

# **Clinical AIDS Care Guidelines**

## **For Resource-poor Settings**

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# HIV

## List of abbreviations

AIDS:	acquired immune deficiency syndrome
AFB:	acid-fast bacilli
ARC:	AIDS-related complex
ARV:	anti-retroviral (drugs)
AZT:	zidovudine
BAL:	bronchoalveolar lavage
CBC	complete blood count
CMV:	Cytomegalovirus
CNS:	central nervous system
CSF:	cerebro-spinal fluid
CVA:	cerebro-vascular accident
COPD:	chronic obstructive pulmonary disease
DOTS:	directly observed treatment, short course
DS:	double strength
EBV:	Epstein-Barr virus
EMB:	ethambutol
ENT:	ear nose throat
ESR:	erythrocyte sedimentation rate
HAART:	highly active anti-retroviral treatment
HIV:	human immunodeficiency virus
HSV:	Herpes simplex virus
INH:	isoniazid
ICU:	intensive care unit
IU:	international unit
KS:	Kaposi's sarcoma
LN:	lymph node
LP:	lumbar puncture
MAC:	<i>Mycobacterium avium</i> complex
NSAID:	non-steroidal anti-inflammatory drugs
PCP:	<i>Pneumocystis carinii</i> pneumonia
PGL:	persistent generalised lymphadenopathy
PLWH/A:	people living with HIV/AIDS
PML:	progressive multifocal leukoencephalopathy
PPD:	purified protein derivative
PPE:	papular pruritic eruption
PT:	preventive treatment

PZA: pyrazinamide  
RIF: rifampicin  
RR: relative risk  
SS: single strength  
TB: tuberculosis  
TLC: total lymphocyte count  
TMP/SMX: trimethoprim-sulfamethoxazole (cotrimoxazole)  
UNAIDS: Joint United Nations Programme on HIV/AIDS  
VCT: voluntary counselling and testing  
WB: Western blot  
WBC: white blood cell  
WHO: World Health Organisation



*The White Rabbit put on his spectacles.  
'Where shall I begin, please your  
Majesty?' he asked.  
'Begin at the beginning,' the King said, very gravely,  
'and go on till you come to the end: then stop.'  
(Lewis Carroll, 1865)*

Two years ago, I began at the beginning, but for now, although there is no end in sight I have decided to stop. Writing clinical AIDS care guidelines for MSF settings is quite a challenge; so was deciding when to stop. AIDS care is evolving rapidly: new scientific information, new AIDS care policies in resource-poor settings, changes in drug availability and MSF's growing commitment to supporting programmes for PLWH/A. These guidelines are therefore incomplete. However, I felt it was time to start field-testing what has been written so far.

The guidelines have a dual objective: first, to give guidance in the diagnosis of opportunistic infections (OI) with limited resources through the use of diagnostic algorithms and second, to propose therapeutic guidelines for OI in people living with HIV-AIDS that could be used as a basis for each project to choose from, depending on available resources and national policies.

Some recommendations may have to be changed again soon. Some diagnostic algorithms will need to be adapted. That is why I would request – and appreciate – feedback from everyone using the guidelines\*. Are the algorithms useful in your daily practice? Are they appropriate for training health-care workers? What topics are not covered in this edition?

I hope these guidelines will contribute towards alleviating the suffering of PLWH/A and facilitating the task of health staff caring for PLWH/A.

#### Acknowledgements

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- Francine Matthys, who was the first to recognise the need and interest of these guidelines and who gave me the opportunity to write them; she has been very patient.
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\* All comments can be sent to the HIV-AIDS resource person at the medical department at MSF-Belgium and to Lut Lynen: [llynen@itg.be](mailto:llynen@itg.be)

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I also would like to thank my patients and colleagues in Cambodia. They helped me to see the reality of HIV/AIDS in this part of the world and stimulated me to write these guidelines.

Lut Lynen  
Phnom Penh  
October 12, 2000

# HIV

## 1. INTRODUCTION

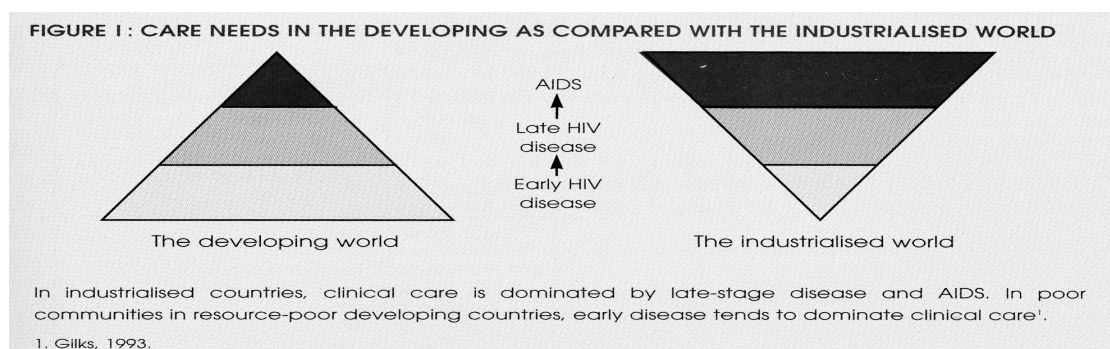
More than 30 million people are HIV-positive and will develop AIDS in the next decade. 90% of this number are living in resource-poor countries. In some settings in Africa and Asia in which MSF is working, AIDS is a public health problem of prime importance. It profoundly affects the functioning of health structures and the social and economic organisation of communities.

MSF medical practitioners will be increasingly confronted with AIDS-related diseases in the future. Prevention remains a priority of AIDS control programmes. However for most people, HIV/AIDS is as much a disease requiring care and support, as it is an infection to avoid. Communities will increasingly judge the credibility of HIV/AIDS programmes by the quality of care they offer.

The WHO proposes a strategy of “*comprehensive care across a continuum*”<sup>1-3</sup> for the optimal health care of people living with HIV/AIDS (PLWH/A); this usually includes clinical management, nursing care, psychological, social and legal support. It should be provided through a network of services extending across a *continuum*, i.e. with interaction between home and community, the health centre and a referral hospital.

In many countries, medical competence for the care of PLWH/A is concentrated in the higher-level facilities. Few organisations play a medical role at the lower level of the health-care pyramid, where smaller hospitals, health centres and home care are to be found. In order to guarantee good care at each level, it is important that the flow between structures is organised in such a way as to avoid unnecessary crowding at the higher level. A possible role for MSF projects is to work on standardising care and training staff. It is with this perspective in mind that these guidelines have been written.

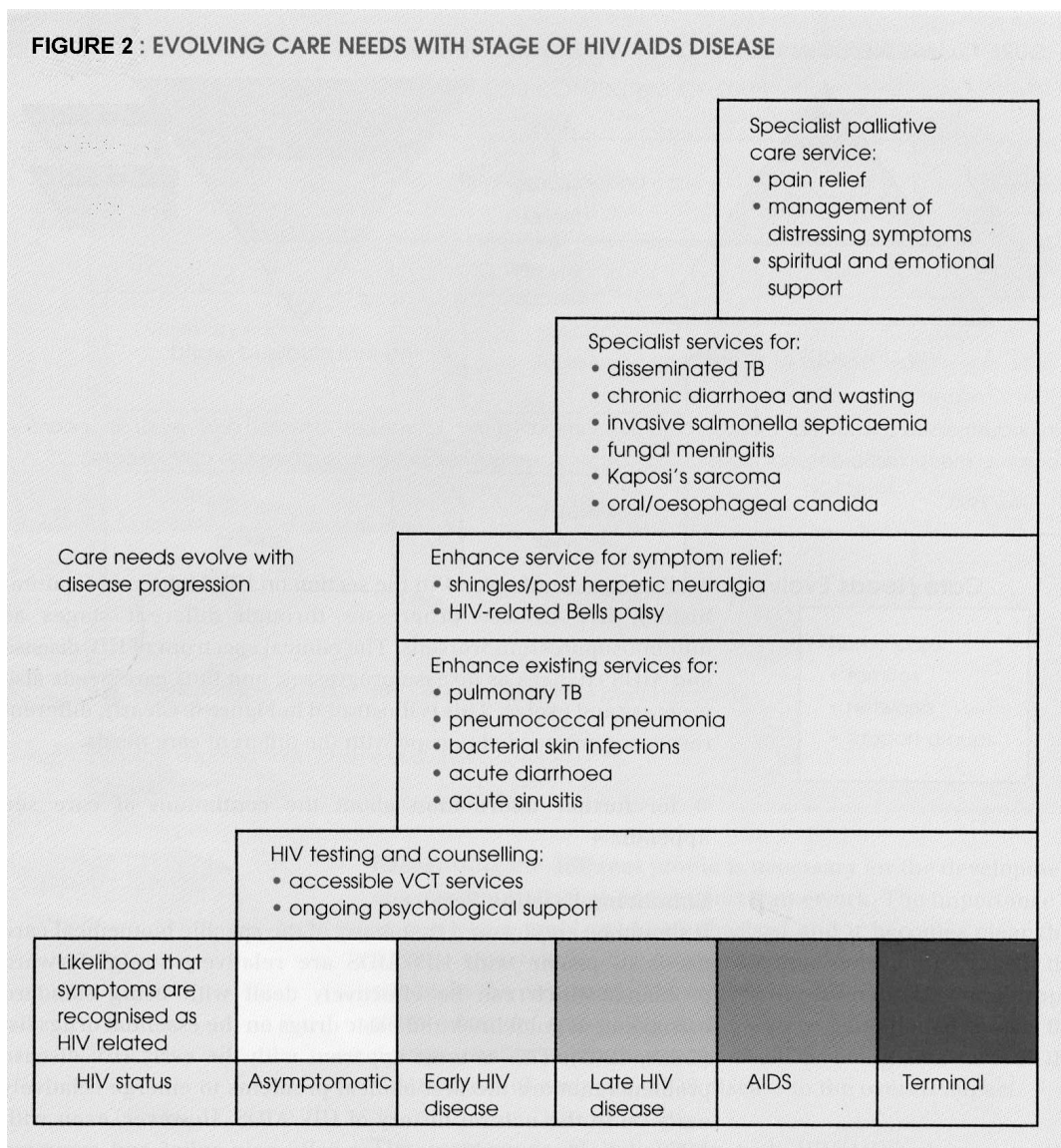
The burden of disease caused by the HIV infection in developing countries and in the industrialised world shows a distinct clinical pattern:



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Early HIV disease and high-grade bacterial pathogens predominate the clinical picture in developing countries.<sup>5</sup> Opportunistic infections (OI) only occur in patients who live long enough to develop profound immunosuppression. Given that most PLWH/A in Africa die of bacterial infections, including TB, the early recognition and treatment of these diseases, together with TMP/SMX and INH prophylaxis, can have an important impact on delaying mortality and improving the quality of life for PLWH/A and their families.

With every stage of HIV/AIDS disease, the care needs evolve:



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The diagnosis and treatment of the high-grade infections in early HIV disease do not require more specialised care than that which the existing health services should already be providing. However, because the number of patients is increasing, these basic services need to be reinforced and sometimes still have to be developed.

The purpose of these guidelines is to develop and describe strategies for managing the health problems of AIDS patients at the different levels of care provision, in order to ensure a continuum of care. A strategy is proposed for each level of care, as well as the necessary equipment and drugs for responding to the health needs of PLWH/A.

A syndromic approach has been used in producing this document, using algorithms that have been adapted from existing WHO guidelines.<sup>6</sup> Different treatment options are described. For some symptoms, the diagnostic tests and necessary equipment have been quite extensively described because there is room for more accurate diagnosis of opportunistic infections in AIDS patients, especially at the referral level. It will be up to the different field teams to choose the level of care that is acceptable and affordable in their situation.

It is clear that these guidelines will have to be adapted to the prevailing situation in each setting. There is no gold standard. The necessary skills and the need for additional training will vary according to the pre-existing level of knowledge, attitude and practice.

The question of primary and secondary prevention of OI, and the follow-up of asymptomatic patients is also dealt with.

This document does not provide guidelines for managing the social problems such as, orphans, unemployment, and stigmatisation. Everyone involved in AIDS care should identify local partners that could help take care of AIDS patients. For MSF, the medical care content is the priority.

Currently debated topics such as ARV treatment and prevention of mother-to-child transmission are not covered here, but other guidelines will deal with these issues.

The development of tools and indicators to monitor and evaluate comprehensive AIDS care programmes will also be covered in the future.

The experiences gained in different projects provide very valuable information that contributes to the enlarging of MSF's medical expertise. In this regard, all comments on this document are welcome and should be sent to the HIV-AIDS resource person at the medical department in MSF Belgium and to [llynen@itg.be](mailto:llynen@itg.be)

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4. Wullaume F. Medical department, MSF-Belgium. Comprehensive care programme for persons living with AIDS. Nairobi, Kenya. Visit report 1997.
5. Gilks CF. The clinical challenge of the HIV epidemic in the developing world. Lancet 1993; 342:1037-1039.
6. WHO, Guidelines for the clinical management of HIV infection in adults. WHO/GPA/IDS/HCS/91.6

A syndromic approach has been used in the writing of these guidelines.

The first part of each chapter briefly describes the most important HIV-related problems (infections, malignancies, etc.) related to the syndrome (e.g. neurological syndrome). The different diagnostic and treatment issues are mentioned.

In the second part of each chapter **clinical diagnostic algorithms** are developed for each level of care.

In most developing countries, diagnostic facilities are severely limited. Management decisions have to be based on clinical features and simple laboratory findings.

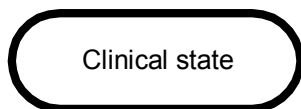
The flowchart algorithms that are proposed in these guidelines are based upon the "WHO guidelines for the clinical management of HIV infection in adults".<sup>1</sup> The use of these guidelines is conditional on the knowledge of the patient's HIV status, either by clinical suspicion, or by HIV testing (see *Diagnosis and Staging of HIV/AIDS*, chapter 3). For example, it is clear that *Pneumocystis carinii* cannot be a possible diagnosis if a patient is not immunosuppressed.

For some complex diagnostic problems (e.g. respiratory problems) a combination of linear algorithms is used. Medical doctors do not use a sequential, dichotomous thinking (algorithm) when they try to solve a complex medical problem. On the contrary, the diagnostic process uses pattern recognition, which is a form of parallel thinking.

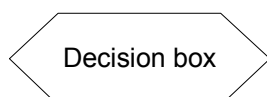
The diagnostic pathways are presented as flowchart algorithms (single or parallel). Further explanations about the treatment options or diagnostic tools are given in the annotations.

The algorithms contain three differently shaped boxes, in analogy with the WHO guidelines, which have the following functions:

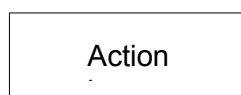
**Clinical state or problem definition box:** the box defines the clinical state or problem.



**Decision box:** the information necessary for taking some sort of decision.



**Action box:** indicates a therapeutic or diagnostic action.



Capital letters between brackets (A) within a box refer to annotations or comments printed on the following pages.

Each algorithm begins with a clinical box describing the symptom or problem. This box is followed by initial steps, after which a certain level of care has to be chosen according to the needs and according to what is available.

A careful history should be taken and a physical examination always carried out **before** an algorithm is applied.

At level C, it is assumed that it is possible to identify those patients who are immunocompromised and to determine the stage of disease either by clinical evidence or by laboratory evidence (lymphocyte count, CD4 count). The diagnostic flowcharts consider only the differential diagnosis in patients with intermediate (stage 3) and late stage (stage 4) of disease or patients with a known CD4<200. In this group of patients, opportunistic infections should be considered first because the probability is high.

If the CD4 count is not known and there is no evidence of immune deficiency, other diseases should be considered. These problems are not taken into account in this manual.



A third part deals with the **palliative, symptomatic and terminal care** related to the syndrome. Before starting symptomatic treatment or palliative care, there must be certainty that all remediable causes are tackled. Therefore, a good interaction between the different levels of care (home care, health centre and hospital) is necessary. At each level of care, however, attention must be paid to involve family members or care-givers, and not to rely solely on drugs. Family members should receive counselling on how to deal with each problem.

A fourth part of each chapter lists the **drugs and diagnostic equipment** that are needed according to the level of care.

Some chapters contain a fifth section describing the laboratory examinations in more depth.

MSF mostly works at the health centre (WHO level A) and district hospital (WHO level B) levels. However, in some projects that specifically target AIDS patients, an upgrading to certain aspects of WHO level C (specialised AIDS care centres at university hospitals) has taken place. These algorithms will also be of particular interest to HIV clinics, which function as a second-line reference in district hospitals.

Each project will have to define which level of care (A, B, C) is appropriate in the different sites of the project area. If a home-care project receives referrals of terminally ill patients from a hospital, it will need support and input from medical professionals, and extra equipment and knowledge compared to home-care programmes run essentially by community health volunteers.

Depending on the possibilities available at each level in your situation, tasks, algorithms and referral patterns can be different from the ones proposed in this document.

## REFERENCE LIST

1. WHO, Guidelines for the clinical management of HIV infection in adults. WHO/GPA/IDS/HCS/91.6



# HIV

## 3. DIAGNOSIS AND STAGING OF HIV/AIDS

Diagnosing and staging of the HIV disease in a person living in a developing country is not as easy and quickly done as might be thought. A good clinical examination and thorough interview of the patient is needed and this can easily take 20 minutes per patient.

For the settings in which MSF is regularly working, the WHO AIDS case definitions and staging system is used, adapted for countries with limited clinical and laboratory diagnostic facilities.

A further refinement of the WHO staging system is also proposed for settings where laboratory monitoring can be offered.

In some articles the CDC AIDS surveillance case definitions<sup>1</sup> are used. For developing countries, however, the WHO adapted clinical and laboratory staging system is more appropriate.

### 1 WHO CASE DEFINITIONS FOR AIDS SURVEILLANCE IN COUNTRIES WITH LIMITED CLINICAL AND LABORATORY DIAGNOSTIC FACILITIES<sup>2, 3</sup>

#### A. ADULTS AND ADOLESCENTS

##### 1. Where HIV testing is not available

The case definition for AIDS is fulfilled in the presence of at least 2 major signs and at least 1 minor sign.

##### Major signs

- weight loss >10% of body weight
- chronic diarrhoea (>1 month)
- prolonged fever (>1 month)

##### Minor signs

- persistent cough for more than one month (in case of TB this criteria should not be used)
- generalised pruritic dermatitis
- history of Herpes zoster
- oropharyngeal candidiasis
- chronic progressive or disseminated Herpes simplex infection
- generalised lymphadenopathy

The presence of either generalised Kaposi's sarcoma or cryptococcal meningitis is sufficient for the case definition of AIDS.

The problem of this method is its low sensitivity and specificity.

## **2. Where HIV testing is available**

The case definition for AIDS is fulfilled if the HIV test is positive and one or more of the following conditions are met:

- weight loss >10 % body weight, or cachexia, with diarrhoea or fever, or both, for at least one month, not known to be due to a condition unrelated to HIV infection
- cryptococcal meningitis
- tuberculosis (pulmonary or extrapulmonary)
- Kaposi's sarcoma
- HIV encephalopathy: neurological impairment which prevents independent daily activities, not known to be due to a condition unrelated to HIV infection
- oesophageal candidiasis
- life-threatening, or recurrent episodes of, pneumonia
- invasive cervical cancer

## **B. CHILDREN**

### **1. Where HIV testing is not available**

The case definition for AIDS is fulfilled if at least two major and at least two minor signs are present.

#### Major signs

- weight loss or abnormally slow growth
- chronic diarrhoea (>1 month)
- prolonged fever (>1 month)

#### Minor signs

- generalised lymph node enlargement
- oropharyngeal candidiasis
- recurrent common infections, such as ear infections and pharyngitis
- persistent cough
- generalised rash

#### Other signs

- neurological problems
- delay in development
- bilateral parotid gland enlargement
- enlarged spleen
- enlarged liver
- recurrent abscesses

- meningitis
- recurrent Herpes simplex.

Confirmed HIV infection in the mother counts as a minor criterion.

## 2. Where HIV testing is available

The WHO case definition is complex and depends on advanced clinical and laboratory diagnostic facilities.

## 2 THE WHO CLINICAL STAGING SYSTEM<sup>4,5</sup>

A list of clinical markers believed to have prognostic significance has been assembled, resulting in four prognostic categories. A performance scale has also been incorporated into the system.

