skin condition as a result of IRIS in 13% of patients (seven out of 53). Despite limitations of this study, including 19% loss to follow-up (10 out of 53 participants), lack of blinding at outcomes assessment and lack of ascertainment of diagnosis by biopsy, it provides evidence for the positive impact of ART on papular pruritic eruption.

Other treatments not considered in recommendations due to lack of RCTs and very low quality evidence

Two prospective non-randomized studies that compared at least two interventions were identified. Oral dapsone versus oral pentoxifylline versus oral antihistamines and topical clobetasol were examined in 30 participants (10 per group) in the first study. Participants treated with pentoxifylline had a faster clinical response and longer remission (Lakshmi et al., 2008). The other study investigated oral promethazine (n=50) versus topical 1% hydrocortisone (n=18).

Reduction in mean pruritus scores was greater in the group receiving oral promethazine (Navarini et al., 2010). Hydrocortisone reduced itch by 16% whereas promethazine reduced itch by 50%.

In a study by Berman and colleagues (1998), among participants who received pentoxifylline 400 mg three times daily for eight weeks the average degree of pruritus was significantly reduced ($p = 0.0009$) from 6.5 at baseline examination to 3.6 at the end of the study. However, due to lack of randomization and small sample size, the study provided very low quality evidence.

6.4 Considerations for development of recommendations

There is a lack of RCTs investigating interventions for papular pruritic eruption. Although the regression of the condition with initiation of ART is recognized (Colebunders et al., 2006), there are few studies systematically documenting the response of papular pruritic eruption to ART. The available evidence on other possible interventions is very limited, and the quality of evidence is very low.

The expert panel considered that there is benefit from using symptomatic therapy in the form of oral antihistamines and topical corticosteroids for treatment of papular pruritic eruption in HIV-infected individuals. It is common practice to use these medications for this condition. Although this treatment provides symptom relief, the papular pruritic eruption does recur. Due to lack of RCTs and even non-RCTs this recommendation is based on expert panel opinion, and therefore graded as conditional with very low quality evidence.

The panel also considered ART initiation, with or without symptomatic therapy, as the best option in HIV-infected children and adults. The present WHO recommendation (WHO, 2013) is ART initiation for all symptomatic patients. ART would be acceptable to most patients who are eligible for treatment, and the incremental cost is probably small. Therefore, the recommendation for ART for papular pruritic eruption in HIV-infected children and adults is graded as strong. However, because of lack of RCTs, and very limited evidence from other studies, the quality of evidence is very low.

For all other treatments studied, such as pentoxifylline, ultraviolet light – B (UVB) phototherapy, and psoralen combined with ultraviolet A (PUVA) therapy, not only is the evidence of very low quality, but the treatments are expensive and neither easily accessible nor feasible to implement in control programmes.

Adverse effects, costs, availability and other implementation considerations

As stated above, the present WHO recommendation is ART initiation for all symptomatic patients. ART would be acceptable to most patients who are eligible for treatment and the incremental cost is probably small. There is free access to ART in most settings.

Topical corticosteroids are easily available at low cost. However, though effective, they do have the potential for side effects, such as striae and telangiectasia, especially with long-term use. Potent topical steroids should not be used for more than three weeks continuously. If a longer duration is needed, the steroid should be gradually tapered to avoid rebound symptoms, and treatment should be resumed after a steroid-free period of at least one week. This intermittent schedule can be repeated chronically or until the condition resolves. Side effects are rare when topical steroids are used for three months or less.

Antihistamines are also easily available at low cost. Antihistamines have been in clinical use for six decades and are relatively free of adverse effects, although no long-term safety studies have been published.

6.5 Research gaps

Research gaps identified included:

- Well-designed, prospective, blinded RCTs in HIV-infected adults and children to provide high quality evidence upon which to base clinical decision-making;
- Establishment of a standardized outcome measure (e.g. time to resolution of the lesions or resolution after three months) to ensure studies are easier to compare.
- Improvement of assessment of other clinical conditions/manifestations, CD4 and viral load associated with these conditions.

7. Evidence and recommendations on eosinophilic folliculitis

7.1 Background

7.1.1 Epidemiology

There are three variants of eosinophilic folliculitis: classic, infancy-associated and immunosuppression-associated (mostly HIV-associated).

The prevalence of HIV-associated eosinophilic folliculitis varies greatly across different populations. The estimated prevalence in HIV-infected adults attending hospital-based dermatology clinics was 18.6% (13 of 70) in Seoul, Korea (Kim et al., 2010), 4% (21 of 528) in Florida, USA (Goldstein et al., 1997), 4.2% (four of 96) in Singapore (Goh et al., 2007) and 2.6% (four of 150) in India (Sud et al., 2009). The prevalence of HIV-associated eosinophilic folliculitis has diminished with the widespread use of ART (Rajendran et al., 2005).

The development of HIV-associated eosinophilic folliculitis is strongly associated with advanced immunosuppression, especially CD4 counts under 250 cells/mm^3, and low CD4 nadir (Rajendran et al., 2005) (see GRADE tables in **WEB APPENDIX 1**). Immune dysregulation and abnormal type 2 T-helper cell immune responses in advanced HIV disease have been implicated in the aetiology of HIV-associated eosinophilic folliculitis. It has been suggested that mast cells (Buchness et al., 1989) and target antigens in serum, such as chemotactic factors for eosinophils (Otley et al., 1995), also play a role. In children, the condition has been classified as an AIDS-defining illness.

7.1.2 Clinical features

HIV-associated eosinophilic folliculitis manifests as 2–3 mm erythematous, highly pruritic wheal-like papules, most frequently affecting the shoulders, trunk, upper arms, neck and forehead. Lesions are follicular and are often markedly excoriated. Pruritus adversely impacts on quality of life and may cause sleep impairment, distress and depression (Yosipovitch et al., 2000; Zachariae et al., 2004; Zachariae et al., 2008). Clinically the differential diagnosis of eosinophilic folliculitis is between papular pruritic eruption or other dermatoses – for example, scabies, urticaria, drug rashes and eczema (see **TABLE 5**).

TABLE 5. DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIC FOLLICULITIS

	EOSINOPHILIC FOLLICULITIS	PAPULAR PRURITIC ERUPTION	SCABIES
Symptoms	• Severe itching	• Severe Itching	• Night-time itching • Partner itching
Skin lesions	• Oedematous, wheal-like papules • Excoriations +/-	• Hyperpigmented & skin-coloured papules • Severe excoriations & scarring, & sometimes prurigo-like lesions	• Small papules, papulovesicles • "Burrows"
Distributions	• Neck, forehead, cheeks, trunk	• Predominantly extensor surface of extremities & trunk	• Finger web spaces, palms, forearms, axilla, areola & nipple, umbilicus, external genitalia • No facial lesions
Histopathology	• Characteristic	• Suggestive but variable	• Suggestive unless mite is visualized in histology

Owing to the wide differential diagnosis of eosinophilic folliculitis, a skin biopsy and histopathological examination is often recommended for diagnosis. The histology shows a folliculocentric inflammatory infiltrate, predominantly of eosinophils and lymphocytes.

7.2 Recommendations

- ART should be considered as the primary treatment of eosinophilic folliculitis in eligible patients (see **SECTION 3**).
  (Strong recommendation, low quality evidence)
- All HIV-infected adults (including pregnant women), adolescents and children who have been initiated on ART and who subsequently develop HIV-associated eosinophilic folliculitis should not discontinue the ART.
  (Conditional recommendation, very low quality evidence)
- Additional symptomatic therapy is recommended for the duration of the persistent symptoms with, depending on severity:
  - oral antihistamine; if no adequate response, add
  - topical corticosteroids (class 3, 4, 5 or 6, e.g. betamethasone valearate); if no adequate response, add
  - oral itraconazole; if no adequate response, add
  - permethrin 5% cream applied above the waist.

  (Conditional recommendation, very low quality evidence)

Remarks

- *Drugs: Even though the quality of evidence is very low, betamethasone should be used if pruritus persists; if betamethasone is not available, other class 3, 4, 5 or 6 potent topical corticosteroids can be used instead.*
- *Caution should be exercised in the use of oral antihistamines in young infants. Dosage should be adjusted by age and weight.*
- *Itraconazole is excreted into human milk and therefore is not recommended for breastfeeding mothers. Cases of congenital abnormalities have been shown following itraconazole treatment.*
- *Relevant drug interactions are described in* **ANNEX 2**.

7.3 Review question and summary of evidence

The systematic review (Chua et al., in preparation) was based on the PICO question: in HIV-infected adults and children (receiving or not receiving ART) (P), does ART or other interventions with or without ART (topical, systemic or phototherapy) (I) compared with a placebo, other interventions, no intervention or a combination of two or more interventions (C) lead to resolution of pruritus, rash or both (primary outcome); or reduction of pruritis, or body surface affected by rash, or improved quality of life (secondary outcome) (O).

No RCTs related to eosinophilic folliculitis treatment were identified. However, a large number and a wide range of interventions have been described in both ART-treated and non-ART-treated adult participants to be beneficial in the treatment of HIV-associated eosinophilic folliculitis.

Three non-randomized uncontrolled open trials of oral itraconazole (Berger et al., 1995), oral isotretinoin (Otley et al., 1995) and topical permethrin (Blauvelt et al., 1995) were included. The effect of a combination of ART and oral isotretinoin was described in a prospective study (Annam et al., 2010). A prospective study by Lim and colleagues (1997) of the efficacy of UVB phototherapy in HIV-positive participants with pruritus included 14 participants with HIV-associated eosinophilic folliculitis. All other included studies were open trials, retrospective chart reviews, case series or case reports with fewer than ten participants.

It is difficult to be certain if the response reported is attributable to the intervention(s) described due to the lack of a comparison group, randomization, allocation concealment, and blinding of participants, investigators and outcome assessors. Findings from the studies included in this review are not easily generalizable due to small sample sizes and high risk of bias.

Based on the findings of prospective studies and open (uncontrolled non-randomized) trials, there is some evidence for the use of oral isotretinoin (40–80 mg/day or 0.5–1.2 mg/kg per day), initiated simultaneously with ART (Annam et al., 2010) or in ART-treated patients (Otley et al., 1995), oral itraconazole (Berger et al., 1995), UVB phototherapy (Lim et al., 1997) and topical 5% permethrin cream (Blauvelt et al., 1995).

ART alone or with other treatments

The favourable impact of ART was outlined in two case reports (Michigami et al., 2009; Sears et al., 2012). The combination of ART and oral dapsone (100 mg per day) resulted in a good response in one patient according to a case report (Filippetti & Muzi, 2012). Annam and colleagues (2010) reported complete response in 16 of 23 participants and partial response in seven participants with the concurrent initiation of ART and oral isotretinoin (40–80 mg/day or 0.5–1.2 mg/kg per day).

Oral itraconazole

Oral itraconazole at doses between 100–400 mg per day was studied in 28 HIV-positive adult participants. Sixteen of the participants were followed up at six months; five participants had complete remission of skin lesions and pruritus after discontinuation of therapy, two were controlled on topical corticosteroids only, five were fully controlled and four were partially controlled on oral itraconazole (Berger et al., 1995). There was one case report of complete remission of pruritus and skin lesions after two months of treatment with oral itrazonazole (Parker et al., 2006).

Oral isotretinoin

An open uncontrolled trial of oral isotretinoin (40-80 mg/day, 0.5–1.2 mg/kg per day) in seven HIV-positive male adult participants already receiving ART showed complete remission for up to nine months after one course of therapy in four participants and after the second course of therapy in three participants (Otley et al., 1995). The efficacy of isotretinoin was described in a case report and one case series of seven participants (Downs et al., 1998).

Phototherapy

One prospective study and case series and reports have described the efficacy of UVB phototherapy (Buchness et al., 1989; Rosenthal et al., 1991; Gnecchi et al., 1998; Kuwano et al., 2006; Misago et al., 1998).

Permethrin

Topical 5% permethrin cream above the waist was reported to be effective when used without interruption in the treatment of HIV-associated eosinophilic folliculitis in six participants (Blauvelt et al., 1995).

Topical corticosteroids and antihistamines

A few case reports and case series have shown that topical corticosteroids and antihistamines alleviate symptoms of eosinophilic folliculitis (Parker et al., 2006; Ferrandiz et al., 1992; Filippetti & Muzi, 2012; Meyer et al., 2010).

7.4 Rationale for recommendations

The GDG considered that the evidence base for all of the interventions was of very low quality, because the studies reviewed either had small sample sizes or were reports of individual cases or small case series. However, although the evidence is of very low quality, there appears to be some

benefit from isotretinon, oral itraconazole with or without oral antihistamines, with or without topical corticosteroids, antihistamines with or without topical corticosteroids, permethrin 5% cream, or UVB phototherapy.

The GDG excluded isotretinoin because of its teratogenic effect, its high cost and unavailability in most low-resource settings. Similarly UVB phototherapy is also unavailable or unaffordable in most resource-limited settings and therefore is not recommended.

Even though itraconazole is not in the WHO *Model list of essential medicines*,[1] the panel considered it important for symptomatic treatment of eosinophilic folliculitis as well as other skin conditions. Oral antihistamines, topical corticosteroids, topical permethrin 5% and doxycycline have also been recommended because of their effectiveness, affordability and availability.

Although the evidence is of very low quality, the GDG strongly recommended the use of ART as a primary treatment of eosinophilic folliculitis based on expert opinion and consensus. This recommendation would probably be acceptable to key stakeholders. In addition, the resources required to implement this recommendation are small (see **ANNEX 3**).

The recommendation for all HIV-infected adults (including pregnant women), adolescents and children who have been initiated on ART and who subsequently develop HIV-associated eosinophilic folliculitis, not to discontinue the ART is based on expert opinion and GDG consensus and therefore stated as conditional. One constraint is that accurate diagnosis of the disease may not be easy in resource-limited settings due to the lack of access to pathology and dermatology services.

The recommendation for oral antihistamines and/or topical corticosteroids and/or oral itraconazole and/or topical 5% permethrin as additional symptomatic therapy for the duration of the persistent symptoms is also based on expert opinion and GDG consensus and therefore stated as conditional. Although the available evidence is very low quality, overall the desirable effects of this recommendation were assessed as probably large relative to any undesirable effects.

Adverse effects, costs, availability and other implementation considerations

As for other conditions, the present WHO recommendation (WHO, 2013) is ART initiation for all symptomatic patients. ART would be acceptable to most patients who are eligible for treatment and the incremental cost is probably small. There is free access to ART in most settings.

Topical corticosteroids are easily available at low cost. However, effective topical corticosteroids do have the potential for side effects, such as striae and telangiectasia, especially with long-term use. Potent topical steroids should not be used for more than three weeks continuously. If a longer duration is needed, the steroid should be gradually tapered to avoid rebound symptoms, and treatment should be resumed after a steroid-free period of at least one week. This intermittent schedule can be repeated chronically or until the condition resolves. Side effects are rare when topical steroids are used for three months or less.

Antihistamines are also easily available at low cost. Antihistamines have been in clinical use for six decades and are relatively free of adverse effects, although no long-term safety studies have been published.

Itraconazole is excreted into human milk and is therefore not recommended for breastfeeding mothers. Cases of congenital abnormalities have been shown following itraconazole treatment. Itraconazole is highly protein bound and inhibits cytochrome p450 enzymes. Therefore drug interactions should be considered when prescribing this drug. Relevant drug interactions are described in **ANNEX 2**.

[1] See http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

7.5 Research gaps

The research gaps identified were similar to those for papular pruritic eruption:

- Well-designed, prospective, blinded RCTs in HIV-infected adults and children to provide high quality evidence upon which to base clinical decision-making;
- Establishment of a standardized outcome measure (e.g. time to resolution of the lesions or resolution after three months) to ensure studies are easier to compare.
- Establishing recurrence rates, time frame and circumstances under which these conditions recur.
- Improvement of assessment of other clinical conditions/manifestations, CD4 and viral load associated with these conditions.

8. Evidence and recommendations on tinea infections

8.1 Background

8.1.1 Epidemiology

Dermatophytes, specifically *trichophyton*, *epidermophyton* and *microsporum* species, are responsible for most superficial fungal infections (Weitzman & Summerbell, 1995). The term "tinea" refers exclusively to dermatophyte infections. Tinea infections are classified according to the affected body site, such as *tinea capitis* (scalp), *tinea barbae* (beard area), *tinea corporis* (skin other than bearded area, scalp, groin, hands or feet), *tinea cruris* (groin, perineum and perineal areas), *tinea pedis* (feet), *tinea manuum* (hands) and *tinea unguium* (nails).

Tinea infections are seen throughout the world, with a higher prevalence of *tinea corporis* in warmer and more humid conditions (Aly, 1994). It is estimated that 10% to 20% of the world's population is affected by fungal skin infections (Drake et al.,1996).

Tinea infections are common in HIV-infected patients; however, the incidence has not been found to be higher in HIV-infected people compared to those who are HIV uninfected. Dermatophyte infections in HIV-infected populations are often more severe and may have an unusual presentation (Coldrion & Bergstresser, 1989).

8.1.2 Clinical features

Tinea corporis, tinea cruris, tinea pedis (all dermatophyte infections of the skin), *tinea unguium* (infection of nails) and *tinea capitis* (infection of scalp hair) all occur in patients with HIV infection.

Tinea pedis, the most common type of dermatophytosis in patients with symptomatic HIV disease, is usually manifested by typical interdigital maceration with scaling and diffuse hyperkeratosis of the sole.

Tinea cruris presents as an expanding scaling plaque of the upper thighs and groin, with central clearing and an erythematous elevated border. In HIV-infected patients, *tinea corporis* is often an extension of infection from the groin to the trunk. In severely immunosuppressed patients the lesions may have little inflammation and lack the typical elevated border and central clearing of tinea.