### Clinical stage 1

1. Asymptomatic infection
2. Persistent generalised lymphadenopathy (PGL)
3. Acute retroviral infection

**Performance scale 1:** *asymptomatic, normal activity.*

### Clinical stage 2

4. Unintentional weight loss, <10% of body weight
5. Minor mucocutaneous manifestations (e.g. seborrheic dermatitis, prurigo, fungal nail infections, oropharyngeal ulcerations, angular cheilitis)
6. Herpes zoster, within the previous 5 years
7. Recurrent upper respiratory tract infections (e.g. bacterial sinusitis)

**Performance scale 2:** *symptoms, but nearly fully ambulatory.*

### Clinical stage 3

8. Unintentional weight loss, >10% of body weight.
9. Chronic diarrhoea, >1 month
10. Prolonged fever (intermittent or constant) >1 month
11. Oral candidiasis (erythematous or pseudomembranous)
12. Oral hairy leukoplakia
13. Pulmonary tuberculosis (typical or atypical) within the previous year
14. Severe bacterial infections (e.g. pneumonia, pyomyositis)
15. Vulvovaginal candidiasis, chronic (>1 month) or poorly responsive to therapy

**Performance scale 3:** *in bed <50 % of normal daytime, but more than normally during the previous month.*

## **Clinical stage 4**

16. HIV wasting syndrome
17. *Pneumocystis carinii* pneumonia
18. Toxoplasma of the brain
19. Cryptosporidiosis with diarrhoea, >1 month
20. Isosporiasis with diarrhoea, >1 month
21. Extrapulmonary cryptococcosis
22. Cytomegaloviral disease of an organ other than liver, spleen or lymph node
23. Herpes simplex virus infection, mucocutaneous (>1 month) or visceral (any duration)
24. Progressive multifocal leukoencephalopathy (PML)
25. Any disseminated endemic mycosis (e.g. histoplasmosis, coccidioidomycosis)
26. Candidiasis of the oesophagus, trachea, bronchi and lungs
27. Atypical mycobacteriosis, disseminated
28. Non-typhoid *Salmonella* septicaemia
29. Extrapulmonary tuberculosis
30. Lymphoma
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy

**Performance scale 4:** in bed for longer than 50% during the day over the previous month.

## **3 WHO STAGES AND LEVEL OF CARE NEEDED<sup>6,7</sup>**

<b>WHO clinical stage(1990)</b>	<b>Patient performance scale</b>	<b>Level of care</b>
Stage 1: Asymptomatic	Normal	None
Stage 2: Minor symptoms	Normal	Standard care
Stage 3: More severe symptoms	Bedridden <50 % of time	Standard care
Stage 4: Other AIDS-defining illness	Bedridden >50 % of time	New AIDS-specific interventions Terminal care

## 4 WHO IMPROVED CLINICAL STAGING SYSTEM

A further refinement of the WHO clinical staging system includes a laboratory axis. The laboratory axis subdivides each category into 3 strata (A, B, C) depending on the number of CD4 cells. If this is not available, total lymphocytes can be used as an alternative marker.<sup>4</sup>

Laboratory axis		Clinical axis				
Lymphocytes*	CD4**	Stage 1 Asympt. PGL	Stage 2 Early HIV	Stage 3 Intermediate (ARC)***	Stage 4 Late AIDS	
<b>A</b>	>2000	>500	1A	2A	3A	4A
<b>B</b>	1000-2000	200-500	1B	2B	3B	4B
<b>C</b>	<1000	<200	1C	2C	3C	4C

\* Reference range total lymphocytes: 1500-4000/mm<sup>3</sup>

\*\* Reference range CD4 count: 450-1400/mm<sup>3</sup>

\*\*\* ARC: AIDS-related complex

Grey area refers to progression to AIDS.

N.B. The reference values used for lymphocytes and CD4 count are based on data available from the developed world. There are indications that Africans may have a physiologically higher lymphocyte count<sup>8</sup>. Projects with laboratory equipment to conduct lymphocyte counts in HIV patients should, if possible, collect data about lymphocyte counts and CD4 counts and correlate them with the disease stage.

## 5 TESTING

HIV infection is diagnosed by a positive HIV test. Many low-income countries cannot afford expensive Western tests in order to diagnose HIV infection. The WHO has therefore recommended testing strategies based on a combination of screening tests that do not require expensive Western blot (WB) confirmation assays.

HIV testing has become much more widely available than had been initially predicted and the diagnosis of HIV purely on clinical features has become less frequent. Confirmatory assays (WB) should only be used to resolve indeterminate results for diagnostic purposes.

The testing strategy used will depend on:

### **A. TEST OBJECTIVES**

1. Transfusion and transplant safety
2. Surveillance
3. Diagnostic

### **B. PREVALENCE OF INFECTION IN THE SAMPLE POPULATION**

Table: UNAIDS and WHO recommendations for HIV testing strategies according to test objectives and prevalence of infection in the sample population<sup>9</sup>.

Objective of testing	Prevalence of infection	Testing strategy
<b>Transfusion and transplant safety</b>	All prevalences	I
	>10%	I
<b>Surveillance</b>	≤10%	II
	Clinical signs of HIV infection	
<b>Diagnostic</b>	>30%	I
	≤30%	II
	Asymptomatic	
	>10%	II
	≤10%	III



In most situations where MSF is involved in clinical care for AIDS patients, the prevalence of HIV infection in the population is high and we are confronted with patients who meet clinical stage 3 or 4 of HIV infection. In this situation, one simple positive screening test is sufficient to diagnose AIDS (testing strategy I).

For safe transfusion, testing strategy I (1 test) is also sufficient to reject blood if it is positive.

In all other situations, at least two tests will be needed for the diagnosis of AIDS (strategy II and III).

HIV testing for individual diagnosis will be performed according to the rules of voluntary counselling and testing (VCT) services.<sup>10</sup>

- Testing is done **voluntarily**, with **informed consent**. No coercion should be exercised. Mandatory testing is out of the question. Everyone has the right to know (or not to know) their HIV status.
- Pre- and post-testing **counselling** services are in place.
- **Confidentiality** must be guaranteed in order to prevent discrimination.
- The test must be **technically sound** and there must be access to a confirmation test.
- The tests are financially (and culturally) **accessible**.
- **Minimal care** is available for the patient.

The rationale behind VCT is that it may reinforce preventive behaviour in seronegative people.

If people know they are seropositive, they can take measures to prevent the development of some opportunistic infections, to prevent further HIV transmission and prepare themselves and their families for the future.

The chance for behavioural change in someone who is tested by coercion is minimal. Behavioural change will only occur if testing is integrated into a comprehensive HIV/AIDS prevention and care package. Health education, condom promotion, prevention and care programmes, psychological, social and legal support are necessary for maximising the benefit of a VCT programme. VCT is an essential part of a comprehensive response to HIV/AIDS, but only if it is correctly accompanied by other supportive programmes. A randomised trial in Kenya, Tanzania and Trinidad showed the beneficial effect of VCT in individuals and couples.<sup>11, 12</sup>

Guidelines for counselling in regard to HIV testing, infection and disease can be downloaded from the websites of UNAIDS ([www.unaids.org](http://www.unaids.org)) and the WHO ([www.who.int](http://www.who.int)).

A document written by Healthlink Worldwide International<sup>13</sup> illustrates the different issues regarding testing and counselling in a very practical way. Concise information on pre- and post-test counselling issues (risk assessment, knowledge assessment, assessment of ability to cope with diagnosis, etc.) can be found in the WHO manual on TB/HIV<sup>2</sup>, p.72. Another excellent reference book on counselling adapted to an African setting is the CARE counselling model handbook.<sup>14</sup>

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## 4. FOLLOW-UP OF ASYMPTOMATIC HIV-POSITIVE PATIENTS

(The sources used in writing this chapter are indicated as numbers 9-12 in the *Reference List* at the end of this chapter.)

Regular medical follow-up of asymptomatic patients will provide an opportunity for the health-care worker to address various questions with PLWH/A, such as the prevention of transmission, how to maintain good nutritional status, how to prevent health-care problems, and opportunistic infections.

Psychological support is also needed. The patient will have many questions and anxieties. It is important that in the post-test counselling the patient is informed as to who to see and where to go with questions. It also shows the patients that they are not abandoned, but will continue to be cared for, if they so desire. This takes away the common belief that nothing can be done to help HIV-infected patients.

Depending on the stage of the disease, the medical team should, together with other institutions, address social and financial problems. It is essential that PLWH/A are offered the opportunity to take part in AIDS support groups.<sup>1,2</sup>

### 1 INITIAL CHECK-UP

#### 1.1 Complete anamnesis

##### Medical history

- STD
- TBC
- Probable route of acquiring HIV infection - to identify risk behaviour.

##### Family history

- social situation
- marital status/sexual partner(s)
- children
- intention to have children
- any other PLWH/A in the family
- any tuberculosis in the family

### Economic situation

- income sources
- food security
- fixed costs

### Spiritual support

- religion
- traditional healers

### Present clinical situation

- current symptoms
- grading following WHO clinical staging system

## **1.2 Physical examination**

Make a **complete** physical examination.

Look for indicator diseases like Herpes zoster, oral candidiasis, wasting, etc. Examine the genital area, and always give women a gynaecological examination.

## **1.3 Other possible tests**

- *Complete blood count* (haemoglobin, WBC, platelets).
- *Lymphocytes* or *CD4* count.
- *ESR*: is usually elevated (>50) in HIV-positive patients. If more than 100, consider TB.
- *VDRL*: 6% false positives, confirm with TPHA. Relapse is common even with the recommended treatment. It is therefore important to perform follow up VDRL at 3-6-9-12 months.
- If *hepatitis B serology* is possible and negative, start vaccination in those countries where hepatitis B vaccination is available. Risk factors for HIV and hepatitis B are the same, and in the US 70-80% of HIV patients have serologic markers for hepatitis B.
- *Chest X-ray*: It is useful in the initial check up because it serves as a comparison to later chest X-rays when pulmonary problems appear. Sometimes, it allows for early detection of TB. Where INH-prophylaxis is possible, chest X-ray is necessary to exclude active TB, prior to starting the prophylaxis. (See *Prevention of opportunistic infections*, chapter 5)
- *PPD skin testing* is not routinely recommended in MSF settings. Skin testing may be false positive due to BCG vaccination or false negative due to anergy. In developing countries there is a very high prevalence of PPD positivity. In this context, INH prophylaxis would be justified in all HIV-positive patients. However, because of the difficulty of excluding active TB, and because of the weakness of TB programmes in most developing countries, large scale INH preventive therapy is difficult.

## 1.4 Health education

Do not try to give all information during the first consultation.

### 1.4.1 Information on HIV transmission

#### 1.4.1.1 How to prevent the transmission of HIV to others

- Give information about how HIV is transmitted, about risk behaviour. Discuss points such as safe sex (condom use) and prevention of transmission.
- Give reassurance that they do not pose a risk for other family members in normal daily life.
- Body fluids that may transmit HIV through contact with abrasive skin are semen, vaginal secretions, and blood. Other risk fluids are peritoneal, pleural, pericardial, amniotic, CSF and synovial fluids, although contact with those fluids is less likely in household environment.
- Urine, stools, sputum, saliva, tears, vomit, and nasal secretion do not transmit HIV unless they are contaminated with blood. (Bartlett 1998, p18).
- Care providers are advised to protect their hands whenever handling body fluids (including soiled bedding and clothes, or cleaning up vomit), or when coming into contact with open wounds. If gloves are not available plastic bags can be used instead.

#### 1.4.1.2 Prevention of vertical transmission

Contraceptive use in women: if pregnancy is desired, discuss the risk of HIV in the offspring (30%) and discuss possible interventions to prevent this (according to the setting).<sup>3-5</sup>

#### 1.4.1.3 Prevention of transmission by exposure to blood

Needles, razor blades, and used condoms should be thrown away in such a way that their re-use is not possible. Do not share syringes or tattoo equipment.

For professionally-acquired exposure to blood, refer to the MSF guidelines.<sup>6</sup>

#### 1.4.1.4 Transfusion

HIV patients should know that they cannot give blood.

## 1.4.2 Hygiene

Good hygiene is necessary for everybody, not only HIV patients. The importance of good personal hygiene should be stressed.

### 1.4.2.1 Environment

- Some professions bring about risks of opportunistic infection. Of particular relevance in situations where MSF works is the issue of health-care workers who are HIV positive, and who are at risk of exposure to infections such as TB, enteropathogens, etc.
- In developing countries where more than 60% of adult hospitalised patients can be HIV positive, it is difficult to avoid contact with infectious patients. It is therefore recommended that cotrimoxazole and INH prophylaxis be offered to health workers wherever possible.
- Wounds and skin lesions should be kept dry and clean. Contact with infectious people or places like hospitals should be avoided when possible, but in a way that ensures that stigmatisation is not increased.
- Handwashing is the most effective way of preventing transmission of infections. Laundry, especially soiled bedding and clothes should be washed with hot water. Clothes stained with blood or body fluid stains should be washed with bleach solution (one part bleach (70%) to ten parts water).

### 1.4.2.2 Animals

Animals are a reservoir for *Salmonella*, *Cryptosporidium*, and *Campylobacter*. Avoid any contact with animal excrement; use gloves to clean up the environment around the house if necessary.

### 1.4.2.3 Nutritional advice

- Water for consumption should be boiled or bottled water should be used instead.
- Good nutrition means balanced food (cereals, fruits, vegetables, oil, meat/fish) prepared in a clean way. Avoid raw foods as much as possible. Meat and eggs should be thoroughly cooked. Fruit and vegetables should always be washed with clean water; vegetables should be cooked before eating.
- When re-heating food, make sure it is very hot throughout. Do not reheat more than once.

### 1.4.2.4 Medical advice

Explain to patients that whenever they develop signs of infection they should contact the health service.



### **1.4.3 Nutrition \***

A balanced food intake is one of the most important ways to stay healthy. Malnutrition and malabsorption are major problems in AIDS patients. Patients should be given an explanation about what to do when eating becomes a problem.

Loss of appetite:

- try to choose foods that the patient prefers
- try small, frequent meals
- allow them to eat whenever they feel like it, not at scheduled times
- physical exercise creates appetite
- ask family or friends to keep the patient company during a meal, even if it takes longer.

Sore mouth:

- choose soft foods that are easy to swallow
- avoid very hot or very cold food
- use a straw for drinking.

Nausea/vomiting:

- sit up to eat
- eat slowly and small amounts
- avoid greasy or spicy food
- in case of vomiting, try soup or bouillon, rather than solid foods.

Diarrhoea:

- continue to eat, even if eating seems to increase the diarrhoea
- avoid alcohol and coffee
- drink much more than usual, but remember that drinks do not replace food
- avoid high-fibre or bulky foods, such as fruit and vegetable peel and whole-grain cereals because they are hard to digest
- After the diarrhoea has stopped, the patient can take an extra meal every day, to make up for the weight loss.

In case of pain on swallowing, signs of dehydration, refusal of food and drinks, and inability to keep food down, patients should seek medical advice.

### **1.4.4 Regular physical exercise**

- Favours digestion and appetite.
- Helps to maintain physical fitness.
- Improves emotional wellbeing.

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\* For further reading, go to references 7 & 8

### **1.4.5 Adequate rest**

### **1.4.6 Emotional well-being**

The medical care-provider has to take into account the emotional wellbeing of the patient. People who are sad and depressed will not take care of their physical wellbeing.

Important social and communication skills are required, but are often neglected because of time constraints. This is a mistake: patients will not feel understood and will stay away, even when they have medical problems. Therefore, it is difficult to imagine AIDS care without a multidisciplinary team that supports the medical care-provider.

It is essential to:

- listen carefully to the patient
- try to understand their feelings
- ask questions in an empathic way
- respect their feelings
- encourage patients when they express emotions
- offer care that helps to maintain self esteem and self confidence
- give correct information; do not give false hope
- help the family to deal with the emotions (the patient's and their own).

Patients should continue to do their daily routine work, and continue to attend the usual religious and community meetings.

Families should be mobilised to take an active part in the care of the patient. They should be advised to learn certain techniques like massage and relaxation so that they can offer it to patients when they need it.

Patients should be encouraged to learn relaxation techniques, which are useful methods for obtaining mental peace and reaching a sense of well-being. These can be done alone or with the help of a teacher (such as traditional healers or monks). This also creates a sense of independence.

Try to put the person in touch with community support groups. Groups will help the members to share their feelings and worries and to give each other support.

Some traditional practices or religious rituals can be helpful. Certain traditional healers, priests, monks or others can play a role in guiding the patient and the family through the process of shock, denial, anger, fear, sadness, hope and acceptance.

Patients should be gently encouraged to think about death and express their feelings.

Patients should participate in the decision making process when dealing with their health problems. This will help them to understand their medical problems and increase self-esteem.

Experience has shown that people involved in care and support programmes for PLWH/A are often confronted with personal stress and demotivation when continuously confronted with terminal patients. It is therefore important to offer stress-counselling opportunities in order to help them express their feelings.

## **2 FOLLOW-UP VISITS**

After being informed about their test results, patients may need closer follow-up (weekly or monthly). Once a relationship has been established, and there has been an opportunity to explain most of the above advice, the interval may be extended to once every three months.

### **2.1 Checklist for follow-up visits (from MSF guidelines for home care in Nairobi)**

Patients will complain about the most disturbing symptoms at the time of presentation. It is important to review with your patient all systems in order to detect health problems early.

See checklist next page.

### **2.2 Blood tests at follow-up**

- Complete blood count every three months.
- CD4 or lymphocytes every six months (ARV projects).
- Other examinations only according to symptoms.

## **Check list**

### **Weight loss/appetite/weakness**

Diarrhoea, dysphagia, oral pain, etc?

### **Fever**

<1 week: malaria, pneumonia, bacteremia

>1 week: TB, PCP, cryptococcosis, etc.

### **Eyes**

Jaundice, anaemia, visual disturbance, etc?

### **Oral cavity**

Oral thrush, ulcers, etc?

### **Lymph nodes**

PGL (>1 month, >2 areas, <2 cm, not painful), infections (syphilis, wound infection, TB,...), lymphoma, Kaposi's sarcoma?

### **Skin problems**

Itching? Duration? Relation to drug intake?

### **Respiratory problems**

Duration of cough? Productive? Dyspnoea? Already taking TB treatment?  
Already taking PCP prophylaxis?

### **Gastrointestinal**

Dysphagia, diarrhoea, abdominal pain?

### **Nervous system**

Central: headache, seizures, paralysis?

Peripheral: paraesthesias, numbness, neuropathy?

### **Genital area**

Discharge, pruritis, lesions?

### **Psychological**

Mood? Sleep disturbances?

### **Clinical staging: (see staging)**

WHO 1-4?

Lymphocytes/CD4: A,B,C?

### **Prevention of opportunistic infection?**

Clinical stage 2, 3 and 4, and all categories C (lymphocytes <1000, or CD4<200) would benefit from TMP/SMX prophylaxis.

**Drugs:** any new prescriptions, compliance, side effects, problems, etc?

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# HIV

## 5. PREVENTION OF OPPORTUNISTIC INFECTIONS

### 1 PRIMARY PREVENTION

The issue of prevention of opportunistic infections (OI) in developing countries is quite different from that in the Western world.<sup>1</sup> The spectrum of OI is different, as are the range of prevention options, and the susceptibility of the infecting pathogen to antimicrobials. Moreover, many AIDS patients in Africa do not survive long enough to develop CMV or MAC. Resources are also limited and for the majority of patients no CD4 counts are available, which would otherwise enable us to follow-up the evolution of the disease. HIV infection is often only diagnosed at an advanced stage of disease in developing countries.

Important opportunistic infections for HIV-infected individuals in the developing world are:

- tuberculosis: widespread
- pneumococcal disease: widespread
- non-typhoid salmonellosis: particularly East and West Africa, Thailand, and Cambodia
- cryptococcosis: particularly East and South Africa, Thailand and Cambodia
- *Pneumocystis carinii* pneumonia: South Africa, and Asia
- penicilliosis: Thailand

Despite these differences, some of the prevention measures recommended in the US are not too expensive and may provide opportunities to prevent OI in developing countries. These include: TMP/SMX for PCP, cerebral toxoplasmosis and various bacterial infections, and INH for tuberculosis.

General measures are also important, such as avoiding unpasteurised dairy products, raw or undercooked eggs, meat, poultry, or fish as sources of salmonella infection, and undercooked meat as a source of toxoplasmosis. If no safe water supply is available, patients and family should be advised to boil drinking water to avoid diarrhoeal diseases such as cryptosporidiosis. Mouldy sugar cane or bamboo has been suggested as a possible source of *Penicillium marneffe* infection in Thailand.

Extensive reviews about prevention of OI in HIV patients in the industrialised world have been published recently<sup>2,3</sup>, giving an exhaustive list of measures to prevent exposure to them.

## 1.1 Cotrimoxazole (TMP/SMX)

Cotrimoxazole has activity against various bacterial infections like *Streptococcus pneumoniae*, Salmonella species and Nocardia. In addition, it is highly effective against *Pneumocystis carinii* and toxoplasmosis. It is also effective against *Isospora belli* and Cyclospora.

According to UNAIDS<sup>4</sup>, cotrimoxazole should be used for prophylaxis in adults and children living with HIV/AIDS (PLWH/A) in Africa as part of a minimum package of care.

### 1.1.1 UNAIDS/WHO recommendations:

#### *Selection criteria*

Cotrimoxazole prophylaxis should be offered to HIV-positive adults (defined as over the age of 13 years) under the following criteria:

- all persons with symptomatic HIV (Stage 2, 3, 4)
- asymptomatic individuals who have a CD4 count of 500 or less or a total lymphocyte count equivalent
- pregnant women after the first trimester.

Prophylaxis should be offered to all HIV exposed infants from 6 weeks of age, under the following criteria:

- any child born to an HIV-infected women irrespective of whether the women received ARV therapy during pregnancy
- any child who is identified as being HIV-infected within the first year of life either by PCR, HIV serology or by a clinical diagnosis of HIV infection (according to WHO/national guidelines)
- children older than 15 months who have had a PCP event, have symptomatic HIV disease, an AIDS defining illness, or have CD4 percentage less than 15.

Where PCR or other special diagnostic tests are available, this can be used to confirm the diagnosis in children.

The use of CD4 count/total lymphocyte counts (TLC) are not recommended for deciding whether to initiate therapy in this period as they are not predictive of the risk of acquiring PCP in infants less than one year of age.

*The following drug regimens are recommended:*

#### *Adults:*

- 1 double strength (DS) tablet daily or 2 single strength (SS) tablets daily:  
1DS = SMX 800 mg + TMP 160 mg  
1SS = SMX 400 mg + TMP 80 mg.



*Children:*

- cotrimoxazole syrup should be administered once a day on a daily basis
- if syrup is unavailable, crushed tablets may be used
- the health professional may switch from syrup to tablet to ensure ongoing access to medication
- the recommended dose is TMP 10 mg/kg, SMX 50 mg/kg.

*Duration:*

- prophylaxis should be given life-long both for adults and children over the age of 15 months
- for infants up to 15 months prophylaxis should continue until HIV infection has been reasonably ruled out and the risk of exposure has ceased
- for children older than 15 months prophylaxis should be administered if they have had a PCP event, have symptomatic HIV disease, an AIDS defining illness, or have CD4 percentage less than 15.

*Criteria for stopping:*

In both adults and children prophylaxis should be stopped:

- in the occurrence of severe cutaneous reactions such as fixed drug reaction and Stevens Johnson syndrome, renal and/or hepatic failure, and severe haematological toxicity
- if antiretroviral agents become available and when CD4 is greater than 500, prophylaxis can be stopped.

*Recruitment:*

- candidates for cotrimoxazole prophylaxis should be recruited from all levels of health care facilities, AIDS service organisations and nongovernmental organisations
- initial prescription of prophylaxis should be prescribed by trained health care personnel
- counselling should be provided.

*Follow up:*

- cotrimoxazole prophylaxis should be used where regular follow-up of patients is possible
- in adults, follow-up should be initially every month and then every three months, if the medication is well tolerated
- children should be evaluated on a monthly basis
- in adults and children, monitoring for toxicity, clinical events and compliance to treatment should be undertaken
- monitoring of adults should also include measurement of haemoglobin and white blood counts every six months, where facilities are available or when clinically indicated.

### *Monitoring, evaluation and research*

Interventions to help people living with HIV in Africa are urgently required. Each country should develop an implementation and monitoring plan for cotrimoxazole prophylaxis. Concurrent monitoring for clinical effectiveness is important, especially in areas where widespread resistance to cotrimoxazole is present. In addition to cotrimoxazole prophylaxis, investigation into new interventions is necessary.

Programme evaluation and clinical effectiveness indicators will be developed by a task force led by UNAIDS. These could include surveillance for:

- background rates of opportunistic infections and antimicrobial resistance
- changes in antimicrobial resistance to cotrimoxazole (including impact on the treatment of malaria)
- acute and cumulative toxicities.

Research activities could cover:

- comparative studies to identify affordable alternative therapies
- further studies on dose and time of initiation
- willingness and ability to pay at the household level for cotrimoxazole prophylaxis
- impact on household income, savings and expenditures.

### Some comments

#### 1.1.1.1 Cost

TMP/SMX in the recommended dose of 1DS daily costs \$US 60/year.

#### 1.1.1.2 Efficacy studies in developing countries

Two randomised, double-blind placebo controlled trials regarding the effect of TMP/SMX on survival were conducted in the Ivory Coast. The first, by Sassan-Morokro et al<sup>5</sup>, assessed the benefit of TMP/SMX prophylaxis in HIV-infected patients with smear-positive TB. There was a 50% reduction in mortality and hospitalisation rate when compared to patients who received only anti-tuberculous treatment with a placebo instead of TMP/SMX. A second study by Angleret et al<sup>6</sup>, showed that TMP/SMX prophylaxis in patients with WHO stage 2 and 3 HIV-disease resulted in a 50% reduction in hospitalisation and severe events (mostly bacterial infections), but that it had no effect on survival. There seems thus to be a significant effect on hospitalisation rates and incidence of severe events, but this results in a survival benefit only for patients with active tuberculosis.

After the results of these two African studies were published, UNAIDS formulated firm recommendations for the use of cotrimoxazole primary prevention in HIV-infected patients, as formulated above.<sup>4</sup>

### 1.1.1.3 Target group

#### a) *Symptomatic HIV patients*

In the experience of the Ivory Coast's TMP/SMX prevention trials, the majority of HIV patients attending for medical reasons were in stage 2 and 3.<sup>6</sup> It was concluded that all HIV patients presenting for a medical reason should receive cotrimoxazole prophylaxis, and that all TB patients should be offered HIV testing and preventive treatment with cotrimoxazole, if HIV positive. There is no need for a CD4 count in this setting.

The UNAIDS recommendations state that all symptomatic patients and all patients who have a CD4<500 should receive TMP/SMX preventive therapy. In most situations, a CD4 count is not available. Many patients present with clinical symptoms and are automatically eligible for TMP/SMX prophylaxis.

In the hospitals and health centres supported by MSF, the situation is comparable to the Ivory Coast. The UNAIDS recommendations stating that all symptomatic HIV patients should receive TMP/SMX prophylaxis is therefore very practical.

It is worth emphasising that HIV-positive patients with active TB need to be offered TMP/SMX preventive therapy whatever their CD4 count, even when there are no other signs of opportunistic infections. The most frequent clinical indicator for starting prophylaxis is the presence of oral thrush (clinical stage 3).

#### b) *Asymptomatic HIV patients*

The criteria for starting TMP/SMX prophylaxis in asymptomatic patients have never been studied in developing countries. Some countries use the threshold of CD4 200 (Thailand) others 350 (Cambodia). In Cape Town, South Africa, the MSF programme uses two different doses depending on the CD4 count (CD4<200: TMP/SMX 1SS daily, CD4<100: TMP/SMX 1DS daily), according to the local guidelines. UNAIDS/WHO guidelines propose CD4 500.

**In the absence of formal studies we recommend using the WHO/UNAIDS guidelines in countries where there is no national policy.**

#### c) *Research issues*

Important questions include:

- Does the widespread use of TMP/SMX prophylaxis have an impact on the development of resistance in bacterial pathogens to TMP/SMX?
- Is there a difference in survival or in the occurrence of severe events if prophylaxis is started early or late (CD4<500 versus CD4<200) in asymptomatic patients in developing countries?
- What is the effect of TMP/SMX prophylaxis in an area with high TMP/SMX resistance?

#### 1.1.1.4 Adverse reactions

Adverse reactions are common, especially in Western countries, and tolerance is said to be better if 1 SS a day or 1 DS three times a week is used.<sup>2,3</sup> Every effort should be made to continue prophylaxis with cotrimoxazole because it is more active against PCP than alternative regimens, and it is also protective against toxoplasmosis, bacterial respiratory infections and some enteric pathogens. Lower doses of cotrimoxazole, although better tolerated, are less effective than the recommended daily DS tablet. Moreover, the efficacy of lower doses of TMP/SMX on other opportunistic infections, in particular toxoplasmosis, is not a given.<sup>7</sup>

#### 1.1.1.5 Alternative regimens

WHO recommends dapsone 50 mg 2 x daily or 100 mg once daily as the first alternative, if a patient does not tolerate TMP/SMX. In patients with CD4<100 and positive Toxoplasma antibodies, pyrimethamine 50 mg weekly + folinic acid 25 mg weekly should be added to this regimen. This regimen is much more expensive and complex than the cotrimoxazole preventive therapy.

Fortunately, the incidence of adverse reactions against cotrimoxazole seems to be lower in Africa and Asia than in Western countries.

Pentamidine aerosols 300 mg/ month are more difficult to implement, are less effective in preventing PCP, and its effect on toxoplasmosis is not entirely understood.

In cases of non-life-threatening adverse reactions, treatment should be stopped for two weeks, then the patient should be re-challenged with TMP/SMX in a gradually increasing dose.<sup>8</sup>

#### Example of a regimen of **gradual dose escalation**:

TMP/SMX suspension (40 mg TMP + 200 mg SMX/5 ml): 1 ml daily for 3 days, 2 ml daily for 3 days, then 5 ml daily for 3 days, then 10 ml daily for 3 days, then 20 ml daily for 3 days, then 1 DS tab daily or 1 SS tab daily (if DS is not supported).

After desensitisation under surveillance, up to 70% of patients may again tolerate TMP/SMX.<sup>3</sup>

Fansidar® (sulphadoxine/pyrimethamine), 1 or 2 tablets weekly, is likely to have a preventive activity against PCP and toxoplasmosis.

#### 1.1.1.6 Distribution

Cotrimoxazole can be given through community clinics and home-care projects. It could be integrated into counselling activities, favouring the regular follow-up of the PLWH/A by a counsellor at the same time as the cotrimoxazole prescription is renewed. The same could be applied to INH prophylaxis if it were not that it is difficult to rule out active TB, especially in symptomatic patients, even at the district hospital level.

## 1.2 Isoniazid (INH)

HIV infection is the strongest known risk factor for the progression of latent TB infection to active TB.

In countries with high TB prevalence, between 2.4% and 7.5% of HIV-infected adults may develop active TB each year. In those with a positive PPD test, the rate rises to between 3.4% and 10% per year with a lifetime risk of 50%.<sup>9,10</sup> The mechanisms of this include reactivation of latent infection and/or a re-infection with *Mycobacterium tuberculosis*, characterised by a rapid progression towards active disease and a rapid progression of primary infection.<sup>11</sup>

### 1.2.1 Background

Before the AIDS epidemic, preventive therapy for tuberculosis was never recommended in developing countries (poor cost-effectiveness, high rate of re-infection) except for breast-feeding infants of mothers with PTB, or children <5 years old living with infectious persons.

Preventive therapy as a public health strategy is now being reconsidered because of the high incidence of TB in HIV-positive patients in developing countries. Active TB might accelerate the clinical course of HIV infection.<sup>12,13</sup> In the pre-AIDS era, several placebo-controlled trials in the USA and Europe demonstrated the efficacy of INH prevention in PPD-positive persons, which is believed to be at least 60%.

A recent review of randomised placebo controlled trials (Haiti, Kenya, Uganda, US) demonstrated that INH prevention reduced the incidence of TB in HIV-positive PPD-positive patients (approximately 70% reduction in risk, RR = 0.32), and delayed the onset of HIV-related disease and death (mortality reduced by 25%).<sup>14</sup> It also reduces the incidence of tuberculosis in PPD-negative patients (RR 0.58; 95% CI 0.39 to 0.87), but in this group there is no effect on mortality. Secondary prophylaxis with INH (or extended treatment, beyond eight or nine months of therapy) reduces the incidence of relapse, but does not improve survival.<sup>15</sup> The cost of this drug is about \$US 60 per year.

### 1.2.2 WHO recommendations

In February 1998, at a joint meeting between the WHO global tuberculosis programme and UNAIDS, a policy statement was drawn up on preventive therapy against tuberculosis in people living with HIV.<sup>9</sup> What follows is a summary of its recommendations.

#### **Preventive therapy (PT) against tuberculosis in people living with HIV**

##### Policy statement

Several large randomised controlled trials have now demonstrated that PT is effective in preventing TB in individuals dually infected with HIV and *M. tuberculosis*. However, studies of the feasibility of PT demonstrate that the process required to target appropriate individuals, to exclude active tuberculosis, to deliver PT, and to achieve compliance is complex and inefficient.

The following prerequisites are identified which should be in place before a PT service is considered:

- adequate capacity for HIV counselling
- sufficiently trained health care staff
- linkage between HIV care and TB control services
- TB treatment services that have a high probability of curing cases of TB identified through the PT service (defaulter and failure rate <10%)

**In settings meeting these standards**, WHO and UNAIDS recommend to governments that:

1. *Preventive therapy against tuberculosis should be part of a package of care for people living with HIV/AIDS.*
2. *Preventive therapy should only be used in settings where it is possible to exclude active TB cases and to ensure appropriate monitoring and follow-up.*
3. *Information about tuberculosis, including preventive therapy, should be made available to people with HIV.*
4. *Preventive therapy should be provided from within settings that include established voluntary counselling and testing (VCT) services for HIV.*
5. *The priority for TB control programmes continues to be the detection and cure of infectious tuberculosis cases.*
6. *National authorities must regulate the procurement and supply of tuberculosis drugs in order to prevent the development of drug resistance.*

Those who have a positive HIV test should receive:

##### *(1) counselling on tuberculosis*

People living with HIV are at risk of developing TB. They should be given health education and encouraged to seek early diagnosis and treatment of cough and other symptoms suggestive of TB.

*(2) screening for active tuberculosis*

PT is inadequate treatment for active TB and could lead to the development of drug resistance if taken in such cases. Active TB should therefore be excluded before PT is started.

While it is recognised that most people with active TB will have symptoms, until the validity of different screening tools or algorithms is established, it is recommended that a chest radiograph is examined from every individual before considering PT. In one Ugandan study, 5% of asymptomatic HIV-positive patients had an abnormal chest X-ray and some of them had active TB.

*(3) targeting of those most likely to benefit from PT*

PT is recommended for PPD-positive HIV-infected individuals who do not have active tuberculosis. In some settings it may not be feasible to perform PPD testing. Under these circumstances the following individuals may still be considered for preventive therapy if they are infected with HIV:

- those living in populations with a high prevalence of tuberculous infection (estimated to be >30%);
- health care workers;
- household contacts of TB patients;
- prisoners;
- miners;
- other selected groups at high risk of acquisition or transmission of TB.

*(4) provision of preventive therapy to those without active tuberculosis:*

*Drug regimens.*

According to a recent review<sup>14</sup>, the strongest evidence is for the use of INH alone. Trials using combination treatment report higher rates of adverse drug reaction. Isoniazid is the regimen recommended in developing countries. Isoniazid may be given as a daily, self-administered therapy for 6 months at a dose of 5 mg/kg to a maximum of 300 mg. These individuals should be seen monthly and given a 1-month supply of medication at each visit. Compliance may be improved by giving an additional 2-week emergency buffer supply to be used if the individual has to defer his or her monthly review. Rifampicin-containing regimens are not recommended in order to eliminate the risk of promoting rifampicin resistance through inadequate screening procedures or by misuse of the tablets.

*Contra-indications for PT*

Preventive therapy is contraindicated in patients with active tuberculosis and in patients with active (chronic or acute) hepatitis. Active tuberculosis must be excluded before beginning preventive therapy. Isoniazid should be given with caution to individuals who consume alcohol daily.

*(5) monitoring for compliance and toxicity of PT*

*Follow-up.*

Patients should be monitored during the routine visits for compliance with treatment, drug toxicity, and signs or symptoms of active tuberculosis. Patients who interrupt therapy may be restarted with the aim of providing at least 6 months of isoniazid therapy during a one-year period. Pill counts and self-reporting may be useful in assessing compliance.

*Interruption of PT*

Clients with symptoms of tuberculosis or toxicity to medication should be evaluated immediately. Preventive therapy should not be continued if the patient develops signs or symptoms of tuberculosis. These suspected cases must be properly evaluated for active tuberculosis and referred to the national TB programme for registration and treatment.

*(6) evaluation of outcome of PT*

Programmes or centres that offer PT should assess the effectiveness of PT regularly. This assessment should include attendance at scheduled appointments, compliance (number of persons who started preventive therapy and number who completed), toxicity and withdrawals from therapy due to toxicity, number of suspected TB cases found by screening, and monitoring of therapy. Individual records should be maintained to document the use of PT.

***Feasibility of preventive therapy***

Although preventive therapy has been shown to be effective in clinical trials, the feasibility of providing it in a programme setting in developing countries is less clear.

Delivery of preventive therapy requires several steps:

- (1) identification of HIV-positive subjects
- (2) screening to exclude active tuberculosis (with a chest X-ray)
- (3) screening to target those most likely to be infected with *M. tuberculosis*
- (4) provision of drugs
- (5) compliance to therapy

In the short term, the delivery of PT will be limited by the number of sites where a sufficient number of people know their HIV status, or where there is sufficient demand for and capacity of VCT services. PT should therefore be promoted as an intervention for those living with HIV, rather than as a primary strategy to control the public health burden of tuberculosis.



### 1.2.3 Conclusion for MSF missions

Most of our target populations have a high prevalence of TB infection. Diagnostic possibilities are limited, making it difficult to exclude active TB in a symptomatic HIV patient. We recommend therefore that:

- Preferably, programmes should have started already with cotrimoxazole prevention in PLWH/A, show proof of good patient compliance and have strategies in place to follow-up defaulters.
- INH prophylaxis is recommended for all known HIV-infected persons, without performing a PPD skin test. Active TB has to be excluded before the start of the PT. In practice this means that only asymptomatic PLWH/A who are in WHO category 1 and 2 and who have a negative chest X-ray will be considered for PT. Patients that have a category 3 disease such as oral candidiasis or oral hairy leukoplakia with no other symptoms might be candidates for starting preventive therapy as well (no prolonged fever, no chronic diarrhoea, no recurrent severe bacterial infections).
- Dose of INH: 5 mg/kg, with a maximum of 300 mg daily, for a duration of 6 months. There has been considerable debate, also within MSF, about the duration of preventive therapy. Recent reviews of prophylaxis for opportunistic infections all recommend a 9-month regimen of INH to prevent tuberculosis.<sup>2,3</sup> Similar conclusions were drawn from a review of the literature on INH prevention in immunocompetent persons.<sup>16</sup> As long as no consensus is reached, we propose to adhere to the WHO guidelines.
- All projects that face difficulties in the control of tuberculosis (high defaulter rates, unregulated drug supply leading to incomplete TB treatment by private providers and national TB programmes, high treatment failure rate, etc.) **should not start INH preventive therapy on a routine base.**
- Projects that want to implement PT should have a close working relationship between HIV and TB services. The programmes should have qualified staff for counselling, a **high cure rate for TB and a low defaulter rate (less than 10%).**
- All projects, except pilot projects in HIV/AIDS care, should follow the national guidelines.

### 1.3 General considerations on INH and TMP/SMX prophylaxis in PLWH/A

Widespread implementation of INH and TMP/SMX preventive therapy for HIV-positive people represents a significant expenditure in resource-poor countries, and is an additional workload for an already overburdened health care system. On the other hand, it may diminish the stress for health-care workers because they have something to offer to an HIV-positive patient. For the HIV-infected individual in Africa and Asia, INH and TMP/SMX prophylaxis may represent the single most useful intervention for prolongation of healthy life. If those preventive therapies are feasible and effective in prolonging healthy life and in delaying the onset of full blown AIDS, this strategy would add a tangible benefit to the voluntary counselling and testing centres.<sup>17</sup>

### 1.4 Other preventive measures

#### a) 23-valent pneumococcal vaccine

HIV-infected people are at increased risk of invasive pneumococcal disease caused by *Streptococcus pneumoniae*. The frequency of recurrent *S.pneumoniae* infection in patients with prior pneumococcal disease is quite high (26% in a group of Kenyan sex workers). It might therefore be appropriate to give the pneumococcal vaccine to this group of people. The 23-valent-pneumococcal vaccine is immunogenic in HIV-infected people.<sup>18</sup> However, it remains to be determined whether these antibody responses translate into clinical efficacy. Indeed, a study in Uganda did not show any benefit. Pneumococcal disease was even more frequent in the vaccinated group than in the control group.<sup>19</sup> It is possible that the 23-valent vaccine may be inadequate for the prevailing pneumococcal serotypes in that region. Ongoing trials in the Gambia, Malawi and South Africa using newer-generation conjugate pneumococcal vaccines may show better results.