Infection of the nail is common in HIV-infected individuals. The nails often appear discoloured; they may be thickened and brittle. Nail infection has been associated with advanced HIV disease and considered a clinical marker of HIV infection (Weismann et al., 1988).

8.2 Recommendations

- In children and adults (including pregnant women) with tinea infections that are not extensive, topical treatment with terbinafine 1% cream/gel (for two weeks) or miconazole (for three to four weeks) should be initiated.
  (Strong recommendation, low quality evidence)
- In children and adults (see comment below regarding pregnant women) with extensive tinea infections or hair/nail involvement, oral griseofulvin should be considered.
  (Conditional recommendation, very low quality evidence)
- If there is no response, then oral terbinafine or itraconazole should be used.
  (Conditional recommendation, very low quality evidence)
- In children and adults having tinea infections with unknown HIV status, an HIV test should be offered (see **SECTION 3**).
  (Strong recommendation, low quality evidence)

Remarks

A variety of topical antifungals are considered efficacious. Topical miconazole and topical terbinafine are listed in the recommendations specifically as they are part of the WHO Model list of essential medicines.[a]

Griseofulvin:

- *Griseofulvin may be used in children aged 2 years and older.*
- *Griseofulvin should be avoided in pregnancy as it may be teratogenic. It is labeled as a Pregnancy Category C drug. There is no evidence of excretion into human milk.*

Other side effects of griseofulvin include gastrointestinal upsets (which may be reduced by administration with food) and photosensitivity in some patients.

Ointment preparations are preferred for thickened, hyperkeratotic lesions. Lotions and solutions are preferred for intertriginous areas and hairy areas of the body, and also appropriate for treating moist, oozy, weepy lesions. Cream formulations are beneficial in the treatment of scaling, non-oozing lesions.

These recommendations apply to HIV-negative children and adults as well.

[a] See http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

8.3 Review question and summary of evidence

The PICO question considered was: in HIV-infected adults and children with tinea infections (either receiving or not receiving ART) (P), does treatment with topical antifungals such as terbinafine, naftifine, azoles, allylamines and benzylamines and oral antifungals such as griseofulvin, terbinafine and itraconazole (I) compared to no intervention or any of the individual antifungals or combined with corticosteroids (C) lead to clinical cure or mycological cure (O).

A Cochrane review (El-Gohary et al., 2014) that examined this question included 129 studies comprising 18 086 participants over 18 years of age. Although all of the studies were RCTs, 27 had a placebo arm, 98 an active control treatment arm and four included both arms. A range of interventions was covered. Antifungals evaluated included azoles (e.g. ketoconazole 1%, miconazole 2%, clotimazole 1% and others), allylamines (terbinafine 1%, naftifine 1%), benzylamines (butenafine 1%), hydroxypyridones (ciclopirox olamine 1%), thiocarbamates (tolnaftate 1%) and others (griseofulvin, itraconazole, fluconazole and others). There was a clear over-representation of the azole group among the interventions evaluated. Participants living with HIV were not included in this review.

Almost all active interventions were effective at achieving mycological cure after two to four weeks compared to a placebo. There appeared to be little difference between active interventions in achieving this outcome, although duration of treatment varied. Clinical cure was also assessed in most studies, and similarly, most active interventions were superior when compared to placebo.

Direct comparisons of allylamines versus azoles show allylamines to be generally more efficacious. Trials directly comparing the two compounds demonstrate the superiority of allylamines. There is little evidence of superiority at two weeks, but this effect becomes detectable in outcomes taken six weeks after treatment begins and appears to remain at 12 weeks. Comparisons between different regimes of allylamines provided little evidence that any one regime is more effective than another.

The Cochrane Review (El-Gohary et al., 2014) compared active interventions for three treatment classes of antifungals (topical azoles, allylamines, benzylamines) and also azoles combined with corticosteroids. Few of the included studies assessed duration of treatment until clinical cure, and none of the studies included participants living with HIV infection. The results suggested that all achieved high mycological cure rates, with either very low or moderate quality of evidence supporting any difference in results. There was no difference in clinical cure rates between azoles and allylamines (RR 0.99; 95% CI 0.95 to 1.03; and RR 0.97; 95% CI 0.92 to 1.02) respectively, nor mycological cure between azoles and benzylamines (RR 1.01; 95% CI 0.94 to 1.07). Clinical cure slightly favoured azole and steroid combination treatments compared to azoles alone (RR 0.67; 95% CI 0.53 to 0.84), but there was no difference in mycological cure rate (RR 0.99; 95% CI 0.93 to 1.05).

Adverse effects were minimal and were mainly irritation and burning with no differences between active interventions and placebo, nor between different classes of treatment.

8.4 Rationale for recommendations

The evidence suggests that all classes of commonly-used topical antifungals achieve substantial mycological and clinical cure rates. However, there is currently not enough evidence to be able to determine if one particular class or individual topical antifungal is superior in terms of mycological and clinical cure. Topical miconazole and topical terbinafine are listed in the recommendations specifically as they are part of the WHO *Model list of essential medicines*.[1] In addition, topical terbinafine may be more appealing as it requires fewer applications and a shorter duration of treatment, and there is widespread global availability of the intervention. Also, side effects of local antifungal creams are minimal. The recommendation of topical miconazole 2% or terbinafine 1% for non-extensive *tinea corporis* is therefore a strong recommendation.

The participants identified in the review were a fairly representative sample, and the GDG did not have any significant concerns about the directness of the evidence. Participants living with HIV were not included in this review. The evidence for the effectiveness of antifungal treatment of tinea infections is strong. However, in view of the more extensive and varied differences in clinical presentation of tinea infections in HIV-infected individuals, the evidence for the effects of these interventions may not be extrapolated directly to immunocompromised participants. The panel, therefore, decided to grade the evidence for HIV populations as low.

For treatment of extensive tinea infections, the panel favoured griseofulvin rather than terbinafine because of the latter's higher cost. The recommendation was made conditional as a result.

Overall, the benefits of treatment would normally outweigh the potential harms, and this recommendation would probably be acceptable to key stakeholders. The cost of the various groups of antifungals that appear to achieve similar outcomes is not significantly different (see **ANNEX 3**).

[1] See http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

Adverse effects, costs, availability and other implementation considerations

Griseofulvin is easily available at low cost and has a favorable safety profile. It may be used in children aged 2 years and older. However, griseofulvin should be avoided in pregnancy as it may be teratogenic and is labeled as a Pregnancy Category C drug. When used for treatment durations of up to eight weeks, laboratory monitoring is not necessary. Other side effects of griseofulvin include gastrointestinal upset (which may be reduced by administration with food) and photosensitivity in some patients.

Potential limitations for terbinafine and itraconazole include an increased potential for drug-drug interaction and possible hepatotoxicity if treatment duration is more than six weeks, although studies confirm that these are not common occurences. Another more practical limitation of terbinafine and itraconazole is their cost.

8.5 Research gaps

The gaps identified included:

- Well-designed, prospective, blinded RCTs in HIV-infected adults and children to provide high quality evidence upon which to base clinical decision-making;
- Establishment of a standardized outcome measure (e.g. time to resolution of the lesions or resolution after three months) to ensure studies are easier to compare.
- Large RCTs to compare the effectiveness of topical amorolfine and butenafine in order to establish an alternative to oral treatments for toenail infections, in both HIV-infected and the general population.
- Better formulations/vehicles for topical therapy for nail infections;
- The effectiveness of specific oral antifungal drugs on specific dermatophytes, which would require future investigators to report the types of dermatophytes cultured at the last outcome assessment for the proportion of participants not cured;
- Treatment doses and frequency for all antifungals, including griseofulvin, in the HIV-infected and general population;
- Issues around development of resistance to drugs.

9. Evidence and recommendations on herpes zoster

9.1 Background

9.1.1 Epidemiology

Approximately 20% to 30% of the general population develop herpes zoster during their lifetime, and this figure rises to as high as 50% for those over 85 years of age (Brisson et al., 2001). HIV-infected patients are at higher risk of developing this condition than age-matched, HIV-uninfected individuals. The overall incidence of herpes zoster in HIV-infected persons is around 30 per 1000 person-years (Buchbinder et al., 1992). In contrast, the overall incidence of herpes zoster in the general population is about 1.5 to 3.0 cases per 1000 persons (Donahue et al., 1995; Ragozzino et al., 1982). This difference is seen even in the paediatric age group, with <1 case per 1000 person-years in the general population (Civen et al., 2009) as compared to 10 cases per 1000 person-years in the HIV-infected population (Gona et al., 2006). Herpes zoster may occur at any time in the course of HIV-induced immunosuppression, and may be the first clinical clue to suggest undiagnosed HIV infection. Recurrent episodes of herpes zoster may occur in HIV-infected patients, and appear to be more common than in the HIV-uninfected population (Buchbinder et al., 1992).

9.1.2 Pathogenesis and clinical features

Primary infection with varicella zoster virus (also known as chickenpox) results in viral latency in dorsal root, cranial and autonomic system ganglia. Reactivation of the varicella virus, due to decreased cellular immunity, often associated with ageing, chemotherapy or immunosuppression, results in herpes zoster infection, also known as shingles. Herpes zoster manifests as painful cutaneous eruptions of clusters of vesicles over an erythematous base distributed over a single dermatome or two or more contiguous dermatomes; they are invariably unilateral and do not cross the midline. Rarely the rash of herpes zoster can be more widespread and affect three or more dermatomes. This condition is called disseminated zoster, which can be difficult to distinguish from varicella. It generally occurs only in people with compromised immune systems.

9.2 Recommendations

- For all HIV-infected children, adolescents and adults (including pregnant women) with herpes zoster, acyclovir is recommended to prevent dissemination and for resolution of disease (at any time in the course of the disease).
  (Strong recommendation, low quality evidence)
- All children, adolescents and adults presenting with herpes zoster with unknown HIV status should be offered an HIV test and, if positive, assessed for ART eligibility.
  (Strong recommendation, low quality evidence)

Remarks

- *Acyclovir, famciclovir and valaciclovir are all effective in the treatment of herpes zoster. Acyclovir is specifically listed due to its inclusion on the WHO* Model list of essential medicines.[a] *Famciclovir and valaciclovir are acceptable alternatives when available.*
- *Relevant drug interactions are described in* **ANNEX 2**.

These recommendations apply to HIV-negative children and adults as well.

[a] See http://www.who.int/medicines/publications/essentialmedicines/en/index.html.

9.3 Review question and summary of evidence

The review question was: among children and adults living with HIV infection (with and without ART) (P), what is the effectiveness of antivirals (acyclovir, valaciclovir, famciclovir or brivudin) for management of herpes zoster (I) comparing one with the other (C) in resolution of lesions and the time to resolution of lesions (O)?

Acyclovir

In the systematic review by Stephen and colleagues done for these guidelines (in preparation), 13 relevant studies were identified. In five studies (Balfour et al., 1983; Bean et al., 1982; McGill et al., 1983; McKendrick et al., 1984; McKendrick et al., 1986) the time to cessation of new lesions was observed in 200 subjects on acyclovir and 206 subjects on placebo. There was significant beneficial effect (earlier stoppage of new lesions) in subjects on acyclovir (hazard ratio [HR] 0.65; 95% CI 0.51 to 0.83). There was very low heterogeneity between studies (I^2=18%). All studies tended to show a beneficial effect of acyclovir, although only two were statistically significant.

Two studies (van den Broek et al., 1984; Wassilew et al., 1987) reported mean time to cessation of new lesions, with a mean difference of 0.59 days (95% CI -1.11 to -0.89), i.e. half a day earlier in the acyclovir group. The numbers examined were 55 in the acyclovir and 53 in the placebo group. Wassilew and colleagues (1987) also reported mean time to healing of lesions, with a mean difference of 7.4 days (95% CI -15.78 to 0.98) which was not significant. There were 29 individuals in each group.

Time to lesion healing was examined in three studies (McKendrick et al., 1984; McKendrick et al., 1986; McGill et al., 1983). Analysis of 135 subjects in the acyclovir and 148 in the placebo group demonstrated a significant beneficial effect of acyclovir (HR 1.48; 95% CI 1.06 to 2.05). There was very low heterogeneity between studies (I^2=20%). All studies tended to show a beneficial effect of acyclovir, although only one study was statistically significant.

Famciclovir

Time to lesion healing was examined in three studies (Shen et al., 2004; Degreef & Famciclovir Herpes Zoster Clinical Study Group, 1994; Tyring et al., 2001). Analysis of 275 subjects in the famciclovir and 294 in the acyclovir group did not demonstrate a significant beneficial effect of famciclovir over acyclovir (HR 1.18; 95% CI 0.98 to 1.41). There was negligible heterogeneity between studies. All studies tended to show a beneficial effect of famciclovir, although none was statistically significant.

Valacyclovir

Analysis of time to cessation of new lesions was only possible in one study (Beutner et al., 1995) with 384 and 375 subjects examined in the valacyclovir and acyclovir groups respectively. However, the difference was not significant (HR 1.03; 95% CI 0.89 to 1.20).

Time to lesion healing was examined in two studies (Beutner et al., 1995; Raju et al., 2011). Analysis of 414 subjects in the valacyclovir and 406 in the acyclovir group did not demonstrate a significant beneficial effect of valacyclovir over acyclovir (HR 1.01; 95% CI 0.88 to 1.16). There was negligible heterogeneity between studies. All studies tended to show a beneficial effect of valacyclovir, although none was statistically significant.

Brivudin

Three studies compared the efficacy of brivudin to acyclovir. There was no significant beneficial effect in subjects of brivudin as compared to acyclovir either for time to cessation of new lesions (HR 1.11; 95% CI 0.99 to 1.27) (Heidl et al., 1991; Wassilew et al., 2003) or time to total healing (HR 0.95; 95% CI 0.85 to 1.06) (Heidl et al., 1991; Wassilew et al., 2003; Wutzler, 1995).

9.4 Rationale for recommendations

Acyclovir, famciclovir and valaciclovir are all effective in the treatment of herpes zoster, in decreasing the time to cessation of new lesions and also in decreasing the time to total healing of rash. Resolution of herpes zoster is accelerated with any of the following: oral acyclovir 800 mg five times daily for seven days; valacyclovir 1000 mg three times daily for seven days; or famciclovir 750 mg once daily, 500 mg twice daily, or 250 mg three times daily for seven days. Although most studies tended to show a beneficial effect for famciclovir and valacyclovir over acyclovir, none was statistically significant.

Although there are no RCTs in children, the generally accepted optimal initial therapy for immunocompromised children with herpes zoster is 80 mg/kg per day by mouth (20 mg/kg four times per day, maximum of 800 mg per dose) or in severe infections intravenous acyclovir 500 mg/m^2 per dose or 10 mg/kg per dose, given intravenously every eight hours. The duration of therapy is seven days, or two days after the cessation of the formation of new lesions (Arvin, 2002).

Adverse effects, costs, availability and other implementation considerations

The safety profiles of acyclovir, valacyclovir and famcyclovir are similar, with headaches and nausea/vomiting the most frequent adverse effects. Caution is required when acyclovir is given to a patient on tenofovir as acyclovir has been incriminated in increasing renal impairment, in particular when intravenous acyclovir and tenofovir are administered in the same patient.

All three drugs are equally effective. However, acyclovir is more likely to be available in low- or medium-resource countries, and it costs much less than the other newer drugs (see **ANNEX 3**). Valacyclovir and famcyclovir offer a simpler dosing schedule than acyclovir. Choosing between these two drugs depends on the patient's compliance and on the physician's habits.

Based on the quality of evidence, the magnitude of effect, balance of benefits versus disadvantages, availability, cost and feasibility, the strength of the recommendation of acyclovir for the treatment of herpes zoster in HIV-infected children and adults is categorized as strong with low quality evidence.

9.5 Research gaps

Areas of needed research identified include:

- Evaluation of different doses of acyclovir treatment, in the HIV-infected and general populations;
- Use of other antivirals against varicella with improved bioavailability (i.e. valaciclovir and famciclovir) in paediatric populations.

10. Evidence and recommendations on scabies

10.1 Background

10.1.1 Epidemiology

Scabies is a parasitic infection of the skin that is caused by the mite of *sarcoptes scabiei var. hominis*. It occurs throughout the world, with an estimated 150 million cases (Hay et al., 2013), but is particularly problematic in areas of poor sanitation, overcrowding and social disruption. The prevalence of scabies in children is estimated to be 0.2% to 24% globally, and 1.3% to 17% in sub-Saharan Africa (WHO, 2005). In HIV-infected populations, prevalence has been reported as between 0.5% to 6% in adults and 2% to 10% in children (Patton et al., 2002). Scabies has been described as occurring both endemically and epidemically. In industrialized countries, it occurs epidemically in institutional settings, such as in nursing homes and prisons.

Scabies transmission occurs by direct skin-to-skin contact with an infected person; the higher the parasite burden, the greater the likelihood of transmission. Transmission via inanimate objects, such as shared clothing, is rare, but occurs in immunocompromised individuals (Chosidow, 2006; Hay et al., 2004; Arlian et al., 1988).

10.1.2 Clinical features

Scabies infection is characterized by intensely pruritic and erythematous papules and papulovesicles. The classical sites of infestation are in the interdigital web spaces of the fingers, the wrists, axillary areas, female breasts (particularly the skin of the nipples), peri-umbilical area, penis, scrotum and buttocks (Chosidow, 2000). The average number of mites reported per patient is approximately five to 15. The female mite burrows downwards into the skin, consuming the horny layer of the epidermis and the sera that seeps into the burrow from the dermis. The burrows are often undetectable, but can be seen as greyish, short, wavy lines in affected areas. Atypical presentations are common in immunosuppressed patients, such as the HIV-infected, or in those with chronic infection. Nodules can occur in some cases, and these take several months to disappear after successful treatment (Walton & Currie, 2007). Papules can develop into secondary lesions with infection, crusting and excoriations.