#### b) Antifungals

In some regions with an unusual high incidence of cryptococcal meningitis or *P. marneffeii*, primary prophylaxis with fluconazole or itraconazole might be considered. However, primary prophylaxis of fungal infections is expensive, and therefore not applicable in developing countries. As the prices of fluconazole continue to go down, it might be reconsidered for regions with a high incidence for cryptococcosis. In the Thai ARV project, all PLWH/A receive fluconazole prophylaxis 200 mg 3 x weekly when the CD4 count is below 50. Other preventive doses used are fluconazole 400 mg weekly, 100 mg daily or 200 mg daily. One randomised study in the USA compared the efficacy of weekly versus daily fluconazole for the primary prevention of deep mycoses and found no difference in efficacy.<sup>20</sup> No randomised trials have been carried out in high prevalence countries. However, even in the industrialised world, most clinicians are reluctant to use azoles for primary prophylaxis because of the potential promotion of azole-resistant candida species.<sup>2,21</sup>

### **c) Hepatitis B vaccination**

HIV-infected patients have a higher risk of hepatitis B because of common risk factors. Patients who are HIV-positive are more likely to develop chronic hepatitis. In the industrialised world, hepatitis B vaccination is recommended for certain risk groups, such as IV drug users, homosexuals, household contacts of hepatitis B carriers, health-care workers and sex workers.

In developing countries, although EPI programmes include vaccination against hepatitis B, it is not routinely recommended in adult HIV patients, because very few countries are able to purchase the vaccine.

## **2 SECONDARY PREVENTION**

Lifelong secondary prophylaxis has been advocated for most OI because of the high rate of recurrence.

### **2.1 Tuberculosis**

Until now, secondary prevention for TB has not been advocated. Extended therapy (beyond 6-9 months of treatment) has been shown to reduce the incidence of relapse, but showed no benefit in terms of survival.<sup>15</sup> However, a recent Haitian study<sup>22</sup> demonstrated that HIV-positive individuals had a ten-fold greater risk of recurrent TB than HIV-negative individuals after completion of a 6-month rifampicin-containing regimen. Half of the recurrences occurred after 18 months of post-treatment follow-up. All cases of recurrent TB happened in patients who had symptomatic HIV disease before the onset of TB (recurrence rate of 13.4 per 100 person-years). Post-treatment INH prophylaxis for one year reduced the incidence of recurrent TB in this group by 80%, but post-treatment INH prophylaxis did not prolong survival. However, a high recurrence rate of TB in HIV + individuals may have many consequences. Cure rates in recurrent TB are lower. Five-drug retreatment regimens are longer and more expensive. It is also more difficult to achieve compliance. Symptomatic HIV-positive individuals often have oral lesions that make it difficult to swallow the necessary number of tablets. The use of streptomycin injection is hazardous for the health-care worker, who risk needle stick injury, and also for the patient, who is often cachexic at this stage, and is unable to tolerate daily injections.

Although no firm recommendation can be made, the results of this study favour the use of secondary INH prophylaxis in patients who had symptomatic HIV disease before the initial diagnosis and treatment of TB.

### **2.2 PCP**

TMP/SMX: 1 DS daily is the recommended dose. Tolerance is improved with lower doses (see notes on *Primary prophylaxis* above).

## 2.3 Fungal infections

- *P. marneffe*: itraconazole 200 mg daily is effective in reducing the relapse of *P. marneffe* in HIV patients who were successfully treated with amphotericin B.<sup>23</sup>
- *Cryptococcus neoformans*: fluconazole 200 mg daily is the first choice<sup>24</sup>, or amphotericin B, IV, once a week, or fluconazole 200 mg 3 x weekly. Another possible regimen that should be explored is fluconazole 400 mg once a week. (Once weekly fluconazole 400 mg was shown to be as effective as daily fluconazole 200 mg in *primary* prevention of deep fungal infection (candidal oesophagitis, candidaemia, cryptococcosis, coccidioidomycosis, blastomycosis and histoplasmosis).<sup>20</sup> The weekly dose was only half as effective as the daily dose in preventing oral thrush.
- *Oral thrush/oesophageal candidiasis*: only if recurrences are severe and frequent: fluconazole 100-200 mg daily.

## 2.4 Toxoplasmosis

TMP/SMX 1DS daily.

## 2.5 Mucocutaneous Herpes simplex

If frequent and severe recurrences: acyclovir 200 mg 3 x daily or acyclovir 400 mg 2 x daily.

## 3 NECESSARY DRUGS AND EQUIPMENT

<i>DRUGS</i>	<i>EQUIPMENT</i>
<i>First choice:</i> Fluconazole Isoniazid Itraconazole TMP-SMX	Chest X-ray Complete blood count (liver function tests)
<i>Second line:</i> Dapsone Fansidar Folinic acid Pyrimethamine	

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**1 INTRODUCTION**

Pulmonary involvement is among the most common complaints in AIDS patients. A cough lasting over >1 month is seen in at least one-third of patients some time during the progression of the disease. Bacterial pneumonia and tuberculosis can occur early in the course of HIV infection at CD4>500. *Pneumocystis carinii* pneumonia (PCP) almost always occurs when the CD4<200. Toxoplasmosis, CMV and *Mycobacterium Avium* complex (MAC) usually occur at a CD4<100. In the advanced stages of the disease, more than one pathogen can often be found. A study carried out in Thailand on 95 patients with respiratory symptoms found the five most frequent agents to be: *Mycobacterium tuberculosis* (37%); PCP (24%), *Cryptococcus neoformans* (15%), *S.pneumoniae* (6%), *Nocardia asteroides* (6%) and *Strongyloides stercoralis* (3%). Two pathogens were found to co-exist in 10% of patients.<sup>1</sup>

**2 OPPORTUNISTIC INFECTIONS**

The differential diagnosis includes the following pathogens:

**Mycobacterial infection:** *M. tuberculosis*, *M. Avium* complex  
**Protozoal infection:** *Pneumocystis carinii*, *Toxoplasmosis gondii*  
**Bacterial infection:** *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella cattharalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*  
**Fungal infection:** *Penicillium marneffe*, *Cryptococcus neoformans*, Histoplasmosis, Coccidioidomycosis, *Aspergillosis*  
**Helminthic infection:** *Strongyloides stercoralis*, *Paragonimus westermanii*

**2.1 Tuberculosis**

TB is one of the most frequent respiratory problems in developing countries. In countries with high TB prevalence, between 2.4% and 7.5% of HIV-infected adults may develop active TB each year. In those with a positive PPD test, the rate rises to between 3.4% and 10% per year with a lifetime risk of 50%.<sup>2,3</sup>

The presentation of PTB depends on the degree of immunosuppression.<sup>3</sup>

Features of PTB	Stage of HIV infection	
	Early	Late
Clinical picture	Often resembles post-primary PTB	Often resembles primary PTB
Sputum smear result	Often positive	Often negative
Chest X-ray appearance	Often cavities	Often infiltrates with no cavities

TB can appear at a level of immunity that is still relatively good, and in that case will present as typical cavitory TB or upper lobe consolidation (post-primary pattern). At lower CD4 levels more atypical presentations are likely: extra-pulmonary TB, disseminated TB, diffuse pulmonary or miliary presentations with usually negative PPD skin tests. Diagnosis of these cases is more difficult.

In up to 35% of patients, signs of primary infection (recent infection) are evident: lower lobe infiltrate, pleural effusion, intra-thoracic adenopathy. Patients with suspected intrathoracic tuberculosis frequently have palpable extrathoracic lymph nodes (cervical and axillary).<sup>4</sup>

### 2.1.1 Diagnosis

**Sputum** examination is the best initial diagnostic test. AFB staining of **expectorated sputum** is positive in around 50% of patients with pulmonary TB. **Sputum induction** is only useful in patients who cannot cough up sputum.

It is important to take a good sample. Early morning samples are best because AFB concentrate in the respiratory secretions overnight. Standard: 3 early morning samples. To reduce delay, WHO recommends 3 sputum samples over 24 hours: 1 on the spot, 1 the next morning and the final one 2 hours later on the spot. This method seems to be almost as sensitive as the 3 morning samples. Some authors even suggest using only 2 smears, as more than 99% of smear positives are positive after 2 smears.<sup>5</sup> Such a strategy could improve overall diagnostic efficiency (fewer smears per patient) and accuracy (more patients with better quality smear examination because of the reduced workload overall).

A study carried out in Harare showed the value of **fine needle aspiration of extra-thoracic lymph nodes** to confirm the diagnosis of smear-negative pulmonary, pleural or pericardial TB. In a group of HIV-positive patients with AFB smear-negative sputum, who did not respond to penicillin and who had no signs of cutaneous or palatal Kaposi's sarcoma, ZN staining of fine needle aspirate (19G) of supraclavicular, cervical or axillary lymph nodes, gave the

diagnosis of TB in up to 87% of cases that were later confirmed to have pulmonary, pericardial or pleural TB!<sup>4</sup>

### 2.1.2 Treatment

HIV-positive patients respond well to treatment with anti-tuberculous drugs. The highest priority is the treatment of smear-positive pulmonary TB. Short-course therapy with an initial intensive phase of 4 drugs is usually advised: 2 months of INH, RIF, PZA and EMB, followed by a 4-month continuation phase of INH and RIF. If resources are scarce, this can be replaced by a 6-month continuation phase with EMB and INH.

The recommended TB treatment regimens according to WHO are presented below:<sup>3, 20</sup>

TB treatment category	TB patients	Alternative TB regimens	
		Initial phase	Continuation phase
1	New smear-positive PTB Seriously ill: Severe EPTB or smear-negative PTB	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE 4 HR 4 H <sub>3</sub> R <sub>3</sub>
2	Sputum smear-positive: Relapse Treatment failure Return after default	2 SHRZE / 1 HRZE 2 SHRZE / 1 HRZE	5 H <sub>3</sub> R <sub>3</sub> E <sub>3</sub> 5 HRE
3	Smear-negative PTB  EPTB (less severe)	2 HRZ or 2 H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub> 2 HRZ or 2 H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub> 2 HRZ or 2 H <sub>3</sub> R <sub>3</sub> Z <sub>3</sub>	6 HE 2 HR / 4 H 2 H <sub>3</sub> R <sub>3</sub> / 4H
4	Chronic case (still sputum-positive after supervised re-treatment)	Not applicable, refer to specialist centre if second-line drugs available	

Alternative treatment regimens for each patient treatment category

All projects should follow national protocols. However, it can be useful to meet the national authorities and discuss some specific practicalities with them, such as a change/drop in daily streptomycin injections, decreasing the danger of accidental exposure to blood and facilitating DOTS in a home-care setting.

It is very important to remember that *thiacetazone* should never be used for people who are known or suspected to be HIV-positive because of the severe hypersensitivity reactions observed (Stevens-Johnson syndrome).

## 2.2 Bacterial pneumonia

Bacterial pulmonary infections are common and severe in HIV disease. The most common causes are *Streptococcus pneumoniae* or *Haemophilus influenzae*. Other frequent bacterial pathogens include *S. aureus*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and *P.aeruginosa*. Pneumonia in HIV-positive patients is more frequently associated with bloodstream infections and they represent a not uncommon cause of early death in HIV patients in developing countries. An acute respiratory illness in a patient known to be HIV-positive, accompanied by high fever and chills, should therefore be treated as an emergency. The onset of symptoms is often abrupt, with high fever, a productive cough and pleuritic type chest pain.

Infiltrates that are localised to one lobe, especially when an air-bronchogram is present, are suggestive of bacterial pneumonia, most likely *S.pneumoniae*. More diffuse infiltrates are more likely to be due to *H.influenzae*.

Bilateral patchy consolidations in a critically ill patient suggest staphylococcal pneumonia. Upper lobe consolidation with cavitation has been observed in pulmonary nocardiosis, and can mimic tuberculosis. In nocardiosis there is often evidence of multiple abscesses (brain, lung, skin, etc.). A Gram stain will show Gram-positive thin branching (mycelium-like) filaments.

### 2.2.1 Diagnosis

The syndrome of fever, purulent sputum and localised infiltrate on the chest X-ray strongly suggests a bacterial pneumonia and additional diagnostic tests are often of little value. Gram stain of sputum and culture yields the diagnosis in 75% of cases. Nocardia stain weakly acid-fast on Ziehl-Neelsen. They are morphologically different however from tubercle bacilli because of their long branching fine mycelium-like threads. They stain good on Gram stain (see: *Laboratory* section at the end of the chapter). Patients with staphylococcal pneumonia often have other signs of staphylococcal infection: pyomyositis, abscess. A Gram stain of aspirated pus (Gram-positive cocci in clusters) can help in the diagnosis.

### 2.2.2 Treatment

For respiratory infections **penicillin** has a narrow spectrum and would only cover *S.pneumoniae* and the anaerobes of the oral cavity involved in aspiration pneumonia. In some countries, more than 30% of Streptococci are resistant to penicillin. In that case, do not use penicillin for empirical therapy in lobar pneumonia.

**Co-trimoxazole** has a broader spectrum, but in patients on TMP/SMX prophylaxis, the use of TMP/SMX to treat bacterial respiratory infections is not indicated. However TMP/SMX remains a useful antibiotic for patients not yet using PCP prophylaxis. Another choice is **Amoxycillin** that has a slightly broader spectrum than penicillin because it also covers +/- 50% of *H.influenzae* strains. **Second-generation cephalosporines** (cefuroxime, cefaclor) and **amoxy-clavulanic acid** (Augmentin®) have very good

respiratory coverage because they are active against *S.pneumoniae*, *Moraxella cattharalis* and *H.influenzae*.

The antibiotic of choice for staphylococcal infections is (flu)cloxacillin 1-2 g 4 x daily IV or 500 mg 4 x daily PO. In addition, chloramphenicol, doxycycline and TMP/SMX are moderately effective against staphylococci.

The recommended treatment for Nocardia is **TMP/SMX** 10/50 mg/kg 2 x daily. This usually corresponds with 2-3 DS tablets 2 x daily. The duration of the treatment varies from 6 weeks (for localised disease) to 6 months (for disseminated disease). An alternative treatment for nocardiosis is minocycline 100 mg 2 x daily combined with amikacin 15-25 mg/kg daily IV, once a day, or ceftriaxone 2 g daily combined with amikacin. The use of aminoglycosides should be limited to 14 days to avoid adverse effects.

Seriously ill patients with a respiratory infection should receive a combination that contains a quinolone or chloramphenicol (or ceftriaxone if available) to cover for Gram-negative infections. Treatment for severe life-threatening pneumonia could be: **ceftriaxone + amikacin** (Gram-negatives + Gram-positives, also staphylococcus), or **chloramphenicol + cloxacillin** (Gram-negatives + Gram-positives, including staphylococcus, atypical bacteria - chlamydia, mycoplasma).

### **2.3 Pneumonia due to *Pneumocystis carinii* (PCP)**

The incidence of PCP varies worldwide, ranging from 64% in the US to <5% in reports from some studies in Africa. (With the occurrence of HAART, the incidence has also dramatically decreased in the Western world.) The reason for this variability is uncertain. Most cases of PCP are believed to represent reactivation of a latent disease. Human-to-human transmission is possible, but only responsible for a minority of cases.

The most typical presenting symptoms of PCP in HIV-positive patients are fever, dry cough and dyspnoea, gradually getting worse. The onset of illness is generally sub-acute. Dyspnoea on exertion is always present. If oxygen saturation measurement is possible, it will always show a decrease in O<sub>2</sub> saturation during physical effort in patients with PCP.

A typical chest X-ray shows bilateral interstitial or alveolar infiltrates (ground glass appearance without air-bronchogram). Sometimes there are nodules or cavities, but the X-ray can be (at first presentation) misleadingly normal (25%). More than 80% of cases of pneumothorax in HIV-infected patients are due to PCP.<sup>7</sup> Therefore all patients with pneumothorax should be given empirical PCP treatment.

#### **2.3.1 Diagnosis**

Whenever practicable, attempts should be made to identify the organism. PCP has many atypical presentations and its treatment (especially adjuvant steroids) may be contra-indicated in patients who actually have TB or bacterial

pneumonia. PCP can be demonstrated in specially prepared induced sputum smears (sens. 60%) or in broncho-alveolar washings (BAL: sens. 90%). In patients who are not taking PCP prophylaxis, the sensitivity of induced sputum may be as high as 90%. The risk of respiratory failure after BAL makes it a difficult technique to use in settings where MSF is working. Measurement of serum lactate dehydrogenase (LDH) might be helpful. A normal LDH makes PCP unlikely. A strongly elevated LDH (>2 times the normal value) suggests that PCP is likely.<sup>8</sup> Rising LDH levels despite treatment heralds a poor prognosis.

### **2.3.2 Treatment**

#### **First choice:**

- **trimethoprim/sulphamethoxazole (TMP/SMX)** IV or PO: TMP 20 mg/kg daily and SMX 100 mg/kg daily divided over 4 doses for 21 days.

Any patient who is hypoxic ( $pO_2 < 70$  mmHg) should receive **prednisolone**.

The first few days of antimicrobial treatment are critical since the decomposition of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, the risk of death at this stage can be substantially reduced, especially in patients whose arterial oxygen tension is less than 70 mmHg, if a corticosteroid (oral prednisolone or intravenous methylprednisolone) is administered as soon as antimicrobial therapy is started.

Prednisolone given orally at a dose of

- 40 mg 2 x daily for 5 days
- followed by 40 mg daily for 5 days
- then 20 mg daily for 11 days.

(A total of 21 days together with TMP/SMX for 21 days.)

#### **Second choice:**

- clindamycin intravenously IV 600 mg 4 x daily and primaquine PO 15 mg daily, or
- dapsone 100 mg daily and trimethoprim 20 mg/kg once daily.

If the patient is unable to tolerate these regimens, pentamidine 4 mg/kg daily can be used intravenously.

Whatever regimen is used to treat PCP, always give prednisolone when the patient is hypoxic.

Signs of improvement may not be evident for 4-8 days, and treatment should be maintained for 3 weeks. For a mild to moderate disease, oral medication can be used throughout the treatment; for a severe disease, the first 7-10 days treatment is normally administered intravenously, if the injectable form of TMP/SMX is available. When no improvement is evident after 7-10 days, clinicians often resort to switching to one of the other regimens. The severe toxicity of pentamidine (renal failure, hypotension, hypoglycaemia) compared to the other regimens has limited its use and it is now used only as a last resort. If a switch to pentamidine is being considered, there should be an overlap of 2-3 days to allow pentamidine to accumulate in the body.

### 2.3.3 Prophylaxis

Every HIV-positive patient who has been successfully treated for pneumonia due to *Pneumocystis carinii* should receive continuous prophylaxis. Various estimates place the 3-month relapse rate among patients not receiving prophylaxis following a course of treatment for PCP at 10%-40%; about one in five of such episodes is fatal.

First choice:	TMP/SMX 1DS daily
Second choice:	dapsone dapsone and pyrimethamine*
Third choice:	pentamidine (nebulised) 300 mg once a month
Fourth choice:	sulfadoxine/pyrimethamine (Fansidar®) 1-2 tablets weekly.

(For a more complete discussion on this subject, see *Prevention of OI*, chapter 5: section 1.1)

### 2.4 Penicilliosis<sup>†</sup>

*Penicillium marneffe* is a common cause of opportunistic infection in HIV-infected patients in Southeast Asia and Southern China with late-stage disease (CD4<100). There are important regional variations in infection rates.<sup>9</sup> In Northern Thailand, it is the third most common opportunistic infection (after extra-pulmonary TB and cryptococcal meningitis). Up to a quarter of AIDS patients are affected, whereas in Southern Thailand the prevalence is ten times less. The exact route of infection in humans is not known. The organism proliferates in macrophages and is disseminated throughout the body, especially to the reticulo-endothelial system.

The most common clinical presentations are an abrupt onset of fever, anaemia, skin lesions and weight loss. Respiratory complaints (cough, shortness of breath) are also common. In these patients, the chest radiograph shows diffuse nodular pulmonary infiltrates or cavitory disease. Less commonly, local or generalised lymphadenopathy, hepatomegaly or splenomegaly also occur. Skin involvement occurs in patients with disseminated disease. The typical appearance is one of multiple papular lesions, often with central umbilication or ulceration, resembling molluscum contagiosum. The lesions are typically on the face, scalp and upper trunk. The differential diagnosis with TB and disseminated cryptococcal disease must be made. If there are no skin lesions, the diagnosis is difficult. The characteristic syndrome would be hepatic disease with fever, hepatomegaly and isolated high alkaline phosphatases.