Secondary infection with *Staphyocccus* and *Streptococcus* can occur, causing complications including impetigo, abscess, cellulitis and septicaemia, as well as immunologic diseases including glomerulonephritis.

10.1.3 HIV infection

A broad spectrum of presentations of scabies occurs in the HIV-infected population. Scabies may present in atypical or crusted forms (Portu et al., 1996).

Crusted scabies is a severe, debilitating disease. It is an uncommon condition, most often presenting in immunocompromised individuals, such as those with HIV infection, especially in association with a low CD4 cell count (Funkhouser et al., 1993), as well as the elderly. The infection is characterized by considerably high numbers of mites where multiplication continues unhindered, producing thousands to millions of mites. The clinical picture shows hyperkeratotic skin crusts that may be loose, scaly and flaky, or thick and adherent. The crusts contain high numbers of mites. The distribution may be localized or extensive, and often in atypical patterns including the neck, face, scalp, eyelids and under the nails (Chosidow, 2000 & 2006).

10.1.4 *Diagnosis*

Diagnosis of scabies is usually made on clinical findings. Confirmatory tests include microscopic identification of the mites, eggs or mite faeces. Secondary bacterial infection of the skin lesions may occur.

10.2 Recommendations

Mild/moderate scabies

- For scabies in HIV-infected children and adults (including pregnant women) topical application of permethrin 5% (two applications) is recommended. If permethrin is not available, benzyl benzoate (at least two applications) should be used.
- If there is poor response to treatment, or permethrin treatment is not feasible, then oral ivermectin at 200 µg/kg is recommended.
  (Strong recommendation, low quality evidence)

Severe or crusted scabies

- For severe or crusted scabies in HIV-infected children ≥15 kg and adults:
  - — two doses (with one to two weeks in-between) of oral ivermectin;
  - — if ivermectin is not available, then treat with topical permethrin 5% (or alternatively benzyl benzoate) until clinically clear, as longer treatments may be required.

  (Conditional recommendation, very low quality evidence)
- For severe or crusted scabies in HIV-infected children <15 kg,
  - — topical permethrin 5% (or alternatively benzyl benzoate) until clinically clear, as longer treatments may be required.

  (Conditional recommendation, very low quality evidence)
- In addition, a keratolytic, such as 5% salicylic acid, may be used to remove scale bulk.
  (Conditional recommendation, very low quality evidence)

Remarks

Patients should be advised that the itch and rash may persist up to two weeks even after successful treatment.

In addition to individual patient management, contact tracing and treatment are necessary to prevent spread of disease and ensure treatment success. All family members and close contacts should be treated simultaneously. In close-contact communities such as nursing homes, hospitals, schools and prisons, all patients and staff are required to have treatment. In addition, household items such as clothes, towels and bedding should be washed, or subjected to heat from an iron or hot clothes dryer (Strong & Johnstone, 2007; Group, 2010). Alternatively the clothes can be placed in sealed bags for a week, by which time the mites will have died.

Drugs

- For adults (including pregnant women), two applications of topical benzyl benzoate 25% can be used as an alternative to permethrin and ivermectin.
- For children less than 15 kg, there is not enough evidence to make recommendations if permethrin is not available, but options include sulfur (8%–10%) and benzyl benzoate (10%–12.5%).
- In crusted scabies, adding permethrin in addition to ivermectin may be considered.
- Lindane is not recommended because of potential neurotoxicity, and it is no longer available in many regions.
- Ivermectin should not be used in areas where Loa Loa prevalence is over 20%, as there is a risk of severe adverse reactions.

- Ivermectin is not recommended for children below 15 kg and pregnant or lactating women.
- Relevant drug interactions are described in **ANNEX 2**.

Other

- There is not enough evidence to make recommendations for infants under 2 months of age, but options include 8% sulphur in white soft paraffin applied for three days in a row, or permethrin 5% cream applied in two applications one week apart in both HIV-positive and HIV-negative babies.
- The appropriate application according to location should be ensured – for HIV-infected individuals and infants (with or without HIV) treated areas should also include face and scalp as these areas are also affected.
- Other management measures should include: treatment of all household members and contacts, and thorough washing of clothing and bed linen with warm water.

These recommendations apply to HIV-negative children and adults as well.

10.3 Review question and summary of evidence

A systematic review (Vekic et al., in preparation) was based on the PICO question: in children and adults living with HIV infection (receiving and not receiving ART) (P), does any anti-scabies treatment (including topical permethrin, benzyl benzoate, oral ivermectin and/or ART) (I) compared to another treatment, no intervention or placebo (C) result in a clinical cure, reduction of itch or disappearance of mites on scrapings (O).

The review carried out for these guidelines (Vekic et al., in preparation) identified a total of 36 relevant studies. It found very little evidence to support any particular intervention for scabies in HIV-infected individuals. However, the review suggested that treatments should be based on severity with separate recommendations for the severe form of scabies with a very high mite burden including crusted scabies, and for the classic mild/moderate type.

For mild/moderate disease in association with HIV infection, treatment efficacy appears to be similar to individuals in the HIV-negative population (Vekic et al., in preparation). A Cochrane review (Strong & Johnstone, 2007) included 22 studies involving 2676 people without HIV (both children and adults). Only one study was a controlled trial with a placebo, and six studies included only children, three included only adults, and 13 included both children and adults. In HIV-negative study subjects with non-crusted scabies, topical permethrin appeared more effective than oral ivermectin (140 participants, two trials, RR 4.61, 95% CI 2.07 to 10.26, fixed-effect model), topical crotamiton (194 participants, two trials, RR 0.24, 95% CI 0.10 to 0.55, fixed-effect analysis) and topical lindane (RR 0.59, 95% CI 0.37 to 0.95, fixed-effect model; 554 participants, the pooled effect for the three trials). Permethrin appeared to be the most effective topical treatment for scabies, and ivermectin appeared to be an effective oral treatment.

Because of the scarcity of articles on the treatment of HIV and scabies, an additional review was undertaken, looking at the treatment of crusted scabies, as this was identified as occurring commonly in immunocompromised hosts, particularly in association with HIV infection. No RCTs for HIV and scabies and no randomized trials for crusted scabies were identified. Currently there are no data on the best treatment for scabies in association with HIV. There is also no evidence that treatment of HIV-associated crusted scabies is different from treatment of non HIV-associated crusted scabies. The use of oral ivermectin (200 µg/kg in two doses, one to two weeks apart) was found to be successful in several reviews (Nofal, 2009; Dourmishev et al., 1998; Leppard & Naburi, 2000; Sullivan et al., 1997; Larralde et al., 1999). Keratolytics were shown to be useful in reducing the mite burden of scabies in all cases.

Use of ART

The use of ART in HIV-infected patients with reconstitution of the immune system will probably reduce the frequency of crusted scabies.

Considerations in choice of drug

Ivermectin is the only oral treatment available for scabies. It is not recommended for pregnant or lactating women and children under 15 kg due to its potential adverse effects including hepatotoxicity, tachycardia and hypotension (Golant & Levitt, 2012). Permethrin 5% cream is recognized as the most effective treatment for scabies in immunocompetent hosts (Strong & Johnstone, 2007). Benzyl benzoate can be used in a diluted form for children, infants and breastfeeding mothers. Topical treatments with benzyl benzoate and permethrin for scabies during pregnancy have shown no increase in adverse pregnancy outcomes in the second and third trimesters of pregnancy (Mytton, 2007). Benzyl benzoate and permethrin are both categorized as drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human fetus.

Although previously effective in treating scabies, lindane is no longer recommended due to the risk of neurotoxicity, especially in children.

Children

No good quality data exist on the treatment of children under the age of two months. There have been three case reports of permethrin being used safely in neonates (Subramaniam et al., 2013; Quarterman & Lesher, 1994; Guerci et al., 2010). Permethrin has a good safety profile and should be well tolerated in neonates as its absorbance is very low. The risk of untreated scabies was considered and valued higher. Safety of the use of crotamiton in newborns and infants has not been well established, and results from a double-blind randomized trial proved that crotamiton cream is significantly less efficacious than permethrin (Meinking et al., 1995).

Sulphur-containing preparations are used extensively, especially in resource-limited countries, but there is little literature to support it. Comparison trials between sulphur and permethrin or benzyl benzoate are not available. Sulphur preparations require compounding, are messy in application and have an unpleasant smell (Mounsey & McCarthy, 2013; Ly et al., 2009).The efficacy of sulphur for three days at 8% to 10% has recently been confirmed for the treatment of adult scabies (Sharquie et al., 2012). Neonates are able to have sulphur preparations applied onto their skin, as for various other skin conditions including seborrhoeic dermatitis, without evidence of harm being reported in its very widespread use (Elish & Silverberg, 2006; Janniger & Schwartz, 1995).

10.4 Rationale for recommendations

Scabies, and especially crusted scabies, is associated with considerable patient distress due to itching and potential stigma, as well as being an entry point for secondary bacterial infection of the skin, which is a significant risk for morbidity and even mortality. Therefore, prompt resolution of the skin manifestations is a priority to patients and their families.

The group considered that permethrin appears to be the most effective treatment for scabies infection. It has been tested against topical crotamiton and oral ivermectin in RCTs, and it appears to be superior in terms of minimizing treatment failure in participants with a clinical diagnosis of scabies. A few trials show no difference in cure rates between permethrin and topical benzyl benzoate. No serious adverse events leading to death or permanent disability were reported.

Ivermectin is currently the only oral treatment for scabies that is in routine use. It appears to be more effective than both placebo and lindane, but less effective than permethrin.

The limited data on crusted scabies in HIV-infected patients suggest a good effect of oral ivermectin. Local ivermectin resistance needs to be assessed and considered.

Currently, there is no evidence of the effects of prophylaxis, either beneficial or adverse, when used for contacts of people with scabies (FitzGerald et al., 2014). However, the GDG considered it important and recommended that contact tracing and treatment are necessary to prevent spread of disease and ensure treatment success. The group also recommended that all family members and close contacts should be treated simultaneously. In close-contact communities such as nursing homes, hospitals, schools and prisons, all patients and staff are required to have treatment.

The community effect of the different options is considered to be similar. On balance, the panel made a strong recommendation with low quality evidence for treatment of classic scabies and a conditional recommendation with very low quality evidence for treatment of severe scabies. The benefits of the recommended treatments outweigh any possible harms of the medication.

Adverse effects, costs, availability and other implementation considerations

Reported adverse reactions with the use of permethrin are rare in both adults and children (Coleman et al., 2005).

Ivermectin has been used extensively in the treatment of onchocerciasis and serious adverse effects have been rare even with repeated doses (DeSole et al., 1989; Pacque et al., 1990). However, minor adverse effects such as aggravation of symptoms as well as headache, hypotension, abdominal pain and vomiting have been reported in some studies.

There are several advantages of oral treatment over topical treatment, most importantly, the ease of use. Ivermectin is easier to use, and proper administration of both permethrin and benzyl benzoate can be challenging. Despite ivermectin being an effective treatment for scabies, it is not presently licensed for this purpose in most countries. It lacks safety data on use in small children and pregnant women.

Considerable variation exists in the price of treatments, especially ivermectin, but in low- and middle-income countries the price is relatively low. A course of permethrin costs about US$ 0.50, 25% benzyl benzoate less than US$ 0.10 and 5% salicylic acid around US$ 0.10.

10.5 Research gaps

Proposed areas for future research on the treatment of scabies include well-designed treatment trials to evaluate the effectiveness of:

- Various dosages of topical permethrin, in HIV-infected and non HIV-infected populations;
- Topical and oral ivermectin, in HIV-infected and non HIV-infected populations;
- The most appropriate treatment for the severe crusted form of scabies;
- Approaches to the control of outbreaks of scabies in institutions and public health programmes in populations with high prevalence, in HIV-infected and non HIV-infected populations.

11. Evidence and recommendations on molluscum contagiosum

11.1 Background

11.1.1 Epidemiology

Molluscum contagiosum is a common viral skin infection frequent in tropical climates. It usually affects young children, but also sexually active young adults and the immunosuppressed, such as people infected with HIV.

The worldwide incidence of molluscum contagiosum is estimated to be between 2% and 8%, while amongst HIV-infected people, the prevalence is estimated at 5% to 18% (Husak et al., 1997).

11.1.2 Clinical features

Molluscum contagiosum is a common superficial viral infection of the epidermis caused by a pox virus and spread by skin-to-skin contact. Lesions are typically pearly white or skin-coloured papules with a central umblication. It can occur anywhere on the body including the external genitalia, but is most commonly seen on the face and trunk in children. The course of the disease is self-limiting, and recurrence is rare in immunocompetent individuals.

In people infected with HIV, molluscum contagiosum lesions are often persistent, frequently recur, have a fulminant clinical presentation and a longer duration of clinical manifestation. They may be disseminated, but with a predilection for the head, neck and genital area (Liota et al., 2000). The lesions may be larger, verrucous and hypertrophic in nature and can coalesce to cause disfigurement and psychological distress to the patient (Martin et al., in press).

11.2 Recommendations

- ART should be considered as the primary treatment of extensive and/or unusually distributed molluscum contagiosum in HIV-infected patients. No additional specific treatment is recommended (see **SECTION 3**).
  (Conditional recommendation, very low quality evidence)
- All adults presenting with new-onset molluscum contagiosum in high HIV-prevalence settings with unknown HIV status should be offered an HIV test and, if positive, assessed for ART eligibility (see **SECTION 3**).
  (Strong recommendation, low quality evidence)

Remarks

- *Symptoms after ART initiation: redness and swelling can occur, and IRIS is possible when ART is initiated. ART should be continued; there is no evidence for any other specific treatment.*
- *Relevant drug interactions are described in* **ANNEX 2**.
- *There is no specific recommendation or precaution for reducing the risk of transmission.*
- *For HIV-negative children and adults, symptomatic treatment may be provided.*

11.3 Review question and summary of evidence

The PICO question for the systematic review was: in children and adults living with HIV infection (receiving and not receiving ART) (P) does ART, surgical excision, cryotherapy, cidofovir, podophyllotoxin, bichloracetic or trichloracetic acid, imiquimod, 5-aminolevulinic acid, photodynamic therapy, tretinoin or cantharidin (I) compared with no treatment (C) result in i) resolution and disappearance of lesions one month after last day of treatment (for ART, one month after initiation) or absence of lesions after three to six months; or ii) reduce the time taken from treatment completion (or initiation in the case of ART) to clinical cure or reduction in lesion count, or prevent recurrence of lesions (O)?

A review to address this question (Martin et al., in press) found that for molluscum contagiosum in HIV-infected children and adults there was only one randomized trial, and only two comparative studies, neither of which was blinded. Most evidence was from small, uncontrolled observational studies heavily prone to selection and performance bias. In 11 of them, no statistical analysis was performed to evaluate the clinical significance of the reported results. Five papers assessed the effect of topical therapy alone, two discussed the effect of antiretroviral therapy on MC, and six discussed physical therapy or a combination of therapy. Vital information was missing from some, and overall the quality of evidence was ranked as very low.

Impact of ART

The systematic review (Martin et al., in press) found that since the advent of ART in the mid 1990s, clinicians have noted a reduction in some dermatological manifestations of HIV (Horn et al.,1998; Hicks et al.,1997; Leahey et al.,1997). At an individual patient level, case studies are the main basis for the anecdotal evidence which suggests that starting ART, and the subsequent rise in CD4 cell count, is associated with resolution of molluscum contagiosum lesions (Horn et al., 1998; Hicks et al.,1997; Calista et al.,1999). One multicentre, longitudinal cohort study assessed the effect of ART on prevalence of skin disease in HIV-infected women. Recent initiation of ART did not have a significant effect on the prevalence of molluscum contagiosum in these women (Maurer et al., 2004).

A few case studies were available on the association between molluscum contagiosum and IRIS after initiation of ART (e.g. Drain et al., 2013), but these had very small sample sizes and were considered of very low quality.

No RCTs assessed the effect of an intervention for molluscum contagiosum in HIV-positive individuals. Selection, performance and/or reporting bias is present in most of the available studies. Therefore the evidence is ranked as very low quality.

11.4 Rationale for recommendations

Although only limited data are available, the GDG was unanimous in its opinion that ART should be considered as the primary treatment of extensive and/or unusually distributed molluscum contagiosum in HIV-infected patients and that no additional specific treatment is needed. The recommendation is conditional due to the lack of evidence on HIV-infected children and adults with molluscum contagiosum. However, molluscum infection is likely to resolve spontaneously in HIV-negative patients, and sparse low quality evidence supports this for HIV patients on ART. Only a few low quality studies show an association between ART and worsening or occurrence of molluscum (e.g. IRIS).

The desirable effects of this recommendation are large, and there are no additional undesirable effects, since the treatment only includes ART.

Adverse effects, costs, availability and other implementation considerations

The present WHO recommendation is ART initiation for all symptomatic patients (WHO, 2013). ART would be acceptable to most patients who are eligible for treatment, and the incremental cost is probably small. There is free access to ART in most settings.

11.5 Research gaps

The identified research gaps include:

- Better understanding and estimates of the burden of disease;
- Evaluation of treatment options for severe molluscum contagiosum;
- Standardized outcome frameworks to allow comparisons to be made across studies;
- Studies of treatments in HIV-infected adults and children and of the sexually-transmitted variant that affects immunocompetent people.