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\* Pyrimethamine should be added in patients with a CD4 count lower than 100/mm<sup>3</sup> and *Toxoplasma gondii* antibody positive, if they do not tolerate TMP/SMX.

† Also called 'Penicillinosis'

### 2.4.1 Diagnosis

The organism may be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain, or Cotton-blue stain. Bone marrow aspirate is diagnostic in 100% of cases. The diagnosis is confirmed by culturing the fungus from clinical specimens.

### 2.4.2 Treatment

Initial treatment should be with amphotericin B 0,6 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg 2 x daily for 10 weeks.

Mortality from disseminated *P.marneffe*i infection in patients with AIDS is about 20%, despite effective anti-fungal therapy.<sup>10</sup>

Long-term suppressive therapy with itraconazole should be given to prevent relapse. Itraconazole in a dose of 200 mg daily is effective although one study in Northern Thailand showed no difference in survival between the treatment and the placebo group. Although ketoconazole is active *in vitro*, the clinical experience of the research team in Chiang Mai is that it is less active in treating the disease and preventing relapses. However, because ketoconazole is much less expensive, it is worthwhile to compare itraconazole and ketoconazole in regard to their ability to prevent relapses of *P.marneffe*i.<sup>10</sup>

## 2.5 Cryptococcosis

Pneumonia is sometimes an early manifestation of cryptococcosis. In PLWH/A, dissemination to extra-pulmonary sites occurs frequently. Cryptococcosis has a tendency to spread to the CNS. However, most patients with cryptococcal meningitis do not have a clinically evident pneumonia. Diagnosis is confirmed by sputum culture.

Treatment of disseminated cryptococcosis is with amphotericin B and fluconazole (for details, see *Neurological Disorders*, chapter 7).

## 2.6 Histoplasmosis, coccidioidomycosis, aspergillosis

These infections are very rare in HIV-infected persons in developing countries. They occur only with profound immune suppression and with severe neutropenia. See also *Lymphadenopathy*, chapter 9: section 2.4

*Histoplasmosis* is treated with amphotericin B 0,5-1 mg/kg daily IV for 2 weeks, followed by itraconazole 300 mg 2 x daily for 3 days and a maintenance therapy with itraconazole 200 mg twice daily.<sup>6</sup>

*Coccidioidomycosis* responds to amphotericin B 0,5 mg/kg daily IV for 8 weeks, followed by a maintenance therapy with fluconazole 200 mg once daily.<sup>6</sup>

*Aspergillosis* is treated with amphotericin B 1-1.4 mg/kg daily IV for 2 weeks, followed by a maintenance therapy with itraconazole 200 mg twice daily.<sup>6</sup>



## 2.7 Helminthic diseases causing respiratory symptoms

*Strongyloides stercoralis* and *Paragonimus westermani*<sup>‡</sup> (lung fluke) can cause acute and chronic respiratory symptoms. X-ray appearance can suggest TB or atypical pneumonia. A fresh sputum examination easily identifies the filariform larvae in pulmonary strongyloidiasis and the eggs of *Paragonimus* (see: *Laboratory* section at the end of this chapter). Paragonimiasis should be excluded in patients with suspected PTB on chest X-ray, who are smear-negative. It is very easy to miss the eggs of *Paragonimus* if the sputum is only examined for *Mycobacterium tuberculosis*. An eosinophilic pleural effusion in endemic regions is suggestive of paragonimiasis. Haemoptoe is also seen with paragonimiasis. The treatment consists of praziquantel 75 mg/kg/day divided into 3 doses for 2 days.

Strongyloides infection should be suspected in patients who have serpiginous erythematous skin lesions (larva recurrens), diarrhoea, abdominal pain and cough. The chest radiograph reveals diffuse pulmonary infiltrates. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full blown hyper-infection syndrome is less common.<sup>11,12</sup> In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, bronchoalveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid. Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days, and is considered by some as the drug of choice for the treatment of systemic strongyloidiasis.<sup>13</sup> An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A monthly maintenance therapy is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once a month). (See *Chronic Diarrhoea*, chapter 8) .

## 2.8 Toxoplasma pneumonitis

Sometimes it is difficult to distinguish from PCP pneumonia. Toxoplasma pneumonitis should be considered in patients who present with fever, cough, and dyspnoea and where the induced sputum fails to demonstrate PCP.

### 2.8.1 Diagnosis

Chest X-ray may show diffuse interstitial pattern or reticulonodular infiltrates. The diagnosis of pulmonary toxoplasmosis can be confirmed by Giemsa staining of BAL.

### 2.8.2 Treatment

A combination of sulfadiazine and pyrimethamine is the regimen of choice. However, studies with high dose TMP/SMX for the treatment of Toxoplasma encephalitis<sup>14,15</sup> have shown similar efficacy. TMP/SMX is a more readily available drug in developing countries.

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<sup>‡</sup> The *Paragonimus* species is mainly found in Southeast Asia (China, Philippines, Laos and Thailand). Case reports exist from Korea, Japan, Congo, West Africa and Latin American countries bordering the Pacific Ocean.

## **2.9 *Mycobacterium Avium* complex (MAC)**

MAC rarely gives pulmonary symptoms.

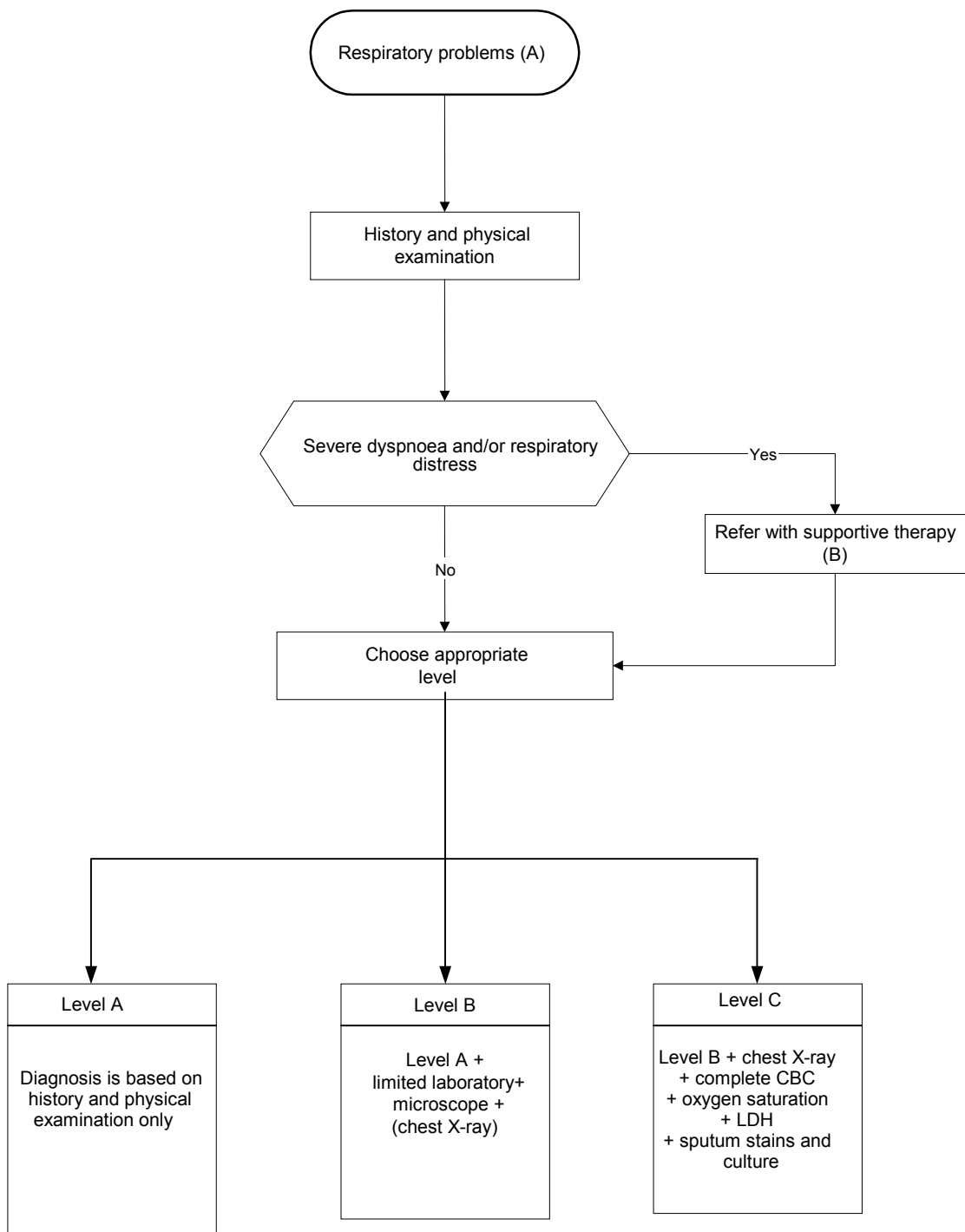
## **3 CLINICAL MANAGEMENT OF RESPIRATORY PROBLEMS**

Diagnosis of pulmonary disease in HIV-positive patients often requires a multi-step approach, starting with a thorough history and physical examination and leading up to chest radiograph and sputum examination. To use resources rationally, it is important to identify those patients who will benefit from additional tests. E.g. in a smear-positive pulmonary TB patient, the diagnosis of PTB is confirmed by the positive smear and treatment effect can be evaluated by examining the smears at certain intervals. A chest X-ray provides no additional benefit.

It is not rare to find more than one pathogen involved. Therefore, in a patient who does not respond to therapy as expected, do not hesitate to review the history and the physical examination, to repeat the algorithm and to add a second or even a third treatment if necessary.

## Respiratory problems

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## **Annotations respiratory problems**

(A) Definition: persistence or worsening of cough and/or chest pain and/or dyspnoea in a patient with symptomatic HIV infection.

### **Possible aetiologies**

#### 1) Infections

- pyogenic bacteria: *Streptococcus pneumoniae*, *Haemophilus influenzae*
- tuberculosis
- PCP
- fungal infections: cryptococcosis, penicilliosis, aspergillosis, histoplasmosis, etc.
- (atypical mycobacteria)
- (CMV, toxoplasmosis)

#### 2) Malignancies

- Kaposi's sarcoma
- lymphoma

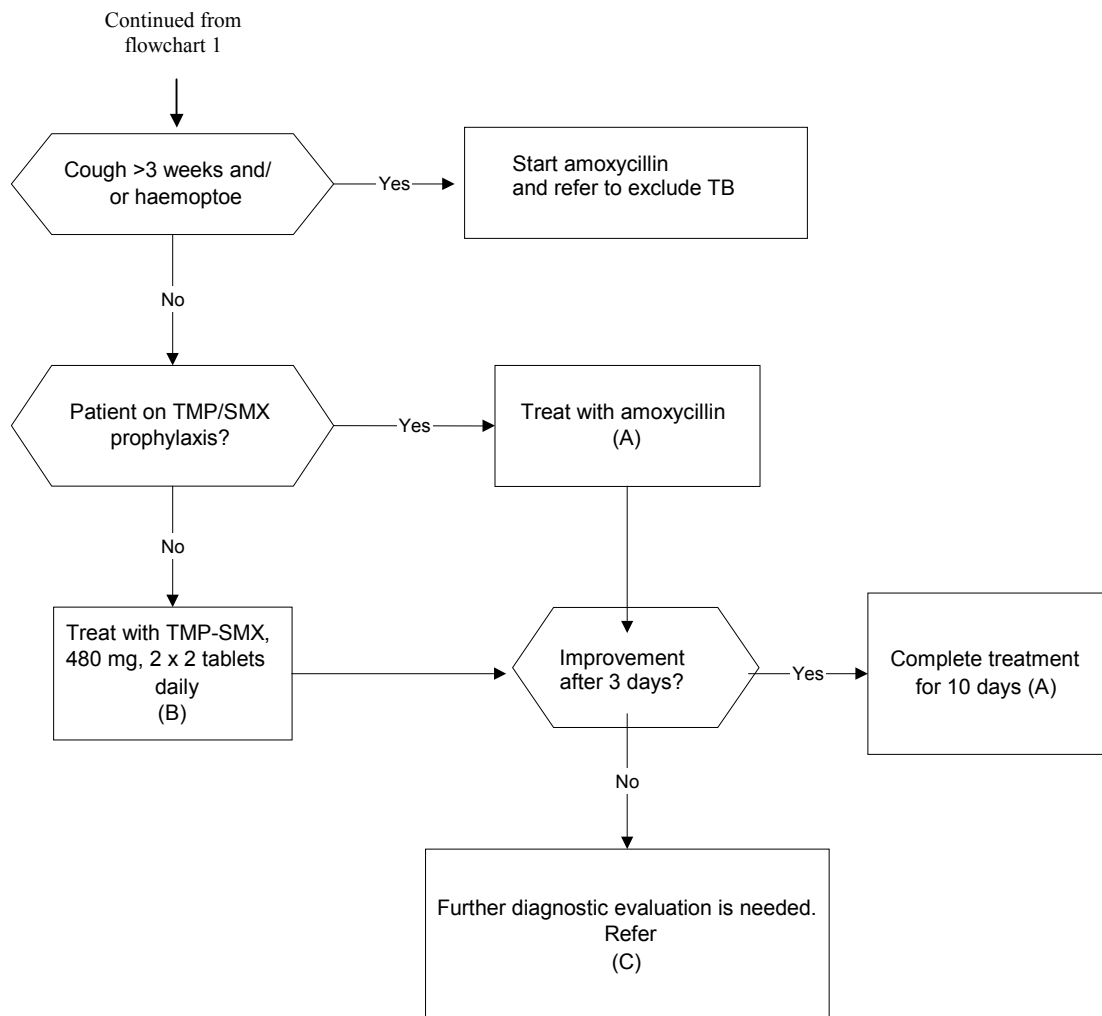
3) Others: lymphoid interstitial pneumonitis.

#### 4) Associated problems

- pleural effusion/empyema (often TB)
- pericardial effusion (often TB)
- pneumothorax (associated with TB, PCP, pneumonia or cancer)

5) Heart failure, pulmonary embolism, asthma, severe anaemia.

(B) If hypoxaemia is present, diagnosed on clinical grounds (dyspnoea, cyanosis), oxygen therapy is indicated. A patient with a respiratory rate of more than 30/minute while resting will need hospitalisation and oxygen and must be referred to the appropriate level.



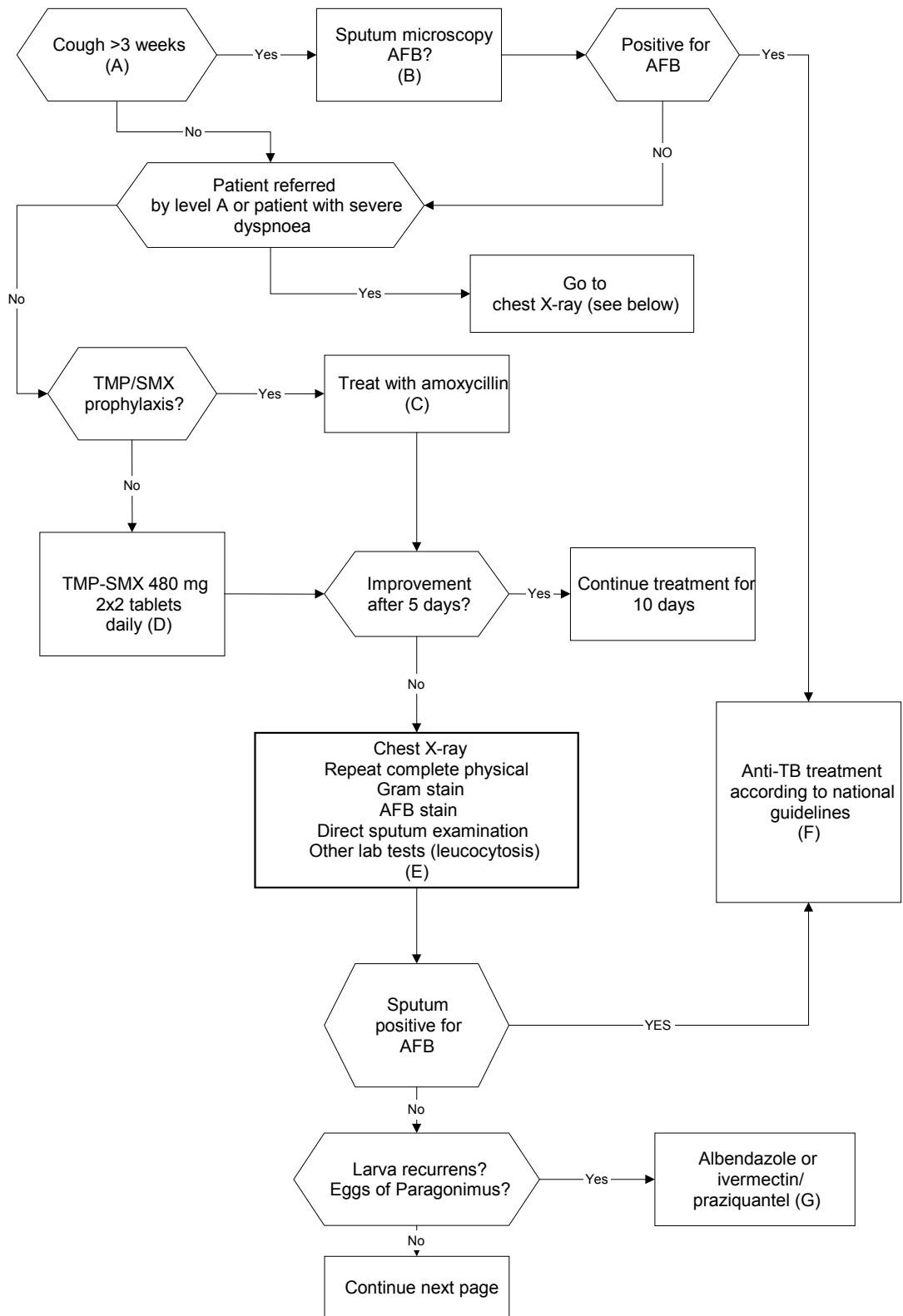
### **Annotations respiratory problems (level A)**

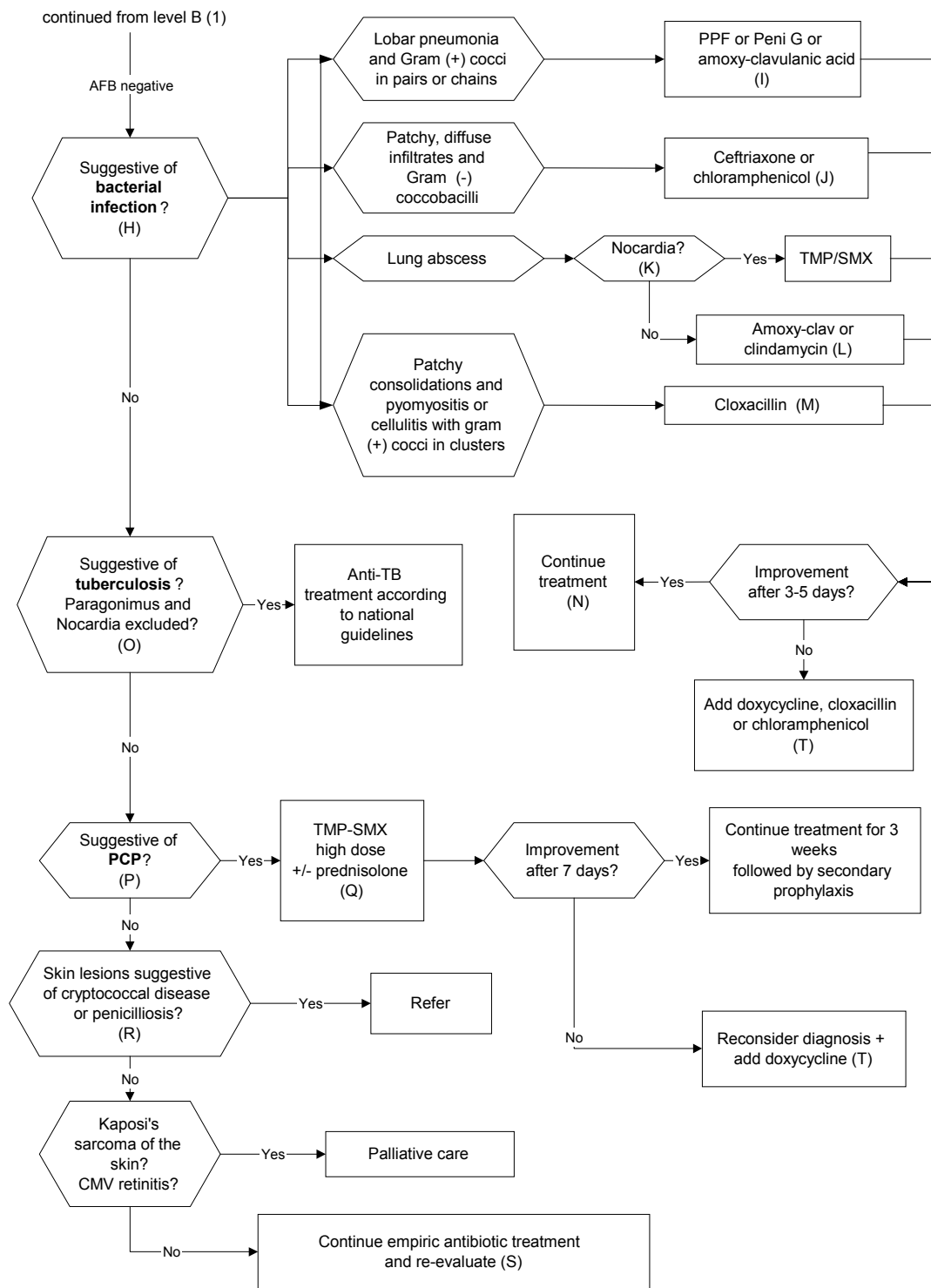
If drugs are available at the home-care level, this algorithm can be followed. If not, the patient must go to the dispensary.

- (A) In most developing countries, bacterial pathogens are the most probable cause of infection. A trial with antibiotics to treat pneumococcal pneumonia is justified. In patients who were taking TMP/SMX prophylaxis, it is better to use amoxycillin 500 mg-1 g 3 x daily for 10 days.
- (B) In patients who are not taking TMP/SMX prophylaxis, the first choice is treatment with TMP/SMX as it covers the most frequent respiratory pathogens: *S. pneumoniae*, *H. influenzae*, *Moraxella cattharalis* and *Klebsiella pneumoniae*. The dose used is TMP/SMX 480 mg 2 x 2 tablets daily for 10 days.
- (C) Exclusion of tuberculosis is now a priority.

# Respiratory problems

**Level B  
(1)**





### Annotations respiratory problems (level B)

- (A) To increase the efficiency of the lab and of patient care, it is important to screen those patients who could benefit the most from a sputum examination for TB. The cut-off for chronic cough is generally put at >3 weeks.
- (B) In countries with a high prevalence for TB, sputum examination for AFB is essential. The highest yield of AFB in smear and culture is with expectorated early-morning sputum. Induced sputum should be used only in people who cannot expectorate. The sensitivity of sputum examination is decreased in HIV-positives and is around 50%.
- (C) In many countries, pyogenic bacteria will be the most probable cause of bacterial pneumonia. If the patient is already using TMP/SMX prophylaxis, the first choice is amoxicillin. If available, amoxy-clavulanic acid or cefuroxime has a broader spectrum and could be the first choice at level B.
- (D) In patients who are not yet on TMP/SMX prophylaxis, TMP/SMX is preferred over amoxicillin because of its broader spectrum. If available, amoxy-clavulanic acid or cefuroxime is the best choice for empirical therapy in respiratory infections.
- (E) If there is no improvement after a 5-day course of antibiotics, the patient should receive more advanced examinations. Repeat the **history and physical examination** thoroughly. Look for additional signs that may help in the differential diagnosis. Skin lesions are present in Kaposi's sarcoma or disseminated cryptococcosis or penicilliosis. Pyomyositis and cellulitis point toward staphylococcal infection. High fever, pleuritic-type chest pain and productive cough are suggestive of bacterial pneumonia. Lymph nodes are usually seen in TB and lymphoma. A chest X-ray and a sputum AFB and Gram stain should be carried out. Direct sputum examination may reveal *Strongyloides stercoralis* larvae or eggs of *Paragonimus* species. Other lab tests could also be included here: WBC count, Gram stain of pus from other sites.



A PTB suspect with 3 negative sputum smears may not have PTB at all.  
Reassess the patient:

Differential diagnosis	Pointers to correct diagnosis
Congestive heart failure	Symptoms of heart failure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, haemoptysis, oedema, epigastric discomfort from hepatic congestion)
Asthma	Intermittent symptoms, generalised expiratory wheezing
Chronic obstructive airway disease	Risk factor (smoking), chronic symptoms, prominent dyspnoea, generalised wheezing
Bronchiectasis	Large amounts of purulent sputum
Bronchial carcinoma	Risk factor (smoking)
Other infections	
Bacterial pneumonia	Response to antibiotic
Lung abscess	Abscess with fluid level on chest X ray
PCP	Dyspnoea prominent
Nocardia	Cavitary infiltrates, Gram-positive branching bacteria
Cryptococcosis, penicilliosis	Skin lesions
Strongyloidiasis	Larva recurrens, diarrhoea
Paragonimiasis	Endemic region, fresh water shrimps
Kaposi's sarcoma	Skin/oral Kaposi's sarcoma lesions
Lymphoma (exceptional)	

A chest X-ray may look normal in PCP, cryptococcus and tuberculosis infections.

- (F) The highest priority is to treat smear-positive pulmonary TB. Follow national treatment guidelines. Short-course therapy with an initially intensive phase of 4 drugs is usually advised: 2 months of INH, RIF, PZA and EMB, followed by a 4-month continuation phase of INH and RIF. If resources are scarce, this can be replaced by a 6-month continuation phase with EMB and INH. Thiacetazone should never be used for patients who are known or suspected to be HIV-positive because of severe hypersensitivity reactions seen (Stevens-Johnson syndrome).
- (G) *Paragonimus*: Praziquantel 75 mg/kg/day in 3 divided doses for 2 days.  
*Strongyloides*: Albendazole 400 mg 2 x daily for 5 days, or ivermectin 12 mg daily for 3 days. Suppressive therapy to prevent recurrence of symptomatic infection: ivermectin 6 mg once monthly, or Albendazole 400 mg once monthly.

(H) An acutely ill patient, with high fever, high leucocytosis and respiratory symptoms is suggestive of a bacterial cause. Chest X-ray and Gram stain may help to differentiate between different causal agents.

(I) A lobar pneumonia and a sputum Gram stain with Gram-positive cocci in pairs is very likely a streptococcal pneumonia. If there is no problem of penicillin-resistant streptococcus in your setting, this antibiotic is the first-choice treatment for lobar pneumonia. You can choose between fortified penicillin procaine, 2,4 MIU a day IM, or Penicillin G, 2 MIU 4 x daily IV. For penicillin-sensitive strains, oral amoxicillin or amoxy-clavulanic acid 625 mg 3 x daily is a good choice. For patients with a penicillin allergy, erythromycin 500 mg 3 x daily is the preferred treatment. Treatment needs to be given for 10-14 days.

In some countries, penicillin-resistant *S.pneumoniae* is a frequent problem. In that case, the treatment should be ceftriaxone 2g once a day, IV in critically ill patients. In stable patients, a fluoroquinolone such as ofloxacin 400 mg 2 x daily or ciprofloxacin 500 mg 2 x daily can be used for 2 weeks.

(J) More diffuse infiltrates and Gram-negative coccobacilli on sputum Gram stain are suggestive of *H.influenzae*. Treatment of choice is ceftriaxone or chloramphenicol. Amoxy-clavulanic acid is a good alternative, if available.

(K) If the X-ray shows an air-fluid level, this indicates a lung abscess. Always carry out a Gram stain on sputum in lung abscess to exclude Nocardiosis. Nocardia can present with multiple abscesses (lung, subcutaneous, etc.). The recommended treatment is TMP/SMX 10/50 mg/kg 2 x daily (for 6 weeks to 6 months) or minocycline 100 mg 2 x daily for several months, combined with amikacin 15-25 mg/kg for 2 weeks or ceftriaxone 2 g daily (for several months) combined with amikacin for 2 weeks. The surgical drainage of abscesses is sometimes necessary.

(L) Lung abscess not due to Nocardia: treatment of choice is amoxy-clavulanic acid 625 mg 3 x daily or clindamycin 600 mg 3 x daily.

(M) The antibiotic of choice for staphylococcal infections is (flu)cloxacillin 1-2 g 4 x daily IV or 500 mg 4 x daily PO. In addition, chloramphenicol, doxycycline and TMP/SMX are moderately effective against staphylococci.

(N) Duration of treatment depends on the condition treated; for nocardiosis treatment may be necessary from 6 weeks up to 6 months. A lung abscess generally needs 3-4 weeks of antibiotics. Other bacterial pneumoniae need 10-14 days of treatment.

(O) A more chronic course, with wasting, night sweats, chest pain and productive cough, high ESR, nodular or cavitary infiltrates, lobar infiltrates that do not disappear with broad spectrum antibiotics, hilar or paratracheal lymph nodes and pleural effusion, are suggestive of pulmonary TB. At this point, the decision must be taken whether or not to start a smear-negative suspected TB patient on TB treatment. Follow the national

recommendations regarding smear-negative pulmonary TB. By treating all smear-negative suspected tuberculosis patients who failed to respond to broad spectrum antibiotics (ampicillin), Wilkinson et al found<sup>5</sup> that the diagnostic sensitivity increased to 80%, but the specificity fell to 78%. In endemic regions, such as Southeast Asia, Paragonimus (related to eating fresh water shrimps and crabs) might first be excluded before starting TB meds. Nocardia can also present with upper lobe infiltrates, and needs to be excluded (by Gram stain) in smear-negative suspected pulmonary TB.

- (P) PCP can be definitively diagnosed if cysts are found in induced sputum, BAL or biopsy specimens. Often these investigations are not available. The diagnosis therefore depends on the clinical and chest X-ray findings, exclusion of TB and response to high-dose co-trimoxazole.

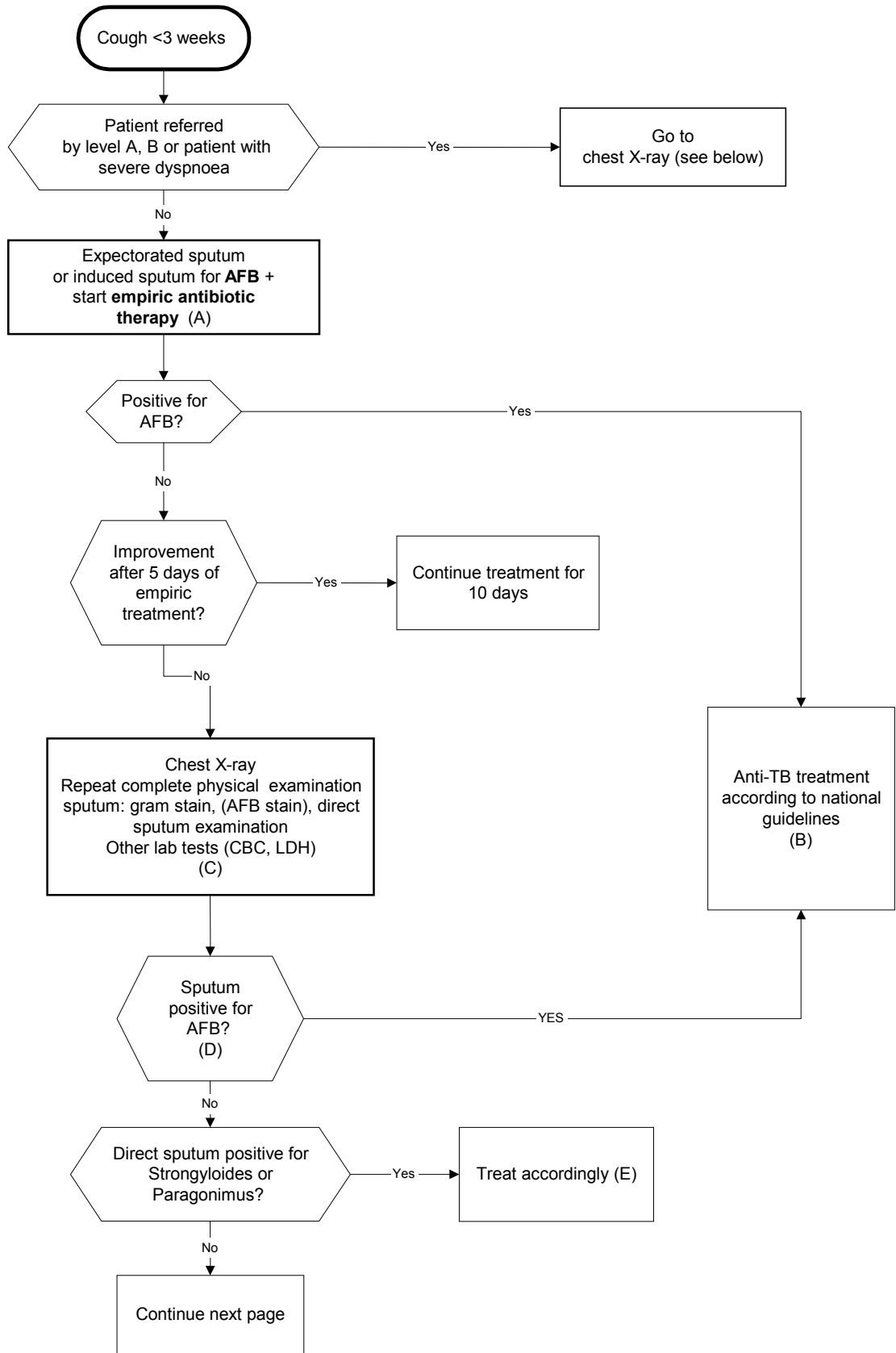
	Typical of PCP	Typical of TB
Symptoms	Dry cough Sputum mucoid, if any Dyspnoea	Productive cough Purulent sputum Pleuritic chest pain
Signs	Normal Fine inspiratory crackles	Signs of consolidation Signs of pleural effusion
Chest X-ray	Bilateral diffuse interstitial shadowing Normal	Lobar consolidation Cavitation Pleural effusion Intrathoracic lymphadenopathy

PCP is suggested by a more severe dyspnoea, hypoxaemia and dry cough. Chest X-ray is abnormal in 90% of cases showing bilateral interstitial infiltrates. PCP is thought to be rare in Africa and Southeast Asia. However, this may be partly due to under-diagnosis. Important regional differences may exist. One study in Zimbabwe<sup>16</sup> found PCP in one-third of patients with acute diffuse pneumonia unresponsive to standard antibiotic therapy. It is therefore important to establish a list of the main causes of OI in your region, based on findings in university hospitals and research centres disposing of more diagnostic facilities than are available to you.

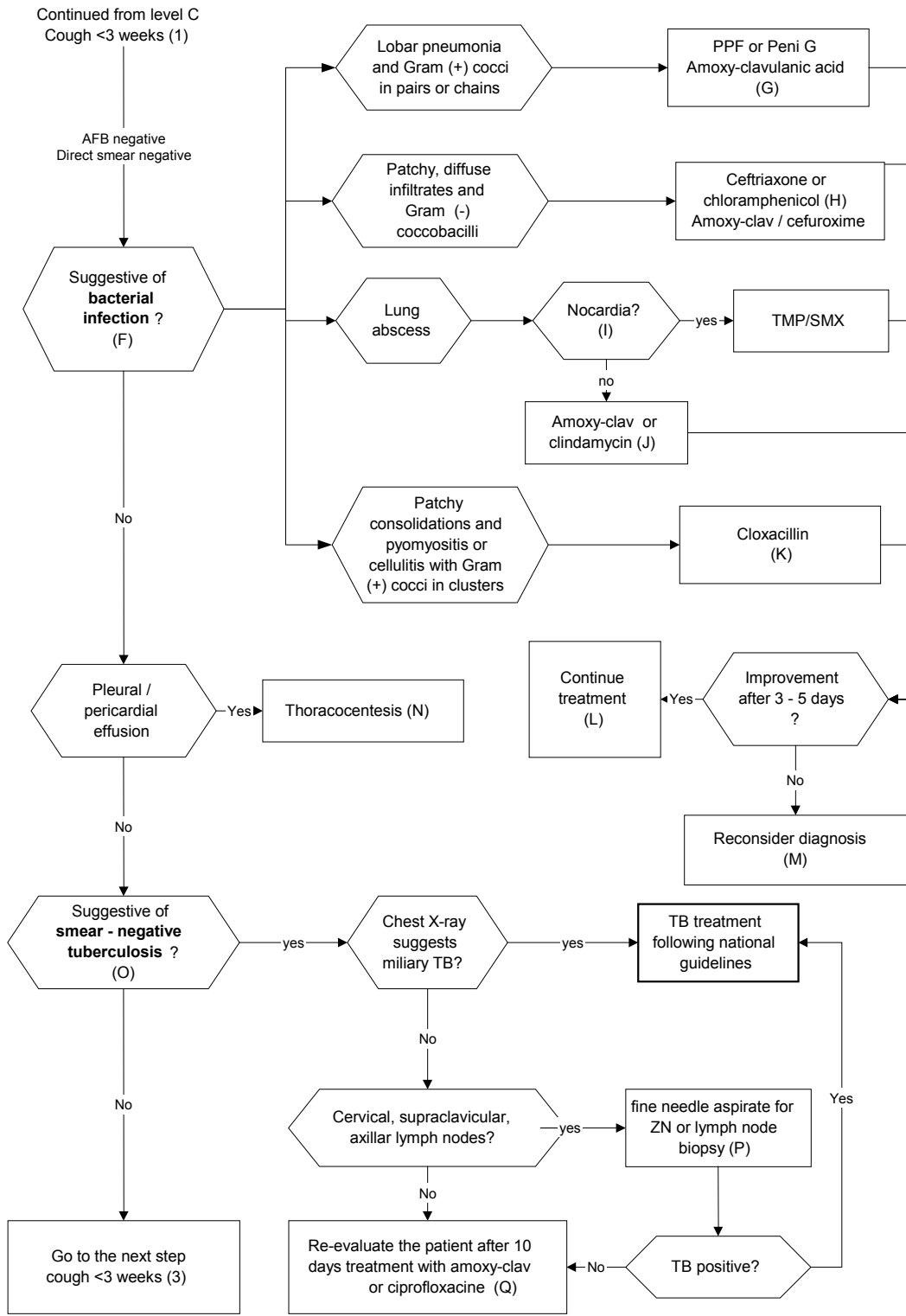
- (Q) **TMP-SMX**: TMP 20 mg/kg daily plus SMX 100 mg/kg daily in 4 divided doses. Assessment of benefit will require at least 7 days as PCP may initially worsen. If the patient responds, continue for at least 21 days in the absence of side effects. The risk of recurrence is high and can be reduced by prophylaxis: TMP-SMX 480 mg 2 tablets daily. Sometimes 480 mg daily or 960 mg 3 x weekly is better tolerated. An alternative is dapsone 100 mg once daily. For the severely ill patient with ongoing dyspnoea despite therapy, or with hypoxaemia since arrival, **prednisolone** is associated in a dose of 40 mg 2 x daily for 5 days, 40 mg once daily for 5 days, then 20 mg daily to completion of treatment.
- (R) Disseminated cryptococcosis and penicilliosis require treatment with amphotericin B. Refer your patient to level C.

- (S) In patients with aspecific respiratory clinical signs, antibiotics other than amoxicillin or TMP-SMX can still be tried (doxycycline, flucloxacillin, chloramphenicol). Another option is to prolong TMP-SMX or amoxicillin for 10 days before deciding to change treatment.
- (T) After 3-5 days treatment for a **presumed bacterial pneumonia** without improvement, add doxycycline for atypical bacteria (mycoplasma and chlamydia). If the patient was already treated with chloramphenicol (covers atypical bacteria) consider the use of cloxacillin to cover for *Staphylococcus aureus*. Conversely, if the patient was already treated with cloxacillin add chloramphenicol. When other symptoms occur repeat the algorithm. If no improvement after 7 days of treatment for **presumed PCP**, add doxycycline to cover for atypical bacteria (high dose TMP/SMX has already a broad respiratory coverage, except for atypical bacteria).