12. Evidence and recommendations on oropharyngeal candidiasis

12.1 Background

12.1.1 Epidemiology

Oropharyngeal candidiasis, or thrush, is a common local infection seen in infants, older adults who wear dentures, patients treated with antibiotics, chemotherapy or radiation therapy to the head and neck, and those with cellular immune deficiency states, such as HIV infection (Shay et al., 1997; Epstein et al., 1993; Iacopino & Wathen, 1992; Sangeorzan et al., 1994).

Several studies have shown that oropharyngeal candidiasis can occur in 45% to 90% of HIV-infected adults in the absence of ART (Yang et al., 2006). It is not only common, but also recurs frequently (Arribas et al., 2000; Greenspan et al.,1992; Gennaro et al., 2008; Reznik, 2005/2006), often presenting as an initial manifestation of the disease (Coogan et al., 2005; Epstein & Polsky, 1998; Nittayananta & Chingpanich, 1997; Rachanis, 2001).

Similarly, in HIV-infected children the prevalence can be as high as 81% (Christine Henneberg, personal communication, 2010). If left untreated, these lesions contribute considerably to the morbidity associated with HIV infection (Oude Lashof, 2004). Interventions aimed at preventing and treating HIV-associated oral candida lesions form an integral component of maintaining the quality of life for affected individuals.

12.1.2 Clinical features

The clinical manifestations include a soft white coating or pseudomembrane on the mucosal surface of the mouth which reveals a red, raw surface when wiped off; depapillation or red/raw surface on the tongue; or thick white plaque which cannot be rubbed off, which is most challenging to diagnose. Though *Candida albicans* is most commonly implicated, other organisms have also been identified.

In patients with oropharyngeal candidiasis a presumptive diagnosis of *Candida esophagitis* can be made if the patient has dysphagia (difficulty in swallowing). Endoscopy is required for definitive diagnosis. Most patients with esophageal candidiasis respond to antifungal therapy within three to seven days (Rabeneck & Laine 1994). If the patient fails to improve with appropriate systemic antifungal therapy, then endoscopy is indicated to exclude other causes of esophagitis including herpes simplex virus or cytomegalovirus, both common causes of esophagitis in immunocompromised populations.

12.2 Recommendations

Specific therapy

In adults

- Oral fluconazole 100–150 mg for seven to 14 days is recommended as the preferred treatment.
- When fluconazole is not available or contraindicated, alternatives include topical therapy with nystatin suspension or pastilles, or clotrimazole troches.
  (Strong recommendation, moderate quality evidence)

In children

- Oral fluconazole 3 mg/kg for children for seven to 14 days is recommended as the preferred treatment.
- When fluconazole is not available or contraindicated, alternatives include topical therapy with nystatin suspension or pastilles, or clotrimazole troches.
- In children with mild oropharyngeal candidiasis, topical therapy with nystatin suspension or pastilles (alternatively clotrimazole troches) is recommended.
  (Strong recommendation, low quality evidence)

ART eligibility

Prompt ART initiation is recommended in all HIV-infected adults (including pregnant and breastfeeding women), adolescents and children with oropharyngeal candidiasis (see SECTION 3).
(Strong recommendation, high quality evidence)

Remarks

- *When there is no response to fluconazole after 14 days of treatment, consider a higher dose. If still no response, consider fluconazole resistance. Itraconazole may be an alternative regimen, but precautions regarding drug interactions should be observed. When there are difficulties in swallowing, oesophageal candidiasis should be considered and treatment should be provided for a longer duration, 14–30 days. The use of maintenance therapy is not recommended.*
- *In HIV-infected patients with oropharyngeal candidiasis, always ask for a history of dysphagia to rule out oesophageal candidiasis, which is always treated with systemic antifungals (fluconazole 3–6 mg/kg per day for 14 days). A diagnostic trial of systemic antifungal treatment is appropriate before performing an endoscopic examination.*
- *The use of gentian violet is no longer recommended.*
- *Relevant drug interactions are described in* ANNEX 2.
- *Check the breasts of a breastfeeding woman when she or her infant has oropharyngeal candidiasis and treat accordingly.*
- *In addition to the drug treatment, ensure that the patient has adequate hydration and nutrition.*

These recommendations apply to HIV-negative children and adults as well.

12.3 Review question and summary of evidence

The systematic review was based on the PICO question: in children and adults living with HIV infection (receiving or not receiving ART) (P) do antifungals (fluconazole, itraconazole, clotrimazole, posaconazole, nystatin, gentian violet) or ART (I) compared to another drug or no treatment (C) achieve complete resolution of the disease, achieve mycological cure or reduce or prevent recurrence (O).

The systematic review (Pienaar et al., 2013) included 34 studies: 23 assessing treatment and 11 assessing prevention of oropharyngeal candidiasis. Six studies were done in developing countries, 16 in the USA and the remainder in Europe.

Treatment of oropharyngeal candidiasis

Treatment was assessed in the majority of trials looking at both clinical and mycological cures. In the majority of comparisons there was only one study. Compared to nystatin, fluconazole favoured clinical cure in adults (one RCT; n=167; RR 1.69; 95% CI 1.27 to 2.23). There was no difference with regard to clinical cure between fluconazole and ketoconazole (two RCTs; n=83; RR 1.27; 95% CI 0.97 to 1.66), itraconazole (two RCTs; n=434; RR 1.05; 95% CI 0.94 to 1.16), clotrimazole (two RCTs; n=358; RR 1.14; 95% CI 0.92 to 1.42) or posaconazole (one RCT; n=366; RR1.32; 95% CI 0.36 to 4.83). Two trials compared different dosages of fluconazole with no difference in clinical cure. When compared with clotrimazole, both fluconazole (two RCTs; n=358; RR 1.47; 95% CI 1.16 to 1.87) and itraconazole (one RCT; n=123; RR 2.20; 95% CI 1.43 to 3.39) proved to be better for mycological cure. Both gentian violet (one RCT; n=96; RR 5.28; 95% CI 1.23 to 22.55) and ketoconazole (one RCT; n=92; RR 5.22; 95% CI 1.21 to 22.53) were superior to nystatin in bringing about clinical cure. A single study compared miconazole with clotrimazole with no difference between the groups for clinical cure.

Two trials, De Wit and colleagues (1993) (n = 56) and Hamza and colleagues (2008) (n=220) compared different dosages of fluconazole. In De Wit and colleagues' study one arm was given 50 mg per day for seven days, and the other arm was given 150 mg as a single dose. Hamza and colleagues compared 150 mg per day for 14 days with 750 mg as a single dose. There was no clear superiority between the dosages for both clinical and mycological cure. Based on clinical experience and the evidence from the systematic review, the GDG recommended a fluconazole dose of 100–150 mg daily for seven to 14 days.

Recurrence of oropharyngeal candidiasis

Eleven trials identified in the review investigated the prevention of recurrence of oropharyngeal candidiasis in adults. Fluconazole was compared with placebo in five studies (five RCTs; n=599; RR 0.61; 95% CI 0.5 to 0.74) (Leen et al., 1990; Stevens et al., 1991; Marriott et al., 1993; Pagani et al., 2002; Schuman et al., 1997) and with no treatment in another (one RCT; n=65; RR 0.16; 95% CI 0.08 to 0.34) (Ramsay et al., 2003). In both instances the prevention of clinical episodes was favoured by fluconazole. Comparing continuous fluconazole treatment with intermittent treatment (two RCTs; n=891; RR 0.65; 95% CI 0.23 to 1.83) (Goldman et al., 2005; Revankar et al., 1998), there was no significant difference between the two treatment arms. Chlorhexidine was compared with normal saline in a single study with no significant difference between the treatment arms (Nittayanta et al., 2008).

There were no trials investigating prevention of recurrence in children, including in HIV-infected children.

Impact of ART

One systematic review compared the incidence of oropharyngeal candidiasis before and after the widespread introduction of ART, and showed a significant reduction in the incidence in both adults and children (Andrea Low & Marie-Renee Lajoie, unpublished data, 2014). In general, after ART immune reconstitution, recurrence is infrequent.

None of the studies included in the systematic review investigated the individual effects of ART or any other form of ART on oropharyngeal candidiasis response and rate of recurrence. Oral lesions associated with HIV form part of the clinical spectrum of immune reconstitution associated with ARV use. Protease inhibitors have been shown to directly attenuate the adherence of *Candida albicans* to epithelial cells in vitro (Bektic et al., 2001; Cauda et al., 1999; Cassone et al.,1999). The systematic review's authors considered that the impact of this intervention warrants further investigation with regard to clinical presentation and mycological effect.

12.4 Rationale for recommendations

The evidence suggests that ketoconazole, fluconazole, itraconazole and clotrimazole are all effective in the treatment of oropharyngeal candidiasis in HIV-infected persons. Oral fluconazole is highly effective, and as a single daily dose is more convenient. Itraconazole is as effective as, but less well tolerated than, fluconazole. Both ketoconazole and itraconazole capsules are less effective than fluconazole because of their variable absorption. Ketoconazole oral tablets were excluded from the recommendation because of their severe adverse effects (e.g. Smith et al., 1991) and significant drug interactions with ART (WHO, 2013).

In a previously published review, Patton and colleagues (2001) found that the efficacy of fluconazole ranged from 87% to 100%, bringing about a complete clinical response, which is the absence of signs or symptoms of oropharyngeal candidiasis, or both. This is similar to the findings in the review by Pienaar and colleagues (2013), namely that the effectiveness of fluconazole in bringing about clinical cure of oropharyngeal candidiasis is the highest, followed by itraconazole.

Even though the only trial on gentian violet, by Nyst and colleagues (1992), showed that it is equally effective as nystatin and ketoconazole, the GDG reached expert consensus that it is no longer effective based on clinical experience and should not be recommended.

Although fluconazole is an effective preventive intervention, the potential for resistant *Candida* organisms to develop as well as the cost of prophylaxis might impact on the feasibility of implementation. Therefore, antifungal prophylaxis is not recommended for oropharyngeal candidiasis.

It is not possible to make recommendations for treatment or prevention of oropharyngeal candidiasis in children based on evidence from the review as there is only one study in children. However, based on expert clinical experience, the GDG recommended oral fluconazole as the preferred treatment in children. When fluconazole is not available or contraindicated, nystatin suspension or pastilles, or clotrimazole troches are alternate treatments. Although rated as a strong recommendation, the evidence is graded as low quality.

Adverse effects, costs, availability and other implementation considerations

The resources required to implement this recommendation are small (see **ANNEX 3**). There may be an issue with availability of antifungals, and also with drug interactions (e.g. with methadone). Overall, the desirable effects of the recommended medicines are probably large relative to any undesirable effect, and this recommendation would probably be acceptable to key stakeholders. Based on the evidence and the above-mentioned factors this recommendation for fluconazole as the first choice of treatment for oropharyngeal candidiasis is rated as strong with moderate quality evidence.

12.5 Research gaps

More research is needed in the following areas:

- Well-designed treatment trials to detect differences in not only clinical, but also mycological response and relapse rates;
- Treatment and prevention of oropharyngeal candidiasis in HIV-infected children and adolescents;
- Development of resistance to current treatments.

13. Evidence and recommendations on Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis

13.1 Background

13.1.1 Epidemiology

SJS and toxic epidermal necrolysis are rare, life-threatening cutaneous disorders characterized by widespread epidermal necrosis.

The incidence of toxic epidermal necrolysis in the general population is 0.4 to 1.2 cases per million per year, whereas the incidence in the HIV-infected population is much higher, at 1000 cases per million per year (Trent et al., 2006). Mortality rates of SJS range from 1% to 5% and that of toxic epidermal necrolysis from 25% to 30% (Harr & French, 2010).

SJS and toxic epidermal necrolysis are both considered to be predominantly drug-induced at least 75% of the time; less commonly, they are thought to be triggered by infections (Léauté-Labrèze et al., 2000).

In HIV-infected patients, SJS and toxic epidermal necrolysis may occur in patients both on and off ART. The most common drugs causing adverse cutaneous reactions in HIV-infected patients are sulfonamides, antituberculosis drugs, especially thiacetazone, amoxicillin-clavulanic acid, clindamycin, and thalidomide. There is also an increasing incidence of nevirapine-induced SJS in the HIV-infected population (Anonymous, 2003; Sulayman et al., 2009).

13.1.2 Clinical features

SJS and toxic epidermal necrolysis are rare, severe mucocutaneous eruptions, characterized by diffuse erythema, blistering and desquamation of the skin and two or more mucosal surfaces (Raviglione et al., 1988). SJS is defined as the detachment of less than 10% body surface area (BSA) plus widespread erythematous or purpuric macules or flat atypical target lesions. Toxic epidermal necrolysis is defined as epidermal detachment of greater than 30% BSA, one variant with spots to include erythematous or purpuric macules and atypical target lesions, the other without spots and sole epidermal detachment. The overlap between SJS and toxic epidermal necrolysis is the detachment between 10% to 30% BSA and widespread erythematous, purpuric or atypical target-like annular patches.

13.1.3 Treatment

Management of SJS and toxic epidermal necrolysis entails discontinuation of the inciting medication and supportive care, but there remains controversy about the effectiveness of various specific interventions such as corticosteroid use and intravenous immunoglobulin therapy. In addition, in HIV-infected patients, the condition may occur in patients both taking and not taking these treatments. The literature is sparse on treatments of SJS and toxic epidermal necrolysis in HIV-infected patients with these adverse reactions.

13.2 Recommendations

- In HIV-infected children and adults with SJS or toxic epidermal necrolysis, the suspected causative drug should be promptly discontinued and supportive therapies should be offered.[a]
  (Strong recommendation, very low quality evidence)
- The use of systemic corticosteroids is not recommended.
  (Conditional recommendation, very low quality evidence)

Remarks

- ART: if the patient is not already on ART, initiation should be done with caution.
- Relevant drug interactions are described in **ANNEX 2**.
- Drugs initiated in the last one to three weeks prior to illness should be considered as potential causes and careful consideration of all drugs the patient is receiving is needed, including over-the-counter and non prescription as well as herbal and traditional medicine.
- There is no reliable laboratory test to determine the offending drug; diagnosis is based on the patient's history and the temporal relationship of suspected drugs (those initiated in the last one to three weeks prior to illness). Provocation tests are not indicated since re-exposure is likely to elicit a new episode of increased severity.
- Supportive care includes intravenous fluids, environmental control, sepsis monitoring, oral antibiotics, wound dressing, dietary support, emollients and physiotherapy, monitoring for eye complications, vaginal complications, and skin-directed medical therapies including topical antibiotics, topical steroids and debridement. Sepsis monitoring, but not prophylactic antibodies, is part of this care.

These recommendations apply to HIV-negative children and adults as well.

[a] according to WHO recommendations on nursing burn care (WHO, 2003; Lehloenya, 2007).

13.3 Review question and summary of evidence

The PICO for the systematic review was: in children and adults living with HIV infection (receiving and not receiving ART) (P) does discontinuation of offending medication, skin-directed medical therapies, systemic steroids, other immunomodulatory therapies, intravenous immunoglobulin, adjunct therapy (e.g. intravenous fluids, antihistamines, ocular therapies) individually or in various combinations (I) compared to no treatment (C) reduce mortality or completely or partially resolve lesions from SJS or toxic epidermal necrolysis (O)?

A total of 89 reports were identified for the systematic review (Rani & Maurer, in preparation); 78 addressed adults only, seven addressed the paediatric population only and four addressed a mixed-age population. No RCTs were identified on the treatment of SJS and toxic epidermal necrolysis in HIV-infected individuals. The available evidence included only case-control or cohort studies. Some case reports, case series and observational studies with other primary purposes, but with data on SJS and/or toxic epidermal necrolysis, were found. The reports included relatively few patients, and reporting bias was likely to have been high. Most of the studies did not comment on the severity of the toxic epidermal necrolysis. The direction or true effect of the treatment approaches listed cannot be estimated, and observational studies are likely to provide an overestimate of the true effect. Therefore, all evidence is considered of very low quality. GRADE tables were not prepared because of the nature of the evidence.

Evidence on the following issues for resource-limited and middle-income countries was found:

- *Discontinuation of inciting drug:* A total of 354 patients in 15 reports had treatment discontinued as the only intervention; 292 (82.5%) survived and 62 died within 28 days of onset of SJS or toxic epidermal necrolysis. There were no reports of paediatric patients receiving this treatment approach. One study described a mixed-age population (n=306), of which 58 died (81.1% survival rate).
- *Adjunctive therapies only (intravenous fluids, environmental control, sepsis monitoring, wound dressing, dietary support and physiotherapy):* A total of 61 patients in three reports were treated with adjunct therapies, and 42 survived (68.9%). All of these patients were adults.
- *Combination of discontinuation of drug with adjunct therapies:* Nineteen patients, reported in a total of 17 articles, were treated with this approach, and 16 had a positive outcome (84.2%). Of the 17 adults treated with this approach, three died (survival rate=82.4%). Two children were treated with this therapy, and both survived.
- *Combination of discontinuation of inciting drug with systemic steroids and adjunct therapies:* A total of 59 patients, reported in 24 studies, were treated with this approach. Forty (67.8%) had a positive outcome, and 19 died. Of the 15 children included in the reports, 13 died, giving a survival rate for this treatment approach of 13.3%.
- *Combination of discontinuation of drug with skin-directed medical therapies (not defined in reviews) and adjunct therapies:* A total of 21 patients in three studies were treated with this combination of approaches. All of the 20 (a mix of adults and children) with reported outcomes by age survived.
- *Steroids:* When steroids were used, 13 of 15 children died. In adults, the addition of steroids did not show a clear benefit to discontinuation of the inciting drug and/or adjunct care. Steroids may also place the HIV-infected patient at risk for OIs and sepsis.

13.4 Rationale for recommendations

This is a complex disease spectrum, and there is limited high quality information on the different types of adjunctive therapies and topical treatments or their desirable and undesirable effects. Considering the potential high mortality rates, the undesirable effects of the recommendation were considered less important.