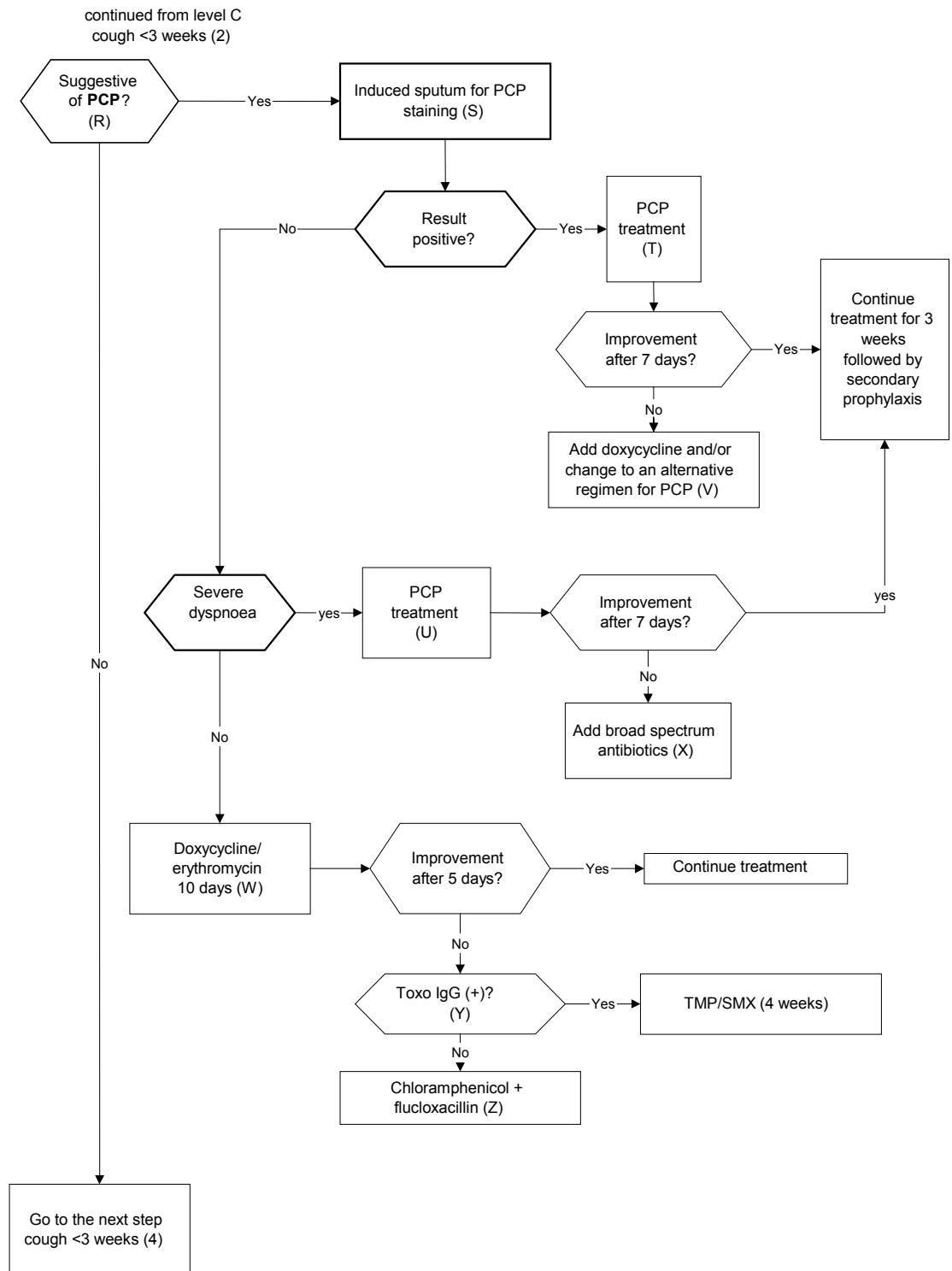
**COUGH <3 weeks (1)**



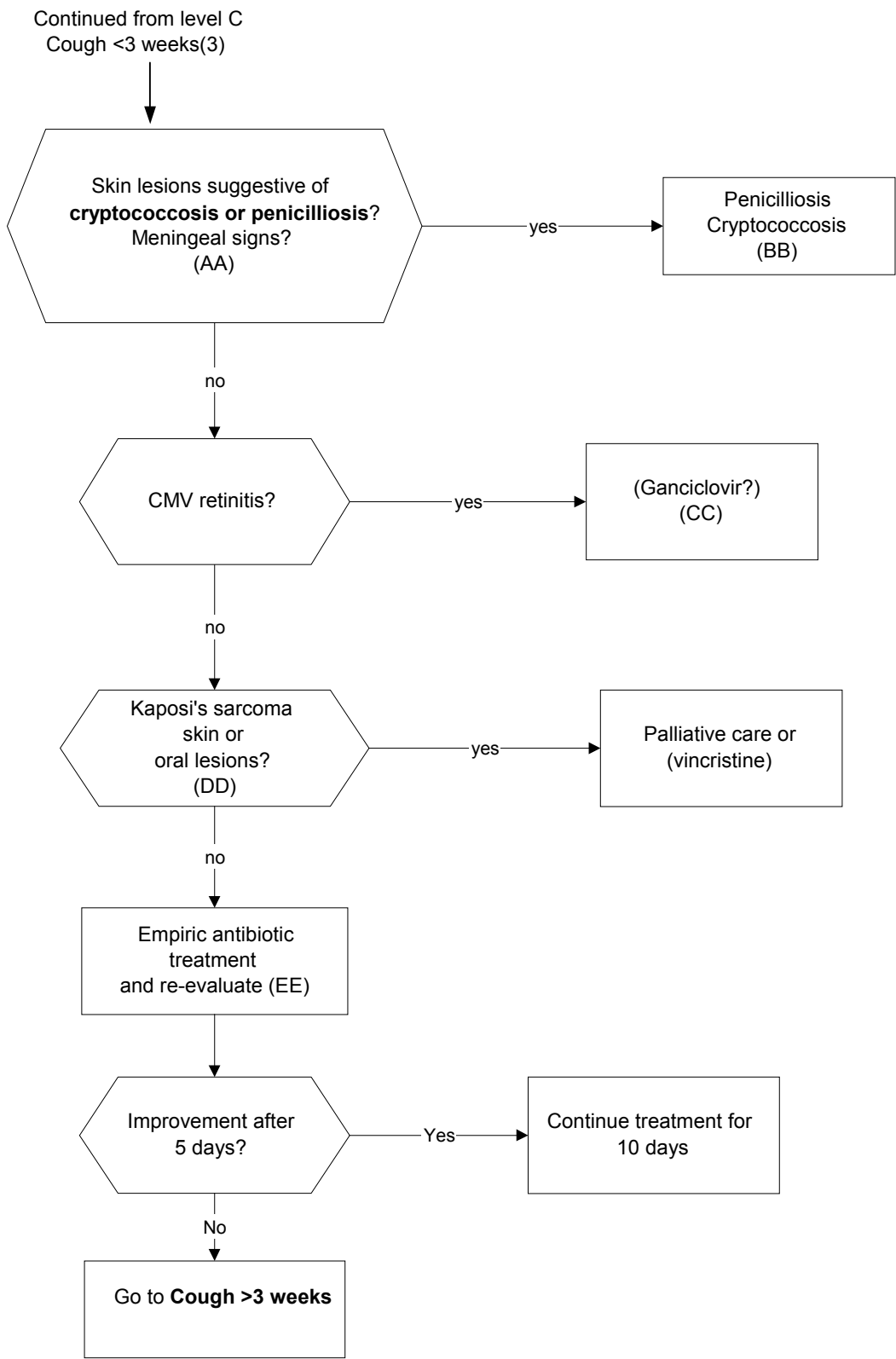
**COUGH <3 weeks (2)**



COUGH <3 weeks (3)



**COUGH <3 weeks (4)**





## **Annotations respiratory problems (level C)**

At level C, several examinations will generally take place at the same time, and not sequentially as proposed in level B. Two different algorithms are described, the starting point determined by the duration of symptoms.

### **Cough <3 weeks**

(A) The most likely diagnosis is a bacterial infection, pneumococcal disease. However PTB can have an acute and rapid course in HIV patients. It is therefore important to exclude TB in patients with productive cough. The highest yield of **AFB in smear** and culture is with **expectorated sputum**. Induced sputum should be used only in people who cannot expectorate. Sputum sensitivity is decreased in HIV-positives and is around 50%. It is important to take a good sample, early morning samples being the best because AFB concentrate in the respiratory secretions overnight.

Standard: 3 early morning samples; however, to reduce delay, WHO recommends 3 sputum samples over 24 hours: the first on the spot, the second the next morning and the third one on the spot 2 hours later. This method seems to be almost as sensitive as the 3 morning samples. Some authors even suggest using only 2 smears, as more than 99% of smear positives are positive after 2 smears<sup>5</sup>. Such a strategy could improve overall diagnostic efficiency (fewer smears per patient) and accuracy (smear examinations of more patients will be of a better quality because of the reduced workload overall).

(B) In many countries, pyogenic bacteria will be the most probable cause of bacterial pneumonia. If the patient is already using TMP/SMX prophylaxis, the first choice is **amoxicillin**. If the patient is not yet on TMP/SMX prophylaxis, TMP/SMX is preferred over amoxicillin because of its broader spectrum. However, if available, amoxy-clavulanic acid or cefuroxime is the best choice for empirical therapy in non life-threatening respiratory infections at level C. Follow the national guidelines.

(C) If no improvement after a 5-day-course of antibiotics, the patient should be given more advanced examinations. If a patient was referred by level A or B, or is severely dyspnoeic, start with this box. Repeat the **history and physical examination** thoroughly. Look for additional signs that may help in the differential diagnosis. **Skin lesions** are present in Kaposi's sarcoma or disseminated cryptococcosis or penicilliosis. **Pyomyositis** and **cellulitis** point toward staphylococcal infection. High fever, pleuritic type chest pain and productive cough are suggestive of bacterial pneumonia. **Lymph nodes** are usually seen in TB and lymphoma. Fundoscopy may show cotton wool spots suggestive of CMV retinitis. A chest X-ray and a sputum AFB, Gram stain and direct examination should be carried out.

**Typical chest X-ray findings** in different pathologies (unfortunately in AIDS patients, findings are seldom typical):

<b>PCP:</b>	bilateral diffuse interstitial shadowing normal
<b>Bacterial:</b>	lobar consolidation unilateral non-lobar infiltrate
<b>Tuberculosis:</b>	lobar consolidation cavitation pleural effusion intrathoracic lymphadenopathy

Other lab tests could also be included here: complete blood count, ESR, Gram stain of pus from other sites, LDH, etc.

(D) Even if former AFB smears were negative, it is useful to repeat this examination in patients who are suspect for pulmonary TB, after a trial with antibiotics.

(E) Paragonimus: treat with praziquantel 75 mg/kg/day in 3 divided doses for 2 days.

Strongyloides: Treat with albendazole (400 mg 2 x daily for 5 days or ivermectin 12 mg once daily for 3 days. Chronic suppressive therapy once a month is necessary to prevent relapses (see: *Introduction* section).

(F) An acutely ill patient with high fever, high leucocytosis and respiratory symptoms suggests a bacterial cause. Chest X-ray and Gram stain may help to differentiate between different causal agents.

(G) A lobar pneumonia and a sputum Gram stain with Gram-positive cocci in pairs is very likely a streptococcal pneumonia. If there is no problem of penicillin-resistant streptococcus in your setting, this antibiotic is the first choice treatment for lobar pneumonia. You can choose between fortified penicillin procaine 2,4 MIU a day IM, or penicillin G 2 MIU 4 x daily IV. For penicillin-sensitive strains, oral amoxicillin or amoxy-clavulanic acid (625 mg 3 x daily) is a good choice. For patients with penicillin allergy, erythromycin 500 mg 3 x daily is the preferred treatment. Treatment must be given for 10-14 days.

In some countries, penicillin-resistant *S.pneumoniae* is a frequent problem. In that case, treatment should begin with ceftriaxone 2 g once daily IV in critically ill patients. In stable patients, a fluoroquinolone such as ofloxacin 400 mg 2 x daily or ciprofloxacin 500 mg 2 x daily can be used for 2 weeks.

(H) More diffuse infiltrates and Gram-negative coccobacilli on sputum Gram stain are suggestive of *H.influenzae*. Treatment of choice is ceftriaxone or chloramphenicol. Amoxy-clavulanic acid is a good alternative, if available.

- (I) Always carry out a Gram stain in a lung abscess to exclude nocardiosis. *Nocardia* can present with multiple abscesses. The recommended treatment is TMP/SMX 10/50 mg/kg x 2 x daily (6 weeks to 6 months), or minocycline 100 mg 2 x daily (for several months), combined with amikacin for 2 weeks, or ceftriaxone 2 g daily (for several months) combined with amikacin. Surgical drainage of abscesses is sometimes necessary.
- (J) If the X-ray shows an air-fluid level, this indicates a lung abscess. Treatment of choice is amoxy-clavulanic acid 625 mg 3 x daily or clindamycin 600 mg 3 x daily for 3 to 4 weeks.
- (K) The antibiotic of choice for staphylococcal infections is (flu)cloxacillin 1-2 g IV 4 x daily. Chloramphenicol, doxycycline and TMP/SMX are also moderately effective against staphylococci.
- (L) The duration of therapy will depend on the causal agent (see *annotation (N) level B*).
- (M) If the patient did not improve with the prescribed treatment, other diagnoses have to be considered. Add treatment for atypical pneumonia: doxycycline 100 mg x 2 day, followed by 1 tablet daily for 10 days. Repeat the X-ray. The X-ray appearance can change rapidly in immune-suppressed patients. Choose the correct entry point in the algorithm according to the result.
- (N) If the chest X-ray and the physical examination are compatible with **pleural effusion**, a thoracocentesis should be performed. Protein, LDH, cell count and differential count are done on pleural fluid.<sup>3</sup> In situations such as in developing countries where tuberculous effusions are frequent and malignant effusions rare, an exudative unilateral pleural effusion is highly predictive of tuberculosis, especially when protein content >50 g/l. The WBC count is usually elevated (1000-2500/mm<sup>3</sup>), mostly *lymphocytes*. In a hospital with limited facilities a patient with unilateral lymphocytic pleural effusion should be treated with anti-tuberculous drugs. ZN staining and culture of the fluid has a low sensitivity. (Histologic examination of a closed pleural biopsy has a good sensitivity and a low complication rate in experienced hands.<sup>17</sup>)

*Neutrophilic exudative pleural effusion*: the differential diagnosis includes pulmonary embolism, post-pneumonic effusion, malignancy, amoebic liver abscess (right side).

*Empyema*: if thick pus is aspirated, a chest drain should be placed to evacuate the pus. Send the pus for Gram stain and ZN stain, and culture if available.

An *eosinophilic pleural effusion* is suggestive of Paragonimus in endemic areas. An eosinophilic exudate is also found in patients with a pneumothorax or a haemothorax.

A large globular heart on chest X-ray, orthopnoea, narrow pulse pressure and distended jugular vein should raise suspicion of **pericardial effusion**. The presence of fluid in the pericardial space can be identified by an ultrasound probe on the sub-xyphoid area. In an HIV-positive patient with a pericardial effusion, tuberculosis is the most likely treatable cause. It is justified to start anti-tuberculous treatment without diagnostic pericardiocentesis. The latter is only necessary when cardiac tamponade is evident (severe dyspnoea, circulatory collapse).

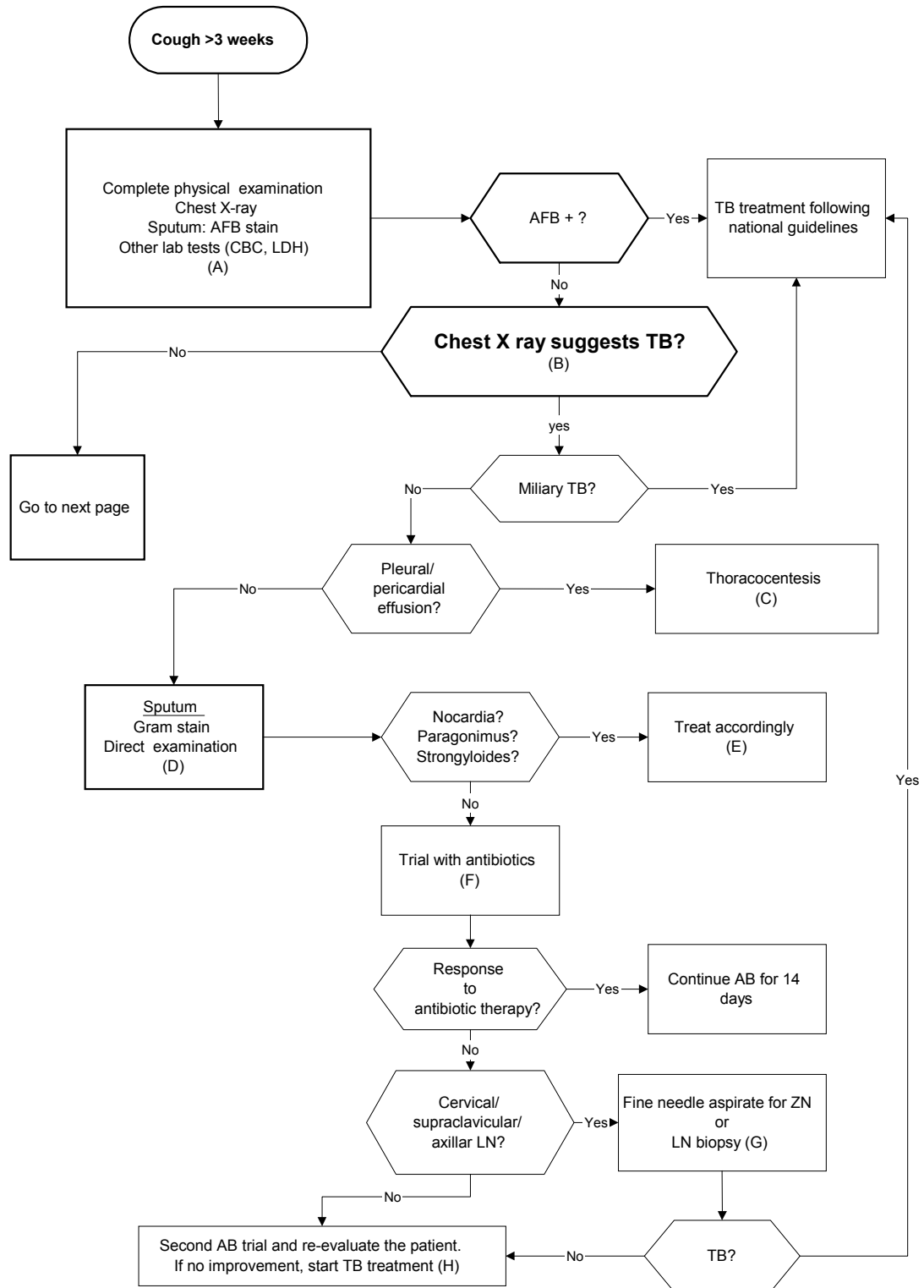
- (O) Wasting, night sweats, chest pain and productive cough, high ESR, nodular or cavitory infiltrates, miliary pattern, lobar infiltrates that do not disappear with broad spectrum antibiotics, hilar or paratracheal lymph nodes all suggest TB.
- (P) In a group of HIV-positive suspected TB patients with sputum smear-negative for AFB, who did not respond to penicillin and had no signs of cutaneous or palatal Kaposi's sarcoma, ZN staining of fine needle aspirate (19G) of supraclavicular, cervical or axillary lymph nodes, gave the diagnosis of TB in up to 87% of cases that were confirmed afterwards to have pulmonary, pericardial or pleural TB!<sup>4</sup>
- (Q) If this second trial of antibiotics fails, a re-evaluation is necessary. Follow the algorithm of **cough present for more than 3 weeks**. At a certain point, a decision will have to be made to start TB drugs for TB-suspected cases that remain smear negative. However, at level C, all efforts should be directed at excluding other pathogens before deciding to start blind TB treatment. In some patients, however, the clinical picture deteriorates so fast that it is not possible to wait for the results of a second trial of AB. As a rule of thumb, it is wise to take these difficult clinical management decisions in a small committee whenever possible.
- (R) Insidious onset, fever on and off, dry cough and dyspnoea on exertion are more suggestive of PCP. Chest X-ray typically shows bilateral alveolar infiltrates but can be normal in 25% of patients. A serum LDH >2 times the upper normal limit is highly suggestive of PCP.
- (S) Staining of induced sputum is a highly sensitive method (60%-90%) to identify *Pneumocystis carinii* pneumonia. Staining of BAL has a sensitivity of 95%. It is not useful to stain expectorated sputum for PCP. For the method of sputum induction and staining for PCP, see: *Laboratory* section at the end of this chapter.
- (T) PCP treatment: TMP-SMX: TMP 20 mg/kg daily plus SMX 100 mg/kg daily in 4 divided doses. The treatment for the severely ill patient with hypoxaemia on admission is prednisolone in a dose of 40 mg 2 x daily for 5 days, 40 mg once daily for 5 days, then 20 mg daily to completion of treatment. If available, IV TMP/SMX is preferred in the first 10 days when the patient is severely ill. Assessment of benefit will require at least 7 days as PCP may initially worsen. If the patient responds, continue for at least 21 days in the absence of side effects. The risk of recurrence is high and can be reduced by prophylaxis: TMP-SMX 480 mg 2 tablets daily.