The experts agreed that early detection of SJS and toxic epidermal necrolysis is critical. Health care providers should be aware of the symptoms, including blistering, tenderness, redness, rash, erosions and photophobia.

The review did not find any good evidence to support the use of oral steroids, immunoglobulins or cyclosporine-A, all common treatments for this condition. The group considered that the use of steroids may decrease survival in the paediatric group, although the evidence was of low quality. Steroids may also place the HIV-infected patient at risk for OIs and sepsis.

Adverse effects, costs, availability and other implementation considerations

Very high costs for treatment are expected, and supportive care costs are also high. It would be possible to implement the recommended approach only in larger hospitals, with good facilities for diagnosis of disease, availability of trained staff and good nursing care, and the possibility of referral. WHO's and other recommendations on nursing burn care should be followed (WHO, 2003; Lehloenya, 2007).

13.5 Research gaps

Areas for further research include:

- RCTs to elucidate the role of adjunctive therapies, such as intravenous immunoglobulin specifically in HIV-infected populations;
- As provocation tests are contraindicated in SJS and toxic epidermal necrolysis, development of other in vitro methods to diagnosis and identify the causative medication in HIV-infected and non HIV-infected populations;
- Evaluation of the effects of treatment with high-dose oral steroids and intravenous immunoglobulins compared with best supportive care, in HIV-infected and non HIV-infected populations;
- Effectiveness of different types of skin care dressings;
- The role of infection prophylaxis, in HIV-infected and non HIV-infected populations.

14. Dissemination, implementation and monitoring of these guidelines

The ultimate goal of these guidelines is to improve the management of the conditions included. Therefore, their dissemination and implementation are crucial steps that should be undertaken by the international community and local health care services.

14.1 Guidelines dissemination

The recommendations in these guidelines will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. They will also be published on the WHO website.

14.2 Guidelines implementation

The first steps in implementation after the final approval of these guidelines will be to revise all WHO publications that deal with these opportunistic conditions, and/or ensure their inclusion in other relevant documents. These include the materials for the Integrated Management of Childhood Illness[1] and the *Pocket book for hospital care of children*.[2]

The successful introduction of evidence-based policies related to management of these conditions into national programmes and health care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national guidelines or protocols based on this document.

The recommendations contained in the present guidelines should be adapted into locally-appropriate documents to meet the specific needs of each country and health service. Modifications to the recommendations, where necessary, should be limited to weak recommendations and justifications for any changes made in an explicit and transparent manner.

An enabling environment should be created for the use of these recommendations, including changes in the behaviour of health care practitioners to enable the use of evidence-based practices. Local professional societies may play important roles in this process, and an all-inclusive and participatory process should be encouraged. WHO's MCA and HIV/AIDS Departments have substantial experience of introduction of WHO guidelines and tools into national programmes.

14.2.1 Implications for programme managers

To put these guidelines into practice, programme managers will need to especially consider a few key issues:

Integration with programme planning for HIV care

The recommendations contained in these guidelines will need to be implemented together with existing programmes for HIV, dermatological and general health care. They should be considered in the process of programme planning, so that they are gradually integrated into routine practices.

[1] See http://www.who.int/maternal_child_adolescent/topics/child/imci/en/.
[2] See http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/.

Model list of essential medicines, drug costs and dosages

The drugs recommended in this document are for the most part on the WHO *Model list of essential medicines*.[1] Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. The *Model list* is a guide for the development of national and institutional essential medicine lists.

Within this context, programme managers will need to consider modifying any existing national lists, and ensuring that adequate quantities of required drugs in the recommended dosages are available to health workers. These drugs would normally be provided through existing health system supply chains. **ANNEX 3** provides information on the costs of the recommended drugs.

Relevant to any review of national drug lists and policy, WHO's 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is a serious and growing problem across the world (WHO, 2014). Countries should strengthen national plans to tackle antimicrobial resistance.

Training

Diagnosing and recognizing skin disorders requires awareness-raising and training for the health workers who will see these conditions. An important issue is that some of these conditions appear differently in individuals of different skin colours.

Training for health workers may be integrated with on-going capacity-building in HIV care or related issues. Resources available include the *Atlas of skin conditions* (Dlova & Mosam, 2009) and the Integrated Management of Adult and Adolescent Illness manuals.

14.2.2 Implications for laboratories

Laboratory services form an essential component of HIV services. The diagnosis of skin conditions associated with HIV may require laboratory investigations when clinical examination is unclear and/or confirmation is required. Even in resource-constrained settings, laboratories should be able to perform skin scrapings (microscopy/culture); skin biopsy; and gram stain of fluid/pus and sometimes culture. Updated training on these issues may be required for laboratory personnel, as well as additional supplies and equipment. Job aids and standard operating procedures related to the required investigations should be available for workers. For full information on laboratory issues, see Integrated Management of Adult and Adolescent Illness manuals.

14.3 Monitoring and evaluating guidelines implementation

Monitoring and evaluation should be built into the implementation process, in order to provide important lessons for uptake and further implementation. With regard to monitoring and evaluation of their impact on quality of care, priority should be given to the strong recommendations.

The implementation of these guidelines should involve national ART programmes collecting and reporting data on the opportunistic conditions included, as well as related outcomes among children and adults on HIV treatment. Putting this into practice may require a review of existing patient monitoring systems, including reporting tools, to ensure that the conditions are adequately addressed.

[1] See http://www.who.int/medicines/publications/essentialmedicines/en/.

Key areas that may require monitoring include:

- diagnosis of opportunistic conditions and determining underlying HIV infections;
- treatment of opportunistic conditions and/or ART;
- response to treatment;
- service delivery.

The monitoring and evaluation strategy will endeavour to ensure that the existing ART patient monitoring tools, such as ART care card, pre-ART and ART registers, contain information on those skin conditions where these guidelines provide strong recommendations. None of these conditions are likely to be included in national HIV core indicators. However, the data could be collected periodically through special surveys or programme reviews.

References

General

Aftergut K, Cockerell CJ. Update on the cutaneous manifestations of HIV infection. Dermatol Clin. 1999; 17:445–7.

Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau J-C et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993; 129:92–6

Battegay M, Opravil M, Wüthrich B, Lüthy R. Rash with amoxicillin-clavulanate therapy in HIV-infected patients. Lancet. 1989;334(8671):1100.

Dlova CN, Mosam A. A clinical atlas of skin conditions in HIV/AIDS: an illustrated management guide for health care professionals. Claremont, South Africa: HPMG; 2005 & 2009.

Dlova CN, Mosam A. Drug reactions and the skin in HIV/AIDS. S Afr J HIV Med. 2006a; March:19–22.

Dlova NC, Mosam A. Inflammatory non-infectious dermatoses of HIV. Dermatol Clin. 2006b; 24:439–48.

Goh B-K, Chan RKW, Sen P, Theng CTS, Tan H-H, Wu Y-J et al. Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. Int J Dermatol. 2007;46:695–9.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650):924–6.

Lim W, Sadick N, Gupta A, Kaplan M, Pahwa S. Skin diseases in children with HIV infection and their association with degree of immunosuppression. Int J Dermatol. 1990; 29(1):24–30.

Muyinda H, Seeley J, Pickering H, Barton T. Social aspects of AIDS-related stigma in rural Uganda. Health Place. 1997; 3:143–7.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf, accessed 31 March 2014.

Schmid-Ott G, Jaeger B, Kuensebeck HW, Ott R, Lamprecht F. Dimensions of stigmatization in patients with psoriasis in a "questionnaire on experience with skin complaints". Dermatology. 1996; 193:304–10.

Siberry GK, Abzug MJ, Nachman S, Brady MT, Dominguez KL, Handelsman E et al. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, Centres for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. J Ped Infect Dis. 2013; 2(4):239–308.

WHO. Model prescribing information: drugs used in skin diseases. Geneva: WHO; 1997.

WHO. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach. Geneva: WHO; 2006.

WHO. Handbook for guideline development. Geneva: WHO; 2012.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

WHO. Antimicrobial resistance: global report on surveillance 2014. Geneva: WHO; 2014.

WHO, UNICEF, UNAIDS. Global update on HIV treatment 2013: results, impact and opportunities. Geneva: WHO; 2013.

Kaposi sarcoma

Amerson E, Buziba N, Wabinga H, Wenger M, Bwana M, Muyindike W et al. Diagnosing Kaposi's sarcoma (KS) in East Africa: how accurate are clinicians and pathologists? Infect Agent Cancer. 2012; 7(Suppl 1):6 (http://www.infectagentscancer.com/content/7/S1/P6).

Anglemyer A, Agrawal AK, Rutherford GW. Treatment for Kaposi's sarcoma in children with HIV-1 infection. Cochrane Database Syst. Rev. 2013; (9):CD009826.

Asiimwe F, Moore D, Were W, Nakityo R, Campbell J, Barasa A et al. Clinical outcomes of HIV-infected patients with Kaposi's sarcoma receiving nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy in Uganda. HIV Med. 2012; 13(3):166–71.

Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst. 2007; 99(12):962–72.

Bodsworth NJ, Bloch M, Bower M, Donnel DI, Yocum R, The International Panretin® Gel KS Study Group. Phase III Vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Am J Clin Dermatol. 2001;2:77–87.

Bower M, Weir J, Francis N, Newsom-Davis T, Powles S, Crook T et al. The effect of HAART in 254 consecutive patients with AIDS-related Kaposi's sarcoma. AIDS. 2009;23:1701–6.

Bower M, Dalla Pria A, Coyle C, Andrews E, Tittle V, Dhoot S et al. Prospective stage stratified approach to AIDS-related Kaposi's sarcoma. J Clin Onco. 2014; Feb 10;32(5):409–14.

Cattelan AM, Calabro ML, Aversa SM, Zanchetta M, Meneghetti F, De Rossi A et al. Regression of AIDS-related Kaposi's sarcoma following antiretroviral therapy with protease. Eur J Cancer. 1999;35:1809–15.

Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Abulafia DM et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer. 2010;116(16):3969–77.

Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. Oncologist. 2007;12:114–23.

Cox C, El-Mallawany N, Kabue M, Kovarik C, Schultze GE, Kazembe PN et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi sarcoma in Malawi and Botswana. Pediatr Blood Cancer. 2013;60:1274–80.

Dedicoat M, Vaithilingum M, Newton RR. Treatment of Kaposi's sarcoma in HIV-1 infected individuals with emphasis on resource poor settings. Cochrane Database Syst Rev. 2009; (1) (originally published 2003).

Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, Di Trolio R, De Placido S, Dezube BJ. Management of AIDS-related Kaposi's sarcoma. Lancet Oncol. 2007;8:167–76.

Dupin N, Rubin De Cervens V, Gorin I, Calvez V, Pessis E, Grandadam M, et al. The influence of highly active antiretroviral therapy on AIDS-associated Kaposi's sarcoma. British J Dermatol. 1999;140:875–81.

Duvic M, Friedman-Kien AE, Looney DJ, Miles SA, Myskowski PL, Scadden DT et al. Topical treatment of cutaneous lesions of acquired immunodeficiency syndrome-related Kaposi sarcoma using alitretinoin gel: results of Phase 1 and 2 trials. Arch Dermatol. 2000;136:1461–9.

Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006; 20(12):1645–54.

Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer. 2010; 103:416–22.

Freeman F, Maurer T, Gbabe O, Okwundu CI, Laker M, Easterbrook PE et al. Treatment for mild and moderate Kaposi's sarcoma in ART-naive HIV-infected individuals. Cochrane Database Syst Rev. (in press).

Gantt S, Kakuru A, Wald A, Walusansa V, Corey L, Casper C et al. Clinical presentation and outcome of epidemic Kaposi sarcoma in Ugandan children. Pediatr Blood Cancer. 2010;54:670–4.

Gbabe O, Okwundu CI, Dedicoat M, Freeman E. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. Cochrane Database Syst Rev. 2003; (3):CD003256. Update (in press).

Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol. 1996;14(8):2353–64.

Gill J, Bourboulia D, Wilkinson J, Hayes P, Cope A, Marcelin AG et al. Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma-associated herpesvirus infection in patients with and without Kaposi sarcoma. J Acquir Immune Defic Syndr. 2002;31(4):384–90.

Grünaug M, Bogner JR, Loch O, Goebel FD. Liposomal doxorubicin in pulmonary Kaposi's sarcoma: improved survival as compared to patients without liposomal doxorubicin. Europ Med Res. 1998; 21(3):13–9.

Hernández DE, Pérez JR. Systemic treatment modalities in the management of AIDS-related Kaposi's sarcoma. J Europe Acad Dermatol Venereol. 1997;9:44–9.

Holkova B, Takeshita K, Cheng MD, Volm M, Wasserheit C, Demopoulos R et al. Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. J Clin Oncol. 2001; 19(18):3848–51.

International Agency for Research on Cancer. GLOBOCAN 2012; Estimated cancer incidence, mortality and prevalence worldwide in 2012 (http://globocan.iarc.fr/Default.aspx, accessed 26 May 2014).

Kasolo FC, Spinks J, Bima H, Bates M, Gompels UA. Diverse genotypes of Kaposi's sarcoma associated herpesvirus (KSHV) identified in infant blood infections in African childhood-KS and HIV/AIDS endemic region. J Med Virol. 2007;79:1555–61.

Krown S, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol. 1989;7:1201–7.

Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol. 1997;15(9):3085–92.

Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol. 2004;22:399–402.

Krown SE. Letter in reply to Nasti N on Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol. 2005; April 1:2433–4.

Laker-Oketta M, Wenger M, Semeere A, Castelnuovo B, Kambugu A, Lukande R et al. Task shifting and skin punch for the histologic diagnosis of Kaposi's sarcoma: a public health solution to a public health problem. Presented at the14th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies, Bethesda, Maryland, November 2013.

Letang E, Lewis JJ, Bower M, Mosam A, Borok M, Campbell TB et al. Immune reconstitution inflammatory syndrome associated with kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS. 2013; Jun 19;27(10):1603–13.

Martin J, Laker-Oketta M, Walusana V, Orem J, Wabinga H, Bennett J et al. Antiretrovirals for Kaposi's sarcoma (ARKS): a randomized trial of protease inhibitor-based antiretroviral therapy for AIDS-associated Kaposi's sarcoma in sub-Saharan Africa. Presented at the 14th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies, Bethesda, Maryland. November 2013.

Martin-Carbonero L, Barrios A, Saballs P, Sirera G, Santos J, Palacios R et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS. 2004;18(12):1737–9.

Mitsuyasu RT. Clinical variants and staging of Kaposi's sarcoma. Semin Oncol. 1987;14:13–18.

Mosam A, Shaik F, Uldrick TS, Esterhuizen T, Friedland GH, Scadden DT et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. J Acquir Immune Defic Syndr. 2012;60(2):150–7.

Msyamboza KP, Dzamalala C, Mdokwe C, Kamiza S, Lemerani M, Dzowela T et al. Burden of cancer in Malawi; common types, incidence and trends: national population-based cancer registry. BMC Res Notes. 2012; 5:149.

Nasti G, Talamini R, Antinori A, Martellotta F, Jacchetti G, Chiodo F et al. AIDS-related Kaposi's sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart era--the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive from Antiretrovirals. J Clin Oncol. 2003; Aug 1;21(15):2876–82.

Northfelt DW, Dezube BJ, Thommes JA, Miller BJ, Fischl MA, Friedman-Kien A et al. Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol. 1998;16(7):2445–51.

Olweny CLM, Borok M, Gudza I, Clinch J, Cheang M, Kiire CF et al. Treatment of AIDS-associated Kaposi's sarcoma in Zimbabwe: results of a randomized quality of life focused clinical trial. Int J Cancer. 2005;113:632–9.

Paparizos VA, Kyriakis KP, Papastamopoulos V, Hadjivassiliou M, Stavrianeas NG. Response of AIDS-associated Kaposi sarcoma to highly active antiretroviral therapy alone. J Acquir Immune Defic Syndr. 2002;30: 257–8.

Pipkin S, Scheer S, Okeigwe I, Schwarcz S, Harris DH, Hessol NA. The effect of HAART and calendar period on Kaposi's sarcoma and non-Hodgkin lymphoma: results of a match between an AIDS and cancer registry. AIDS. 2011; 25:463–71.

Polesel J, Franceschi S, Suligoi B, Crocetti E, Falcini F, Guzzinati S et al. Cancer incidence in people with AIDS in Italy. Int J Cancer. 2010; 127:1437–45.

Rudek MA, Flexner C, Ambinder RF. Use of antineoplastic agents in patients with cancer who have HIV/AIDS. Lancet Oncol. 2011;12(9):905–12.

Sarmati L. HHV-8 infection in African children. Herpes. 2004;11:50–3.

Semeere AS, Busakhala N, Martin JN. Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-rich and resource-limited settings. Curr Opin Oncol. 2012; 25(5):522–30.

Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2011; 117:1089–96.

Stefan DC, Stones DK, Wainwright L, Newton R. Kaposi sarcoma in South African children. Pediatr Blood Cancer. 2011;56:392–6.

Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. J Clin Oncol. 1998;16(2):683–91.

Vaz P, Macassa E, Jani I, Thome B, Mahagaja E, Madede T et al. Treatment of Kaposi sarcoma in human immunodeficiency virus-1 infected Mozambican children with antiretroviral drugs and chemotherapy. Pediatr Infect Dis J. 2011;30(10):891.

Walmsley S, Northfelt D, Melosky B, Conant M, Friedman-Kien A, Wagner B et al. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical Alitretinoin (9-cis-retinoic acid) gel. JAIDS. 1999;22:235–46.

WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV Infection. Geneva: WHO; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013).

Seborrhoeic dermatitis

Apasrawirote WM, Rattanamongkolgul S. Topical antifungal agents for seborrheic dermatitis: systematic review and meta-analysis. J Med Assoc Thai. 2011;94(6):756–60.

Berrey MM, Schacker T, Collier AC, Shea T, Brodie SJ, Mayers D et al. Treatment of primary human immunodeficiency virus type 1 infection with potent antiretroviral therapy reduces frequency of rapid progression to AIDS. J Infect Dis. 2001; 183(10):1466–75.

Chatzikokkinou P, Sotiropoulos K, Katoulis A, Luzzati R, Trevisan G. Seborrheic dermatitis – an early and common skin manifestation in HIV patients. Acta Dermatovenerol Croat. 2008; 16(4):226–30.

Dunic I, Vesic S, Jevtovic DJ. Oral candidiasis and seborrheic dermatitis in HIV-infected. HIV Medicine. 2004; 5:50–4.

Elewski BE. Safe and effective treatment of seborrheic dermatitis. Cutis. 2009;83(6):333–8.

Faergemann J, Borgers M, Degreef H. A new ketoconazole topical gel formulation in seborrhoeic dermatitis: an updated review of the mechanism. Expert Opin Phamacother. 2007;8(9):1365–71

Gupta AK, Bluhm R. Seborrheic dermatitis. J Eur Acad Dermatol Venereol. 2004; 18:13–26.

Gupta AK, Richardson M, Paquet M. Systematic review of oral treatments for seborrheic dermatitis. J Eur Acad Dermatol Venereol. 2013; 28(1):16–26.

Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviral therapy. AIDS. 2000;14(8):1069–70.

Janniger CK. Infantile seborrheic dermatitis: an approach to cradle cap. Cutis. 1993; 51:233–5.

Janniger CK, Schwartz RA. Seborrheic dermatitis. Am Fam Physician. 1995; 52:149–55,159–60.

Langtry JA, Rowland Payne CM, Staughton RC, Stewart JC, Horrobin DF. Topical lithium succinate ointment (Efalith) in the treatment of AIDS-related seborrhoeic dermatitis. Clin Exp Dermatol. 1997; 22(5):216–9.

Maietta G, Fornaro P, Rongioletti F, Rebora A. Patients with mood depression have a high prevalence of seborrhoeic dermatitis. Acta Derm Venereol. 1990; 70:432–4.

Marino CT, McDonald E, Romano JF. Seborrheic dermatitis in acquired immunodeficiency syndrome. Cutis. 1991; 50:217–8.

Mastrolonardo M, Diaferio A, Logroscino G. Seborrheic dermatitis, increased sebum excretion, and Parkinson's disease: a survey of (im)possible links. Med Hypotheses. 2003; 60:907–11.

Milani M, Di Molfetta AS, Gramazio R, Fiorella C, Frisario C, Fuzio M et al. Efficacy of betamethasone valerate 0.1% thermophobic foam in seborrhoeic dermatitis of the scalp: an open-label, multicentre, prospective trial on 180 patients. Curr Med Res Opin. 2003;19(4):342–5.

Naldi L. Seborrheic dermatitis. NEJM. 2009;360(4):387–96.

Naldi L. Seborrheic dermatitis. Clin Evid (online). 2010;pii:1713.

Shin H, Kwon OS, Won CH, Kim BJ, Lee YW, Choe YB et al. Clinical efficacies of topical agents for the treatment of seborrheic dermatitis of the scalp: a comparative study. J Dermatol. 2009;36(3):131–7.

Ortonne JP, Lacour JP, Vitetta A, Le Fichoux Y. Comparative study of ketoconazole 2% foaming gel and betathasone dipropionate 0.05% lotion in the treatment of seborrhoeic dermatitis in adults. Dermatology. 1992;184(4):275–80.

Reygagne P, Poncet M, Sidou F, Soto P. Colbetasol propionate shampoo 0.05% in the treatment of seborrheic dermatitis of the scalp: results of a pilot study. Cutis. 2007;79(5):397–403.

Stephen J, Raj T, Radhakrishna K, Thomas T. Interventions for seborrheic dermatitis in HIV-infected children and adults: a systematic review (in preparation).

Thiers, BH. Treatment of skin diseases in HIV-infected patients. Dermatol Clin. 1995; 13:231–8.

Wiwanitkit, V. Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases. Int J Dermatol. 2004; 43:265–8.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

Papular pruritic eruption

Bason MM, Berger TG, Nesbitt LT. Pruritic papular eruption of HIV disease. Int J Dermatol. 1993; 32:784–9.

Berman B, Flores F, Burke G. Efficacy of pentoxifylline in the treatment of pruritic papular eruption of HIV-infected persons. J Am Acad Dermatol. 1998; 38:955–9.

Boonchai W, Laohasrisakul R, Manonukul J, Kulthanan K. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. Int J Dermatol. 1999;38(5):348–50.

Castelnuovo B, Byakwaga H, Menten J, Schaefer P, Kamya M, Colebunders R. Can response of a pruritic papular eruption to antiretroviral therapy be used as a clinical parameter to monitor virological outcome? AIDS. 2008; 22:269–73.

Chua SL, Radhakrishnan K, Stephen J, Zangenberg M. Systemic review: interventions for papular pruritic eruption of HIV (in preparation).

Colebunders R, Mann JM, Francis H, Bila K, Izaley L, Kakonde N et al. Generalized papular pruritic eruption in African patients with human immunodeficiency virus infection. AIDS. 1987;1(2):117–21.

Colebunders R, Moses KR, Laurence J, Shihab HM, Semitala F, Lutwama F et al. A new model to monitor the virological efficacy of antiretroviral treatment in resource-poor countries. Lancet Infect Dis. 2006; 6:53–9.

Lakshmi SJ, Rao GR, Ramalakshmi, Satyasree, Rao KA, Prasad PG et al. Pruritic papular eruptions of HIV: a clinicopathologic and therapeutic study. Indian J Dermatol Venereol Leprol. 2008;74(5):501–3.

Lowe S, Ferrand RA, Morris-Jones R, Salisbury J, Mangeya N, Dimario M et al. Skin disease among human immunodeficiency virus-infected adolescents in Zimbabwe: a strong indicator of underlying HIV infection. Pediatr Infect Dis J. 2010;29(4):346–51.

Navarini AA, Stoeckle M, Navarini S, Mossdorf E, Jullu BS, Mchomvu R et al. Antihistamines are superior to topical steroids in managing human immunodeficiency virus (HIV)-associated papular pruritic eruption. Int J Dermatol. 2010; 49:83–6.

Panya MF, Magonda YM, Massawe AW. The pattern of mucocutaneous disorders in HIV–infected children attending care and treatment centres in Dar es Salaam, Tanzania. BMC Public Health. 2009; 9:234.

Penneys NS, Nayar JK, Bernstein H, Knight JW. Chronic pruritic eruption in patients with acquired immunodeficiency syndrome associated with increased antibody titers to mosquito salivary antigens. J Am Acad Dermatol. 1989;21:421–5.

Resneck JS, Van Beek Jr M, Furmanski L, Oyugi J, LeBoit PE, Katabira E et al. Etiology of pruritic papular eruption with HIV infection in Uganda. JAMA. 2004; 292:2614–21.

Rosatelli JB, Machado AA, Roselino AMF. Dermatoses among Brazilian HIV-positive patients: correlation with the evolutionary phases of AIDS. Int J Dermatol. 1997; 36:729–34.

Sivayathorn A, Srihra B, Leesanguankul W. Prevalence of skin disease in patients infected with human immunodeficiency virus in Bangkok, Thailand. Ann Acad Med Singapore. 1995; 24:528–33.

Smith KJ, Skelton HG, James WD, Frissman DM, Barrett TL, Angritt P et al. Papular eruption of human immunodeficiency virus disease. A review of the clinical, histologic, and immunohistochemical findings in 48 cases. The Military Medical Consortium for Applied Retroviral Research. Am J Dermatopathol. 1991;13(5):445–51.

Uchigasaki S, Baba S, Kakinuma H, Suzuki H, Sawada S, Kasori J et al. Pruritic papular eruptions and candidiasis due to HIV infection. J Dermatol. 1996;23(8):572–6.

Wiwanitkit V. Prevalence of dermatological disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases. Int J Dermatol. 2004; 43:265–8.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

Eosinophilic folliculitis

Annam V, Yelikar BR, Inamadar AC, Palit A, Arathi P. Clinicopathological study of itchy folliculitis in HIV-infected patients. Indian J Dermatol Venereol Leprol. 2010;76(3):259–62.

Berger TG, Heon V, King C, Schulze K, Conant MA. Itraconazole therapy for human immunodeficiency virus-associated eosinophilic folliculitis. Arch Dermatol. 1995; 131:358–60.

Blauvelt A, Plott RT, Spooner K, Stearn B, Davey RT, Turner ML. Eosinophilic folliculitis associated with the acquired immunodeficiency syndrome responds well to permethrin. Arch Dermatol. 1995;131:360.

Buchness M, Gregory N, Lim H, Soter N. The role of mast cells and eosinophils in eosinophilic pustular folliculitis of the acquired immunodeficiency syndrome. J Invest Dermatol. 1989; 92(3):408.

Chua SL, Radhakrishnan K, Stephen J, Zangenberg M. Systematic review: interventions for eosinophilic folliculitis (in preparation).

Downs A, Lear J, Oxley J, Kennedy C. AIDS associated eosinophilic folliculitis which responded to both high dose co-trimoxazole and low dose isotretinoin. Sex Transm Infect. 1998;74:229–30.

Ferrandiz C, Robera M, Barranco JC, Clotet B, Lorenzo JC. Eosinophilic pustular folliculitis in patients with acquired immunodeficiency syndrome. Int J Dermatol. 1992;31:193–5.

Filippetti R, Muzi A. Papuloerythroderma (Ofuji's disease): a report of three cases. J Invest Dermatol. 2012; 132:S18.

Gnecchi L, Caccialanza M, Piccinno R, Beretta M. Phototherapy of HIV-associated eosinophilic folliculitis: preliminary results. G Ital Dermatol Venereol. 1998;133:411–5.

Goh B-K, Chan RKW, Sen P, Theng CTS, Tan H-H, Wu Y-J et al. Spectrum of skin disorders in human immunodeficiency virus-infected patients in Singapore and the relationship to CD4 lymphocyte counts. Int J Dermatol. 2007; 46:695–9.

Goldstein B, Berman B, Sukenik E, Frankel SJ. Correlation of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. J Am Acad Dermatol. 1997, 36:262–4.

Kim TG, Lee KH, Oh SH. Skin disorders in Korean patients infected with human immunodeficiency virus and their association with a CD4 lymphocyte count: a preliminary study. J Eur Acad Dermatol Venereol. 2010;24(12):1476–80.

Kuwano Y, Watanabe R, Fujimoto M, Komine M, Asahina A, Tsukada N et al. Treatment of HIV-associated eosinophilic pustular folliculitis with narrow-band UVB. Int J Dermatol. 2006;45:1265–7.

Lim HW, Vallurupalli S, Meola T, Soter NA. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. J Am Acad Dermatol. 1997;37:414–7.

Michigami M, Matsumura Y, Koreeda S, Miyachi Y. A case of human immunodeficiency virus-associated eosinophilic folliculitis. Skin Res. 2009; 8:551–5.

Meyer T, Lopez-Navarro N, Herrera-Acosta E, Gallego E, Bosch RJ, Herrera E. Human immunodeficiency virus (HIV)-associated eosinophilic folliculitis and follicular mucinosis in a black woman. Int J Dermatol. 2010;49:1308–10.

Misago N, Narisawa Y, Matsubara S, Hayashi S. HIV-associated eosinophilic pustular folliculitis: successful treatment of a Japanese patient with UVB phototherapy. J Dermatol. 1998;25:178–84

Otley CC, Avram MR, Johnson RA. Isotretinoin treatment of human immunodeficiency virus-associated eosinophilic folliculitis. Results of an open, pilot trial. Arch Dermatol. 1995; 131:1047–50.

Parker SRS, Parker DC, McCall CO. Eosinophilic folliculitis in HIV-infected women: case series and review. Am J Clin Dermatol. 2006;7:193–200.

Rajendran PM, Dolev JC, Heaphy Jr MR, Maurer T. Eosinophilic folliculitis: before and after the introduction of antiretroviral therapy. Arch Dermatol. 2005; 141:1227.

Rosenthal D, LeBoit PE, Klumpp L, Berger TG. Human immunodeficiency virus-associated eosinophilic folliculitis: a unique dermatosis associated with advanced human immunodeficiency virus infection. Arch Dermatol. 1991;127:206.

Sears A, Wee J, Natkunarajah J. Human immunodeficiency virus-associated eosinophilic folliculitis: an important late pick up. Br J Dermatol. 2012; 167(S1):117.

Sud N, Shanker V, Sharma A, Sharma NL, Gupta M. Mucocutaneous manifestations in 150 HIV-infected Indian patients and their relationship with CD4 lymphocyte counts. Int J STD AIDS. 2009; 20:771–4.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

Yosipovitch G, Goon A, Wee J, Chan YH, Goh CL. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol. 2000; 143:969–73.

Zachariae R, Zachariae C, Ibsen HH, Mortensen JT, Wulf HC. Psychological symptoms and quality of life of dermatology outpatients and hospitalized dermatology patients. Acta Derm Venereol. 2004; 84: 205–12.

Zachariae R, Zachariae CO, Lei U, Pedersen AF. Affective and sensory dimensions of pruritus severity: associations with psychological symptoms and quality of life in psoriasis patients. Acta Derm Venereol. 2008; 88:121–7.

Tinea infections

Aly R. Ecology and epidemiology of dermatophyte infections. J Am Acad Dermatol. 1994; 31(3 Pt 2):S21–5.

Coldrion BM, Bergstresser PR. Prevalence and clinical spectrum of skin disease in patients infected with human immunodeficiency virus. Arch Dermatol. 1989;125:357–61.

Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hardinsky MK et al. Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea curiris, tinea faciei, tinea manuum, and tinea pedi. Guidelines/Outcomes Committee. American Academy of Dermatology. J Am Acad Derm. 1996; 34(2 Pt 1):282–6.

El-Gohary M, van Zuuren EJ, Fedorowicz Z, Burgess H, Doney L, Stuart B et al. Topical antifungal treatments for tinea cruris and tinea corporis. Cochrane Database Syst Rev. 2014; (8):CD009992.

Hay RJ, Johns NE, Williams HC. The global burden of skin disease: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol. 2013; Oct 28 doi: 10.1038/jid.2013.446 (epub ahead of print).

Weismann K, Knudsen EA, Pedersen C. White nails in AIDS/ARC due to trichophyton rubrum infection. Clin Exp Dermatol.1988; 13:24–5.

Weitzman I, Summerbell RC. The dermatophytes. Clin Microbiol Rev. 1995; 8(2):240–59.

Herpes zoster

Arvin AM. Antiviral therapy for varicella and herpes zoster. Semin Pediatr Infect Dis. 2002; 13(1):12–21.

Balfour HH Jr, Bean B, Laskin OL, Ambinder RF, Meyers JD, Wade JC et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med. 1983; 308(24):1448–53.

Bean B, Braun C, Balfour HH Jr. Acyclovir therapy for acute herpes zoster. Lancet. 1982; 2(8290):118 –21.

Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother. 1995; 39(7):1546–53.

Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001; 127(2):305–14.

Buchbinder SP, Katz MH, Hessol NA, Liu JY, O'Malley PM, Underwood R et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis. 1992; 166(5):1153–6.

Civen R, Chaves SS, Jumaan A, Wu H, Mascola L, Gargiullo P et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. Pediatr Infect Dis J. 2009; 28(11):954–9.

Degreef H, Famciclovir Herpes Zoster Clinical Study Group. Famciclovir, a new oral antiherpes drug: results of the first controlled clinical study demonstrating its efficacy and safety in the treatment of uncomplicated herpes zoster in immunocompetent patients. Int J Antimicrob Agents. 1994; 4(4):241–6.

Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med. 1995; 155: 1605–9.

Gona P, Van Dyke RB, Williams PL, Dankner WM, Chernoff MC, Nachman SA et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA. 2006; 296(3):292–300.

Guess HA, Broughton DD, Melton LI, Kurland LT. Epidemiology of herpes zoster in children and adolescents: a population based study. Pediatrics. 1985; 76:512–7.

Heidl M, Scholz H, Dörffel W, Hermann J. Antiviral therapy of varicella-zoster virus infection in immunocompromised children – a prospective randomized study of aciclovir versus brivudin. Infection. 1991; 19(6):401–5.

McGill J, MacDonald DR, Fall C, McKendrick GD, Copplestone A. Intravenous acyclovir in acute herpes zoster infection. J Infect. 1983; 6(2):157–61.

McKendrick MW, Care C, Burke C, Hickmott E, McKendrick GD. Oral acyclovir in herpes zoster. J Antimicrob Chemother. 1984; 14(6):661–5.

McKendrick MW, McGill JI, White JE, Wood MJ. Oral acyclovir in acute herpes zoster. Br Med J (Clin Res Ed). 1986; 293(6561):1529–32.

Ragozzino MW, Melton LJ III, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore). 1982; 61:310–6.

Raju GN, Raza M, Kumar TN, Singh G. Comparative study of the efficacy of valacyclovir and acyclovir in herpes zoster. Int J Pharm Biomed Res. 2011; 2(2):119–23.

Shen MC, Lin HH, Lee SS, Chen YS, Chiang PC, Liu YC. Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. J Microbiol Immunol Infect. 2004; 37(2):75–81.

Stephen J, Radhakrishna K, Thomas T, Waghmare A. Treatment of herpes zoster in HIV-infected children and adults: a systematic review (in preparation).

Tyring S, Belanger R, Bezwoda W, Ljungman P, Boon R, Saltzman RL et al. A randomized, double-blind trial of famciclovir versus acyclovir for the treatment of localized dermatomal herpes zoster in immunocompromised patients. Cancer Invest. 2001; 19(1):13–22.

van den Broek PJ, van der Meer JW, Mulder JD, Versteeg J, Mattie H. Limited value of acyclovir in the treatment of uncomplicated herpes zoster: a placebo-controlled study. Infection. 1984; 12(5):338–41.

Wassilew SW, Reimlinger S, Nasemann T, Jones D. Oral acyclovir for herpes zoster: a double-blind controlled trial in normal subjects. Br J Dermatol. 1987; 117(4):495–501.

Wassilew SW, Wutzler P, Brivudin Herpes Zoster Study Group. Oral brivudin in comparison with acyclovir for improved therapy of herpes zoster in immunocompetent patients: results of a randomized, double-blind, multicentered study. Antiviral Res. 2003; 59(1):49–56.

Wutzler P, de Clercq E, Wutke K, Färber I. Oral brivudin vs. intravenous acyclovir in the treatment of herpes zoster in immunocompromised patients: a randomized double-blind trial. J Med Virol. 1995; 46(3):252–7.

Scabies

Arlian LG, Estes SA, Vyszenski-Moher DL. Prevalence of Sarcoptes scabiei in the homes and nursing homes of scabietic patients. J Am Acad Dermatol. 1988; 19(5 Pt 1):806–11.

Chosidow O. Scabies and pediculosis. Lancet. 2000; 355(9206):448–50.

Chosidow O. Scabies. N Engl J Med. 2006; 354:1718–27.

Coleman CI, Gillespie EL, White CM. Probable topical permethrin-induced neck dystonia. Pharmacotherapy. 2005; 25(3):448–50.

DeSole G, Remme J, Awadzi K, Accorsi S, Alley ES, Ba O et al. Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. Bull World Health Organ. 1989; 67(6): 707–19.

Dourmishev A, Serafumova D, Dourmishev L. Efficacy and tolerance of oral ivermectin in scabies. J Eur Acad Dermatol Venereol. 1998; 11:247–51.

Elish D, Silverberg NB. Infantile seborrheic dermatitis. Cutis. 2006; 77:297–300.

FitzGerald D, Grainger RJ, Reid A. Interventions for preventing the spread of infestation in close contacts of people with scabies. Cochrane Database Syst Rev. 2014;(2): CD009943.

Funkhouser ME, Ross A, Berger TG. Management of scabies in patients with human immunodeficiency virus disease. Arch Dermatol. 1993; 129(7):911–3.

Golant AK, Levitt JO. Scabies: a review of diagnosis and management based on mite biology. Pediatr Rev. 2012; 33(1):48–59.

Group AE. Therapeutic guidelines: antibiotic: scabies. Melbourne, Australia: Therapeutic Guidelines Limited; 2010.

Guerci S, Cappellaro E, Contratti M, Corna A, Fazi MC, Orini S et al. A sign of the changing times: neonatal scabies. Minerva pediatrica. 2010; 62(3):329–32.

Hay RJ. Scabies – learning from animals. J Eur Acad Dermatol Venereol. 2004; 18:129–30.

Hay RJ, Johns NE, Williams HC. The global burden of skin disease: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol. 2013; Oct 28 doi: 10.1038/jid.2013.446 (epub ahead of print).

Janniger CK, Schwartz RA. Seborrheic dermatitis. Am Fam Physician. 1995; 52:149–55,159–60.

Larralde M, Mijelshon LM, Gonzalez A, Mora E, Constantakos N. Ivermectin-responsive crusted scabies in four patients. Pediatr Dermatol. 1999; 16(1):69–70.

Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. Br J Dermatol. 2000; 143(3):520–3.

Ly F, Caumes E, Ndaw CAT, Ndiaye B, Mahe A. Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. Bull World Health Organ. 2009; 87:424–30.

Meinking TL, Taplin D, Hermida JL, Pardo R, Kerdel FA. The treatment of scabies with ivermectin. N Engl J Med. 1995; 333:26–30.

Mounsey KE, McCarthy JS. Treatment and control of scabies. Curr Opin Infect Dis. 2013; 26:133–9.

Mytton OT, McGready R, Lee SJ, Roberts CH, Ashley EA, Carrara VI et al. Safety of benzyl benzoate lotion and permethrin in pregnancy: a retrospective matched cohort study. BJOG. 2007;114(5):582–7.

Nofal A. Variable response of crusted scabies to oral ivermectin: report on eight Egyptian patients. J Eur Acad Dermatol Venereol. 2009; 23(7):793–7.

Pacque MC, Dukuly Z, Greene BM, Munoz B, Keyvan-Larijani E, Williams PN et al. Community-based treatment of onchocerciasis with ivermectin: acceptability and early adverse reactions. Bull World Health Organ. 1989; 67(6): 721–30.

Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, Mbuguye TL. Prevalence and classification of HIV-associated oral lesions. Oral Dis. 2002; 8(S 2):98–109.

Portu JJ, Santamaria JM, Zubero Z, Almeida-Llamas MV, Aldamiz-Etxebarria San Sebastian M, Gutiérrez AR. Atypical scabies in HIV-positive patients. J Am Acad Dermatol. 1996; 34(5 Pt 2):915–7.

Quarterman MJ, Lesher JL. Neonatal scabies treated with permethrin 5% cream. Pediatr Dermatol. 1994;11(3):264–6.

Sharquie KE, Al-Rawi JR, Noaimi AA, Al-Hassany HM. Treatment of scabies using 8% and 10% topical sulfur ointment in different regimens of application. J Drugs Dermatol. 2012; 11(3):357–64.

Strong M, Johnstone P. Interventions for treating scabies (Review). Cochrane Database Syst Rev. 2007; (3):CD000320.

Subramaniam S, Rutman MS, Wegner JK. A papulopustular, vesicular, crusted rash in a 4-week-old neonate. Pediatr Emer Care. 2013; 29(11):1210–2.

Sullivan JR, Watt G, Barker B. Successful use of ivermectin in the treatment of endemic scabies in a nursing home. Aust J Dermatol. 1997; 38:137–40.

Vekic, DA, Abbott LMC, Asher EM, Whitfeld MJ. Interventions for treating scabies in people infected with human immunodeficiency virus: a systematic review (in preparation).

Walton SF, Currie BJ. Problems in diagnosing scabies, a global disease in human and animal populations. Clin Microbiol Rev. 2007; 20(2):268–79.

WHO. Epidemiology and management of common skin diseases in children in developing countries. Geneva: WHO; 2005.

Molluscum contagiosum

Calista D, Boschini A, Landi G. Resolution of disseminated molluscum contagiosum with highly active anti-retroviral therapy (HAART) in patients with AIDS. Eur J Dermatol. 1999; 9(3):211–3.

Drain K, Mosam A, Gounder L, Gosnell B, Manzini T, Moosa MY. Recurrent giant molluscum contagiosum immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy in an HIV-infected South African male. Int J STD AIDS. 2013; published online before print July 19 2013 doi: 10.1177/0956462413497702.

Hicks CB, Myers SA, Giner J. Resolution of intractable molluscum contagiosum in a human immunodeficiency virus-infected patient after institution of antiretroviral therapy with ritonavir. Clin Infect Dis. 1997; 24(5):1023–5.

Horn CK, Scott GR, Benton EC. Resolution of severe molluscum contagiosum on effective antiretroviral therapy. Br J Dermatol. 1998; 138(4):715–7.

Husak R, Garbe C, Orfanos CE. Mollusca contagiosa in HIV-patients. Clinical manifestations, relation to the immunological status and prognostic significance. [German] Mollusca contagiosa bei HIV-Infektion. Klinische Manifestation, Beziehung zum Immunstatus und prognostische Wertigkeit bei 39 Patienten. Hautarzt. 1997; 48(2):103–9

Leahey AB, Shane JJ, Listhaus A, Trachtman M. Molluscum contagiosum eyelid lesions as the initial manifestation of acquired immunodeficiency syndrome. Am J Ophthalmol. 1997; 124(2):240–1.

Liota E, Smith KJ, Buckley R, Menon P, Skelton H. Imiquimod therapy for molluscum contagiosum. J Cutan Med Surg. 2000; 4(2):76–82.

Martin P. Interventions for molluscum contagiosum in people infected with human immunodeficiency virus: a systematic review. HIV Medicine (in press).

Maurer T, Rodrigues LKE, Ameli N, Phanuphak N, Gange SJ, DeHovitz J et al. The effect of highly active antiretroviral therapy on dermatologic disease in a longitudinal study of HIV type 1-infected women. Clin Infect Dis. 2004; 38(4):579–84.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: WHO; 2013.

Oropharyngeal candidiasis

Arribas JR, Henandez-Albujar S, Gonzalez-Garcia JJ, Pena JM, Conzalez A, Canedo T et al. Impact of protease inhibitor therapy on HIV-related oropharyngeal candidiasis. AIDS. 2000; 14(8):979–84.

Bektic J, Lell CP, Fuchs A, Stroiber H, Speth C, Lass-Florl C et al. HIV protease inhibitors attenuate adherence of Candida albicans to epithelial cells in vitro. FEMS Immunol Med Microbiol. 2001; 31:65–71.

Cassone A, De Bernadis F, Torosantucci A, Tacconelli E, Tumbarello M, Cauda R. In vitro and in vivo anticandidal activity of human immunodeficiency virus protease inhibitors. J Inf Dis. 1999; 180:448–53.

Cauda R, Tacconelli E, Tumbarello M, Morace G, De Bernadis F, Torosantucci A et al. Role of protease inhibitors in preventing recurrent oral Candidosis in patients with HIV infection: a prospective case-control study. J Acquir Immune Defic Syndr. 1999; 21(1): 20–5.

Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. Bull World Health Organ. 2005; 83(9):700–6.

De Wit S, Goossens H, Clumeck N. Single-dose versus 7 days of fluconazole treatment for oral candidiasis in human immunodeficiency virus-infected patients: a prospective, randomized pilot study. J infect Dis. 1993;168(5):1332–3.

Epstein JB, Freilich MM, Le ND. Risk factors for oropharyngeal candidiasis in patients who receive radiation therapy for malignant conditions of the head and neck. Oral Surg Oral Med Oral Pathol. 1993;76(2):169.

Epstein JB, Polsky B. Oropharyngeal candidiasis: a review of its clinical spectrum and current therapies. Clinical Therapeutics. 1998; 20:40–57.

Gennaro S, Naidoo S, Berthold P. Oral health & HIV/AIDS. MCN Am J Mat Child Nurs. 2008; 33(1):50–7.

Goldman M, Cloud GA, Wade KD, Reboli AC, Fichtenbaum CJ, Hafner R et al. A randomized study for the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40. Clinical Infectious Dis. 2005; 41:1473–80.

Greenspan JS, Barr CE, Scuibba JJ, Winkler JR, US Oral Aids Collaborative Group. Oral manifestations of HIV infection: definitions, diagnostic criteria and principles of therapy. Oral Surg Oral Med Oral Pathol. 1992; 73(2):142–4.

Hamza OJM, Matee MIN, Bruggemann RJM, Moshi MJ, Simon ENM, Mugusi F et al. Single-dose fluconazole versus 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial. Clin Infect Dis. 2008; 47:1270–6.

Iacopino AM, Wathen WF. Oral candidal infection and denture stomatitis: a comprehensive review. J Am Dent Assoc. 1992;123(1):46.

Leen CL, Dunbar EM, Ellis ME, Mandal BK. Once weekly fluconazole to prevent recurrence of oropharyngeal candidiasis in patients with AIDS and AIDS-related complex: a double-blind placebo-controlled study. [erratum appears in J Infect. 1990; 21(2):183.]. J Infect. 1990; 21(1):55–60.

Marriott DJ, Jones PD, Hoy JF, Speed BR, Harkness JL. Fluconazole once a week as secondary prophylaxis against oropharyngeal candidiasis in HIV-infected patients. A double-blind placebo-controlled study. Medical J Australia. 1993; 158(5):312–6.

Nittayananta W, Chingpanich S. Oral lesions in a group of Thai people with AIDS. Oral Diseases 1997; 3(S 1):41–56.

Nittayananta W, DeRouen TA, Arirachakaran P, Laothumthut T, Pangsomboon K, Petsantad DS et al. A randomized clinical trial of chlorhexidine in the maintenance of oral candidiasis-free period in HIV infection. Oral Diseases. 2008; 14:665–70.

Nyst MJ, Perriens JH, Kimputu L, Lumbila M, Nelson AM, Piot P. Gentian violet, ketoconazole and nystatin in oropharyngeal and esophageal candidiasis in Zairian AIDS patients. Ann Soc Belg Med Tropicale. 1992; 72(1):45–52.

Oude Lashof AML, De Bock R, Herbrecht R, de Pauw BE, Krcmery V, Aoun M et al. An open multicentre comparative study of the efficacy, safety and tolerance of fluconazole and itraconazole in the treatment of cancer patients with oropharyngeal candidiasis. European J Cancer 2004; 40(9):1314–9.

Pagani JL, Chave JP, Casjka C, Galuser MP, Bille J. Efficacy, tolerability and development of resistance in HIV-positive patients treated with fluconazole for secondary prevention of oropharyngeal candidiasis: a randomized, double-blind, placebo-controlled trial. J Antimicrobial Chemotherapy. 2002; 50:231–40.

Patton LL, Bonito AJ, Shugars DA. A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92:170–9.

Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst Rev. 2013; (9):CD003940.

Rabeneck L, Laine L. Esophageal candidiasis in patients infected with the human immunodeficiency virus. A decision analysis to assess cost-effectiveness of alternative management strategies. Arch Internal Medicine. 1994;154(23):2705–10.

Rachanis CC. Looking into the mouth – oral manifestations of HIV infection. South Afr J HIV Med. 2001; 5:27–31.

Ramsay C. How do you include trials with more than two groups into a single meta-analysis? (http://www.epoc.uottawa.ca/FAQmultiplegroups2003.pdf 2003;Vol., accessed 17 February 2005).

Revankar SG, Kirkpatrick WR, McAtee RK, Dib OP, Fothergill AW, Redding SW et al. A randomized trial of continuous or intermittent therapy with fluconazole for oropharyngeal candidiasis in HIV-infected patients: clinical outcomes and development of fluconazole resistance. American J Med. 1998; 105(1):7–11.

Reznik DA. Oral manifestations of HIV disease. Top HIV Med. 2005/2006; 13(5):143–8.

Sangeorzan JA, Bradley SF, He X, Zarins LT, Ridenour GL, Tiballi RN et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am J Med. 1994;97(4):339.

Schuman P, Capps L, Peng G, Vasquez J, El-Sadr W, Goldman AI et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Annals Intern Med. 1997; 126(9):689–96.

Shay K, Truhlar MR, Renner RP. Oropharyngeal candidosis in the older patient. J Am Geriatr Soc. 1997; 45(7):863.

Smith DE, Midgley J, Allan M, Connolly GM, Gazzard BG. Itraconazole versus ketaconazole in the treatment of oral oesophageal candidosis in patients infected with HIV/AIDS. 1991; 5:1367–71.

Stevens DA, Greene SI, Lang OS. Thrush can be prevented in patients with acquired immunodeficiency syndrome and the acquired immunodeficiency syndrome-related complex. Randomized, double-blinded, placebo-controlled study of 100 mg oral fluconazole daily. Archives Internal Med. 1991; 151(12):2458–64.

WHO. Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Annex Table Section 7.4. Geneva: WHO; 2013.

Yang YL, Lo HJ, Hung CC, Li Y. Effect of prolonged HAART on oral colonization with candida and candidiasis. BMC Infect Dis. 2006; 20(6):8.

Stevens-Johnson syndrome/toxic epidermal necrolysis

Anonymous. Cutaneous drug reaction case reports: from the world literature. Am J Clin Dermatol. 2003; 4(2):141–7.

Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010; 5:39.

Léauté-Labrèze C, Lamireau CT, Chawki D, Maleville J, Taïeb A. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. Arch Dis Child. 2000; 83:347–52.

Lehloenya R. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis. Current Allergy & Clinical Immunology. 2007; 20(3): 124–8.

Rani M, Maurer T. A systematic review of treatment of drug-induced Stevens Johnson syndrome and toxic epidermal necrolysis in people with human immunodeficiency virus (in preparation).

Raviglione MC, Dinan WA, Pablos-Mendez A, Palagiano A, Sabatini MT. Fatal toxic epidermal necrolysis during prophylaxis with pyrimethamine and sulfadoxine in a human immunodeficiency virus-infected person. Arch Intern Med. 1988; 148(12):2683–5.

Sulayman H, Wanoyi, I, Ramadan, A. Steven-Johnson syndrome seen in a HIV-positive pregnant patient: a case report. Int J Gynecol Obstet. 2009; 107:S557.

Trent J, Halam M, French LE, Kerdel F. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. Semin Cutan Med Surg. 2006; 25(2):91–3.

WHO. Surgical care at the district hospital. Geneva: WHO; 2003.

Annex 1. ART recommendations[1]

The following table summarizes the WHO recommendations formulated for the 2013 guidelines on HIV testing and counselling, ART and HIV service delivery. It also briefly summarizes the guidance provided for programme managers.

HIV TESTING AND COUNSELLING	
TOPIC AND POPULATION	**RECOMMENDATIONS**
Community-based testing	In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling *(strong recommendation, low-quality evidence)*. In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling *(strong recommendation, low-quality evidence)*.
HIV testing and counselling of adolescents	HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) *(strong recommendation, very-low-quality evidence)*. In generalized epidemics HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents *(strong recommendation, very-low-quality evidence)*. We suggest that in low and concentrated epidemics HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents *(conditional recommendation, very-low-quality evidence)*. We suggest that adolescents be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose *(conditional recommendation, very-low-quality evidence)*.
WHEN TO START ART IN PEOPLE LIVING WITH HIV	
TOPIC AND POPULATION	**RECOMMENDATIONS**
When to start ART in adults and adolescents	As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3 *(strong recommendation, moderate-quality evidence)*. ART should be initiated in all individuals with HIV with CD4 count between 350 and 500 cells/mm^3 regardless of WHO clinical stage *(strong recommendation, moderate-quality evidence)*. ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 count in the following situations: • Individuals with HIV and active TB disease *(strong recommendation, low-quality evidence)*. • Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease *(strong recommendation, low-quality evidence)*. • Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners *(strong recommendation, high-quality evidence)*.

[1] From: *Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach* (WHO, 2013).

WHEN TO START ART IN PEOPLE LIVING WITH HIV	
TOPIC AND POPULATION	**RECOMMENDATIONS**
When to start ART in pregnant and breastfeeding women	All pregnant and breastfeeding women infected with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART *(strong recommendation, moderate-quality evidence)*. For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women infected with HIV should initiate ART as lifelong treatment *(conditional recommendation, low-quality evidence)*. In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased *(conditional recommendation, low-quality evidence)*.
ARVs and duration of breastfeeding	The key principles and recommendations established in 2010 remain, including: National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context. In settings where national authorities have decided that maternal and child health services will principally promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival: • Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided *(strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months)*.
When to start ART in children	ART should be initiated in all children infected with HIV below five years of age, regardless of CD4 count or WHO clinical stage. • diagnosed in the first year of life *(Strong recommendation, moderate-quality evidence)*. • children infected with HIV between one and below five years of age *(Conditional recommendation, very low-quality evidence)*. ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤500 cells/mm^3, regardless of WHO clinical stage. • CD4 count ≤350 cells/mm^3 *(Strong recommendation, moderate-quality evidence)*. • CD4 count between 350 and 500 cells/mm^3 *(Conditional recommendation, very-low-quality evidence)*. ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 count *(strong recommendation, moderate-quality evidence)*. ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection *(strong recommendation, low-quality evidence)*.

WHAT ART REGIMENS TO START	
TOPIC AND POPULATION	**RECOMMENDATIONS**
First-line ART regimens for adults and adolescents	First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). • TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART *(strong recommendation, moderate-quality evidence)*. • If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended: — AZT + 3TC + EFV — AZT + 3TC + NVP — TDF + 3TC (or FTC) + NVP *(Strong recommendation, moderate-quality evidence)*.
	• Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities *(strong recommendation, moderate-quality evidence)*.
First-line ART for pregnant and breastfeeding women and their infants	A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped *(strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants)*. The infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum *(strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding)*.
First-line ART for children younger than 3 years of age	An LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen *(strong recommendation, moderate-quality evidence)*. Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained *(conditional recommendation, low-quality evidence)*. In infants and children younger than three years infected with HIV, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the original regimen should be restarted *(strong recommendation, moderate-quality evidence)*. For infants and children younger than three years infected with HIV, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC *(strong recommendation, low-quality evidence)*.
First-line ART for children 3 years of age and older	For children infected with HIV three years of age and older, EFV is the preferred NNRTI for first-line treatment and NVP is the alternative *(strong recommendation, low-quality evidence)*. For children infected with HIV three years and older to less than 10 years of age (or less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order: • ABC + 3TC • AZT or TDF + 3TC or FTC *(Conditional recommendation, low-quality evidence)* For adolescents infected with HIV (10 years and older) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order: • TDF + 3TC or FTC • AZT + 3TC • ABC + 3TC *(Strong recommendation, low-quality evidence)*

MONITORING ART RESPONSE AND DIAGNOSIS OF TREATMENT FAILURE	
TOPIC AND POPULATION	**RECOMMENDATIONS**
Adults, adolescents and children	Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure *(Strong recommendation, low-quality evidence)*. If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(Strong recommendation, moderate-quality evidence)*.
SECOND-LINE ART: WHAT ARV REGIMEN TO SWITCH TO	
TOPIC AND POPULATION	**RECOMMENDATIONS**
What ARV regimen to switch to in adults and adolescents *(includes adolescents, pregnant and breastfeeding women)*	Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI). The following sequence of second-line NRTI options is recommended: • After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens. • After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens. • Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach *(strong recommendation, moderate-quality evidence)*. Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART *(strong recommendation, moderate-quality evidence)*.
What ARV regimen to switch to in children	After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI *(strong recommendation, moderate-quality evidence)*. After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken *(conditional recommendation, very-low-quality evidence)*. After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI *(conditional recommendation, low-quality evidence)*. After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC *(strong recommendation, low-quality evidence)*. After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC) the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) *(strong recommendation, low-quality evidence)*.
THIRD-LINE ART	
TOPIC AND POPULATION	**RECOMMENDATIONS**
All populations	National programmes should develop policies for third-line ART *(conditional recommendation, low-quality evidence)*. Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs *(conditional recommendation, low-quality evidence)*. Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen *(conditional recommendation, very low-quality evidence)*.
Special considerations for children	Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children who have more therapeutic options available to them, constructing "third-line" ARV regimens using novel drugs used in treating adults such as ETV, DRV and RAL may be possible (for details on using these drugs in children, see Web Annex X). Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. When stopping ART may have to be considered, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

MAJOR OPERATIONAL AND SERVICE DELIVERY	
TOPIC AND POPULATION	**RECOMMENDATIONS**
Interventions to optimize adherence to ART	Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions *(strong recommendation, moderate-quality evidence)*.
Service integration and linkage	In generalized epidemic settings, ART should be initiated and maintained in eligible pregnant and postpartum women and in infants at maternal and child health care settings, with linkage and referral to ongoing HIV care and ART, where appropriate *(strong recommendation, very-low-quality evidence)*. In settings with a high burden of HIV and TB, ART should be initiated for an individual living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART *(strong recommendation, very-low-quality evidence)*. In settings with a high burden of HIV and TB, TB treatment may be provided for an individual living with HIV in HIV care settings where TB diagnosis has also been made *(strong recommendation, very-low-quality evidence)*. ART should be initiated and maintained in eligible people living with HIV at care settings where opioid substitution therapy (OST) is provided *(strong recommendation, very-low-quality evidence)*.
Decentralization of treatment and care	The following options should be considered for decentralization of ART initiation and maintenance. • Initiation of ART in hospitals with maintenance of ART in peripheral health facilities *(strong recommendation, low-quality evidence)*. • Initiation and maintenance of ART in peripheral health facilities *(strong recommendation, low-quality evidence)*. • Initiation of ART at peripheral health facilities with maintenance at the community level (that is, outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits *(strong recommendation, medium-quality evidence)*.
Task-shifting	Trained non-physician clinicians, midwives and nurses can **initiate** first-line ART *(strong recommendation, moderate-quality evidence)*. Trained non-physician clinicians, midwives and nurses can **maintain** ART *(strong recommendation, moderate-quality evidence)*. Trained and supervised community health workers can **dispense** ART between regular clinical visits *(strong recommendation, moderate-quality evidence)*.
GUIDANCE FOR PROGRAMME MANAGERS	
TOPIC AND POPULATION	**RECOMMENDATIONS**
Guidance for programme managers	For deciding on the implementation of the clinical and operational recommendations, it is recommended that: • the national authorities do so using a transparent, open and informed process. This process should have broad stakeholder engagement, including meaningful participation from the affected communities, and take into account the specifics of the recommendations under discussion, • the decision-making process take into account data on the national and local HIV epidemiology, current ART programme performance and the socioeconomic, policy and legal context, including the budgetary, human resource requirements and other health system implications. The latter would identify which inputs and systems are currently available and which areas require additional investment, • the decision-making process take into account the ethics, equity and human rights, the impact and cost–effectiveness and the opportunity and risk dimensions of alternative implementation options.

Annex 2. Drug Interactions

The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions.

Drug interactions involving oral azole antifungal drugs

EFFECT		AZOLE(S) INVOLVED
DECREASED PLASMA CONCENTRATION OF AZOLE		
Decreased absorption of azole		
	Antacids, H2 receptor antagonists, sucralfate, omeprazole, didanosine (oral)	Itraconazole
Increased metabolism of azole		
	Isoniazid, phenytoin, carbamazepine, phenobarbital, nevirapine, efavirenz	Itraconazole
	Rifampin	Itraconazole, fluconazole
INCREASED PLASMA CONCENTRATION OF COADMINISTERED DRUG		
	Cyclosporine, phenytoin, sulfonylureas, warfarin, triazolam, alprazolam, midazolam, protease inhibitors	Itraconazole, fluconazole
	Tacrolimus, nortriptyline, rifabutin, zidovudine, stavudine	Fluconazole
	Loratadine, felodipine, nifedipine, lovastatin, digoxin	Itraconazole

Modified from Hoesley C, Dismukes WE. Overview of oral azole drugs as systemic antifungal therapy. Semin Resp Crit Care Med. 1997; 18:301–9, quoted in: Dismukes WE. Introduction to antifungal drugs. Clin Infect Dis. 2000;30:653–7.

Drug interactions involving oral griseofulvin

EFFECT	
DECREASED PLASMA CONCENTRATION OF CO-ADMINISTERED DRUG	
	Oral contraceptives (e.g. ethinyl estradiol/norethindrone)

The combination of alcohol and griseofulvin may cause flushing and a fast heart rate. Use alcohol cautiously during treatment with griseofulvin.

Drug interactions involving oral antiviral drugs

EFFECT	ANTIVIRAL INVOLVED
INCREASED PLASMA CONCENTRATIONS OF CO-ADMINISTERED DRUG	
Tenofovir	Acyclovir, valaciclovir, famciclovir[a]

[a] There is increased concentration of both drugs and both are nephrotoxic; renal function needs to monitored when co-administered. For ART drug interactions refer to WHO's ART guidelines (WHO, 2013).

Drug interactions involving ivermectin[a]

DECREASED PLASMA CONCENTRATION OF IVERMECTIN	
	Nevirapine, efavirenz, rifapentine
DECREASED PLASMA CONCENTRATION OF IVERMECTIN	
	Sirolimus
INCREASED PLASMA CONCENTRATION OF COADMINISTERED DRUG	
	Tacrolimus, warfarin, sirolimus

[a] These are some of the reported interactions, may not need dose modifications.

Annex 3. Drug treatment regimens, dosage and cost

HERPES ZOSTER						
Recommendation	**Medication**	**Dose**		**Duration**	**Other comments**	**Median supplier price: unit cost (US$)**
		Adults	**Children**			
1st line	Acyclovir	800 mg 5 times a day		Until full crusting of lesions, usually 7–10 days	In HIV-uninfected persons, the usual recommendation is to initiate treatment within 72 hours of onset. However, in HIV-infected persons treatment is to be initiated any time before full crusting of lesions	0.0502 (200 mg tablet); 0.0959 (400 mg tablet); 0.1284 (800 mg tablet)
Other options	Valacyclovir	1000 mg TID		Until full crusting of lesions, usually 7–10 days		7.5875 (500 mg tablet)
	Famciclovir	500 mg TID		Until full crusting of lesions, usually 7–10 days		0.546 (250 mg tablet); 0.904 (500 mg tablet)
OROPHARYNGEAL CANDIDIASIS						
Recommendation	**Medication**	**Dose**		**Duration**	**Other comments**	**Median supplier price: unit cost (US$)**
		Adults	**Children**			
1st line	Fluconazole	100 mg od	3 mg/kg per day	7–14 days		0.0931 (100 mg tablet); 0.0675 (150 mg tablet, capsule)
2nd line	Nystatin pastilles	(100,000 units/ml), 4–6 ml QID		7–14 days		0.0336/ml
	Clotrimazole troches	10 mg PO 5 times daily		7–14 days		1.207 (10 mg troche)
	Itraconazole	200 mg solution OD		28 days	for esophageal candidiasis resistant to fluconazole	0.94/mg (150 ml of 10 mg/ml solutions costs US$142)

TINEA

Tinea that is not extensive (includes: *tinea corporis, cruris, faceii, barbae, pedis*)

Recommendation	Medication	Dose		Duration	Other comments	Median supplier price: unit cost (US$)
		Adults	Children			
1st line	Terbinafine	1% cream/gel to be applied twice daily		1–2 weeks		0.3700/g
2nd line options *In patients who have failed topical therapy*	Griseofulvin	500 to 1000 mg per day (microsize) or	20 to 25 mg/kg per day (microsize)	2–4 weeks		0.0192/tablet (125 mg) 0.0342/tablet (250 mg) 0.0596/tablet (500 mg)
		375 to 500 mg per day (ultramicrosize)	10 to 25 mg/kg/day (ultramicrosize)			
	Terbinafine	(Oral) 250 mg daily	10 to 20 kg: 62.5 mg daily	1–2 weeks		0.571 (250 mg tablets)
			20 to 40 kg: 125 mg daily			
			> 40 kg: 250 mg daily			
	Itraconazole	200 mg daily	3 to 5 mg/kg daily	1–2 weeks		0.2799/tablet
Tinea that is extensive or hair or nail infections						
1st line	Griseofulvin	500 to 1000 mg per day (microsize) or	20 to 25 mg/kg per day (microsize)	4–6 weeks Longer duration for nail infections		0.0192/tablet (125 mg) 0.0342/tablet (250 mg) 0.0596/tablet (500 mg)
		375 to 500 mg per day (ultramicrosize)	10 to 25 mg/kg/day (ultramicrosize)			
2nd line options	Terbinafine	250 mg OD	10 to 20 kg: 62.5 mg daily	2 weeks for skin infections 4–6 weeks for hair infections 6 weeks for fingernail infections & 12 weeks for toenail infections		0.571 (250 mg tablets)
			20 to 40 kg: 125 mg daily			
			> 40 kg: 250 mg daily			
	Itraconazole	200 mg OD	3 to 5 mg/kg daily			0.2799/tablet
		Itraconazole pulse therapy for nail infections 200 mg BD		for one week per month, with the treatment repeated for two to three months (i.e., two to three "pulses")		0.2799/tablet

SCABIES						
Recommendation	**Medication**	**Dose**		**Duration**	**Other comments**	**Median supplier price: unit cost (US$)**
		Adults	**Children**			
1st line	Permethrin	5% cream/lotion	5% cream/lotion	Single 12 hour overnight application for classical scabies Multiple applications at weekly intervals for crusted scabies	To be applied to all parts of the body from the neck down In children, to be applied to all parts of the body, including the head and neck	0.145/gm (4.35/30 gm tube)
2nd line	Ivermectin	200 µg /kg	200 µg /kg	Single dose for classical scabies 2 doses for crusted scabies	Not recommended for children <15 kg, pregnant and lactating women	8.7 (3 mg tablets), 17.3 (6 mg tablets)
Other options	Benzyl benzoate	25% lotion	12.5% lotion	Two 12 hour applications on two consecutive days	To be applied to all parts of the body from the neck down In children, to be applied to all parts of the body, including the head and neck	0.0048/ml
	Crotamiton	10% cream/lotion	10% cream/lotion	Two 12 hour applications on two consecutive days		1.44/gm; 1.05/ml

SEBORRHOEIC DERMATITIS						
Recommendation	**Medication**	**Dose**		**Duration**	**Other comments**	**Median supplier price: unit cost (US$)**
		Adults	**Children**			
1st line	Ketoconazole	2% lotion/shampoo		2–3 times per week for four weeks, with a maintenance treatment once per week as needed		0.1243/g
2nd line	Ketoconazole plus topical corticosteroids	Mid- to high-potency topical corticosteroids can be used in combination with other medications (antifungals such as ketoconazole) but should be reserved for short-term therapy in severe seborrhoeic dermatitis or flare. Treatment of seborrhoeic dermatitis on sensitive areas such as the face should be limited to low-potency agents, whenever possible.				0.0407/g (with 1% HC cream), 0.0487/g (with 1% HC ointment)

EOSINOPHILIC FOLLICULITIS

Recommendation	Medication	Dose		Duration	Other comments	Median supplier price: unit cost (US$)
		Adults	Children			
1st line	ART	(Refer to WHO Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection)				
Other treatments	Topical corticosteroids	Class III or above, potent e.g. betamethasone				0.0393/g (betamethasone cream)
	Itraconazole	200 mg/day		4 weeks		0.2799/tablet
	Permethrin	5 % cream/lotion	5 % cream/lotion	Repeated weekly applications as required		0.145/gm (4.35/30 gm tube)
	Antihistamines[a]					
	Cetrizine	5–10 mg OD	6–11 yrs: 5–10 mg OD			0.28 (10 mg tablets)
			6 mo–5 yr: 2.5–5 mg OD			
	Loratidine	10 mg OD	5 mg OD (2–9 yr) or 10 mg OD (6–11 yr)			
	Desloratidine	5 mg OD	5 mg OD (≥ 12 yr)			
	Fexofenadine	180 mg OD	60 mg BD or 120–180 mg OD (≥ 12 yr)			
	Levocetirizine	5 mg OD	5 mg OD (≥ 6 yr)			
	Hydroxyzine	25 mg TID	10–15 mg TID			0.33 (10 mg tablets)
	Promethazine (phenergan)		0.1 mg/kg PO Q 6h (Max dose 12.5 mg /day)			0.19/mg

[a] Motala C. H1 antihistamines in allergic diseases. Curr Allergy Clin Immunol. 2009;22(2):71-4.

Abbreviations: TID: three times per day; OD: once daily; QID: four times per day; PO: orally; BD: twice daily; Q: every