Sometimes 480 mg daily or 960 mg 3 x weekly is better tolerated. An alternative is dapsone 100 mg once daily.

- (U) In case of severe dyspnoea, be sure to rule out a pneumothorax, which can be seen in PCP (as well as in TB). If a pneumothorax is present, a chest tube must be inserted. Start PCP treatment with steroids and repeat induced sputum for PCP the following day.
- (V) Doxycycline is added to cover for atypical pneumonia (chlamydia and mycoplasma). If no improvement after 7 days, despite a treatment with CTX and prednisolone (in case of hypoxaemia), some physicians prefer to switch to an alternative PCP regimen: clindamycin IV 600 mg 4 x daily and primaquine PO 15 mg daily or dapsone 100 mg daily and trimethoprim 20 mg/kg once daily.
- (W) Bilateral alveolar infiltrates, dry cough, negative PCP staining and no severe respiratory distress: treat for atypical pneumonia with doxycycline or erythromycin.
- (X) Treat with ceftriaxone and doxycycline, or chloramphenicol and flucloxacillin.
- (Y) If no improvement or clinical deterioration after 5 days and patient has serologic evidence of previous toxoplasmosis, treat with high dose TMP/SMX to cover *Toxoplasma pneumonitis*. If available, Giemsa staining of BAL can identify *T. gondii*.
- (Z) Switch to chloramphenicol (500 mg 4 x daily) + flucloxacillin (500 mg 4 x daily).
- (AA) Fungal respiratory infections are difficult to diagnose in field conditions. Bronchoscopy, cytological examination and special culture techniques are required. However, in some studies in Africa using bronchoscopy and BAL, cryptococcosis was more frequent than PCP. In the presence of skin lesions (or meningitis), the diagnosis of disseminated cryptococcal disease or penicilliosis is facilitated because samples of the skin are easier to obtain. Cotton-blue stain is an easy method to visualise fungal elements in material (see: *Laboratory* section). In the case of meningeal signs, India ink stain on CSF is a sensitive test for diagnosing disseminated cryptococcosis.
- (BB) Penicilliosis: Initial treatment should be with amphotericin B 0,6 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg 2 x daily for 10 weeks. In mild cases, itraconazole can be used throughout.<sup>6</sup> Long-term suppressive therapy with itraconazole should be given to prevent relapse. Itraconazole 200 mg daily is effective in preventing relapses. For more details on this topic, see: *Introduction* section. For cryptococcosis, fluconazole is the preferred maintenance drug. (See *Neurological Disorders*, chapter 7)

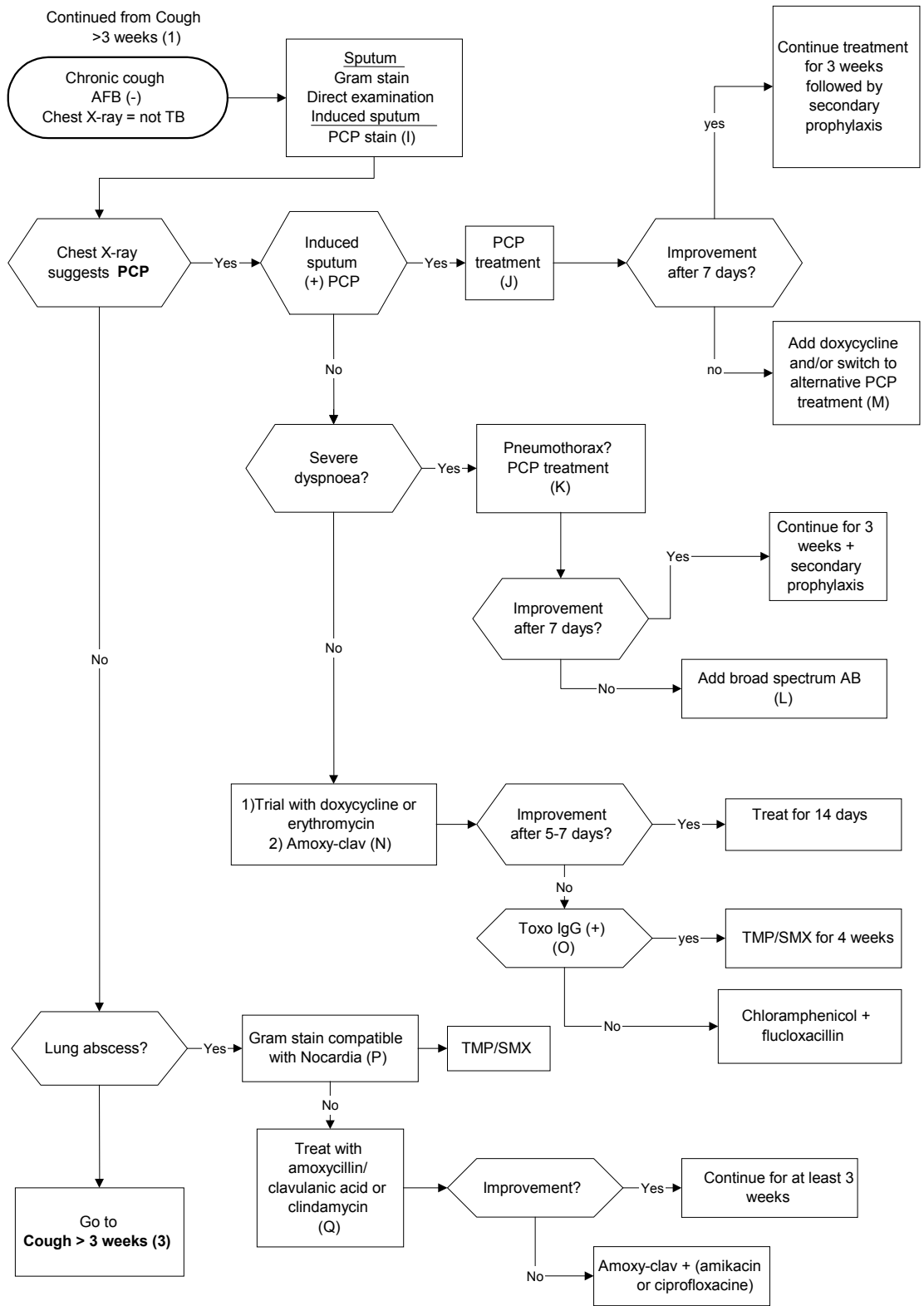
- (CC) CMV pneumonia is part of systemic CMV infection and occurs in patients with advanced immune suppression. Visual disturbance due to CMV retinitis is almost always present. If available, ganciclovir can be used for treatment. However, this drug is beyond the means of most developing countries. Offer palliative care.
- (DD) Pleural Kaposi's sarcoma often gives a bloody pleural fluid, nodular infiltrates and mediastinal lymphadenopathy. The diagnosis is suggested when associated with typical skin and mouth lesions. Bronchoscopy may reveal bronchial KS lesions. Pulmonary Kaposi's sarcoma is usually aggressive and rapidly fatal. Offer palliative care or chemotherapy when available (vincristine).
- (EE) Atypical respiratory symptoms: treat with empirical antibiotic therapy for 10 days. The choice depends on previous antibiotic therapy. Broad-spectrum respiratory coverage is obtained with amoxy-clavulanic acid + doxycycline, or chloramphenicol. If symptoms persist, proceed to the algorithm of chronic cough.

**CHRONIC RESPIRATORY SYMPTOMS  
or COUGH >3 weeks (1)**



**CHRONIC RESPIRATORY SYMPTOMS  
Or COUGH >3 weeks (2)**

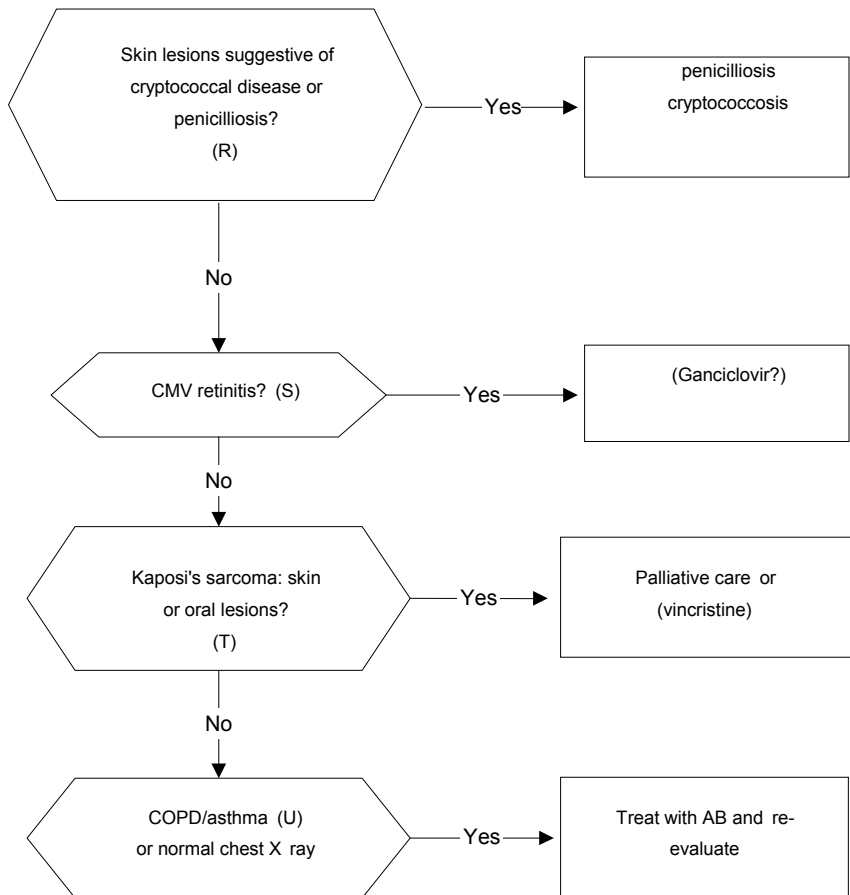
**Chest X-ray not suggestive of TB**





**CHRONIC RESPIRATORY SYMPTOMS  
Or COUGH >3 weeks (3)**

Continued from Cough >3 weeks (2)



<b>Chronic respiratory symptoms: cough &gt;3 weeks</b>
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(A) For patients with chronic respiratory symptoms, the initial evaluation consists of a thorough history, a physical examination, sputum for AFB and a chest X-ray. If blood is drawn, check CBC and LDH. Tuberculosis will be a frequent diagnosis in this group of patients in developing countries.

**Typical chest X-ray findings** in different pathologies (unfortunately, the findings are seldom typical in AIDS)

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<b>PCP:</b>	bilateral diffuse interstitial shadowing normal
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<b>Bacterial:</b>	lobar consolidation unilateral non-lobar infiltrate
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<b>Tuberculosis:</b>	lobar consolidation cavitation pleural effusion intrathoracic lymphadenopathy
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(B) If the AFB smear is negative, but the chest X-ray suggests TB, other possible pathogens must be excluded before starting TB treatment. An exception is the patient presenting with miliary TB who should be treated with TB drugs without further delay.

(C) Thoracocentesis: protein, LDH, cell count and differential count are performed on **pleural fluid**.<sup>3</sup> In situations such as in developing countries where tuberculous effusions are frequent and malignant effusions rare, an exudative unilateral pleural effusion is highly predictive of tuberculosis, especially when the protein content is >50 g/l. The WBC count is usually elevated (1000-2500/mm<sup>3</sup>), mostly *lymphocytes*. In a hospital with limited facilities, a patient with unilateral lymphocytic pleural effusion should be treated with anti-tuberculous drugs. ZN staining and culture of the fluid has a low sensitivity. (Histological examination of a closed pleural biopsy has a good sensitivity and a low complication rate in experienced hands.<sup>17</sup>) Neutrophilic exudative pleural effusion: the differential diagnosis includes pulmonary embolism, post-pneumonic effusion, malignancy; amoebic liver abscess (right side).

*Empyema*: if thick pus is aspirated, a chest drain should be placed to evacuate the pus. Send the pus for Gram stain and ZN stain, and culture if available.

An *eosinophilic pleural* effusion is suggestive of Paragonimus in endemic areas. An eosinophilic exsudate is also found in patients with a pneumothorax or a haemothorax.

*Hemorrhagic pleural fluid* suggests Kaposi's sarcoma. Look for typical skin and oral lesions.

A large globular heart on chest X-ray, orthopnoea, narrow pulse pressure and distended jugular vein should raise suspicion of **pericardial effusion**. The presence of fluid in the pericardial sac can be confirmed with the ultrasound probe on the sub-xyphoid area. In an HIV-positive patient with a pericardial effusion, tuberculosis is the most likely treatable cause. It is justified to start anti-tuberculous treatment without diagnostic pericardiocentesis. The latter is only necessary when cardiac tamponade is evident (severe dyspnoea, circulatory collapse).

- (D) Nocardiosis, Paragonimus, Strongyloides can all present with chronic respiratory symptoms and abscesses or cavitary infiltrates on chest X-ray. Because sputum Gram stain and direct examination of sputum is a non-invasive test, it is good to do this before proceeding to lymph node biopsy or aspirate.
- (E) Strongyloides: recommended treatment is ivermectin or albendazole (see: *Introduction* section).  
Paragonimus: praziquantel.  
Nocardia: high dose TMP/SMX for 6 weeks to 6 months (See: *Introduction* section).
- (F) The choice of antibiotic will depend on previous antibiotic intake and on the local epidemiology of respiratory pathogens and their antimicrobial sensitivity patterns. Amoxicillin is good as a first-line treatment. If a patient has taken already amoxicillin or TMP/SMX, a good broad-spectrum antibiotic for empirical therapy in respiratory infections is amoxy-clavulanic acid. Alternatives are ciprofloxacin or chloramphenicol.
- (G) In a group of HIV-positive suspected TB patients with sputum smear-negative for AFB, who did not respond to penicillin and who had no signs of cutaneous or palatal Kaposi's sarcoma, ZN staining of fine needle aspirate (19G) of supraclavicular, cervical or axillary lymph nodes, gave a diagnosis of TB in up to 87% of cases that were confirmed afterwards to have pulmonary, pericardial or pleural TB!<sup>4</sup>
- (H) Give a second course of antibiotics (other class). If no result after a second antibiotic trial, start TB treatment. By treating all smear negative suspected tuberculosis patients who failed to respond to broad spectrum antibiotics (ampicillin), Wilkinson et al found<sup>5</sup> that the diagnostic sensitivity increased to 80%, but the specificity fell to 78%.
- (I) When the sputum for AFB is negative and the chest X-ray is not suggestive of TB, proceed to direct examination and Gram stain of expectorated sputum and PCP staining of induced sputum. (See *Annotation (S) in cough <3 weeks*).
- (J) See *Annotation (T) in cough <3 weeks*.

- (K) Start PCP treatment. Always exclude a pneumothorax. In case of pneumothorax, put a chest tube. 80% of the cases of pneumothorax in HIV patients is due to PCP. Repeat induced sputum and PCP staining the next day.
- (L) Chronic respiratory symptoms with severe dyspnoea, PCP staining 2 times negative and not improving after 7 days of PCP treatment: start broad spectrum antibiotics: chloramphenicol + flucloxacillin or ceftriaxone + doxycycline. **If no improvement after 2 days, start TB therapy.**
- (M) Doxycycline is added to cover for atypical pneumonia (chlamydia and mycoplasma). If no improvement after 7 days, despite full dose treatment with TMP/SMX and prednisolone (in the case of hypoxaemia), some physicians prefer to switch to an alternative PCP regimen: clindamycin intravenously IV 600 mg x 4 daily and primaquine oral 15 mg daily or dapsone 100 mg daily and trimethoprim 20 mg/kg once daily.
- (N) Bilateral alveolar infiltrates, dry cough, negative PCP staining and no severe respiratory distress: treat for atypical pneumonia with doxycycline or erythromycin. In case of productive cough with purulent sputum a pyogenic bacterial infection is more likely: treat with amoxy-clavulanic acid.
- (O) Toxoplasma IgG positive: Toxoplasma pneumonitis. Treat with high dose TMP/SMX for 4 weeks.
- (P) See *annotation (I) in cough <3 weeks*.
- (Q) Lung abscess: recommended treatment: amoxy-clavulanic acid 625 mg 3 x daily, or clindamycin 600 mg 3 x daily. If not better after 10 days treatment, switch to amoxy-clavulanic acid + amikacin (25 mg/kg daily) or ciprofloxacin (500 mg 2 x daily)
- (R) See *Annotation AA and BB in cough <3 weeks*.
- (S) See *Annotation CC in cough <3 weeks*.
- (T) See *Annotation DD in cough <3 weeks*.
- (U) COPD<sup>§</sup>/asthma: chronic respiratory symptoms can be due to chronic obstructive lung disease. They are defined as more than 3 episodes of bronchitis/year within the past 3 years. Acute exacerbations are treated with antibiotics and salbutamol inhalations. In case of severe dyspnoea, a short course of steroids is indicated to decrease airway inflammation.

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<sup>§</sup> Chronic obstructive pulmonary disease

## 4 SYMPTOMATIC AND PALLIATIVE CARE<sup>18</sup>

- Avoid smoking or other irritants in a patient's room.
- Avoid feeding when a patient is in a supine position.
- Assure good ventilation of the room.
- Separate TB patients from non-TB patients as much as possible.

### 4.1 Cough

It is important to distinguish between a productive and non-productive cough. Home-care workers and family members have to be aware of the possibility of TB or another infection whenever a patient is coughing and should send the patient to the appropriate treatment level. If a patient is suspected of TB, also check family members for symptoms and encourage them to seek medical advice. If the patient is under treatment or an infection has been excluded, cough can be combated with symptomatic treatment.

Put the patient in a semi-sitting position. Always ask the patient to cover his/her mouth while coughing. Be sure that expectorations can be collected in a small container or in a tissue, to avoid the airborne transmission of certain pathogens.

Drug: codeine 15-60 mg PO 4-6 x daily (even when taking another opioid).

Besides its antitussive effect, codeine also works as an antidiarrhoeal and analgesic agent. If given for cough, be sure to avoid constipation. Codeine can be given on levels A, B and C.

### 4.2 Increased quantity or difficulty clearing airway secretions

- Maintain adequate hydration.
- Keep mucous membranes moist.
- Increase humidity in the room.
- If available, try nebulised saline to loosen thick secretions (not so often a problem with HIV-related pulmonary diseases).
- Aromatherapy (eucalyptus, pine oil in hot water or to the chest. (Vick, tigre balm).
- Postural drainage.
- Massage/respiratory physiotherapy (gentle clapping on back to move sputum).
- Oropharyngeal or nasopharyngeal suction: try to avoid because it is very irritating.

Drug: atropine: 0,4-0,6 mg SC, IM, IV 6-8 x daily (levels B and C).

### 4.3 Dyspnoea, respiratory distress

- Reduce environmental irritants and smoking.
- Elevate head of bed.
- Use fans to keep air moving.
- Minimise number of people in the room.
- Teach and support family.
- Manage anxiety: (see under respiratory distress and anxiety).

#### 4.3.1 Treat underlying causes of dyspnoea (level B or C)

##### Bronchospasm in known asthma/COPD patients

###### Acute phase

- salbutamol nebuliser if available + oxygen
- if no effect, salbutamol 0,5 mg/ml SC or epinephrine 1:1000 0,3 ml SC to be repeated after 20-30 minutes, if necessary.
- If the above therapy has no effect, use aminophylline 6 mg/kg, to be given over a period of 20 minutes, diluted in the same amount of IV fluid; continue with 4 mg/kg 4 x daily.
- Treat acute airway inflammation with a short course of steroids = 1 week 40 mg prednisone daily.

###### Maintenance

- salbutamol tablets 2-4 mg 3 to 4 x daily, or
- aminophylline tablets 100 mg 3 x daily.

##### Hypoxia

Use oxygen judiciously (it is a rare resource in most hospitals). It is not essential to reduce the sense of being short of breath. Oxygen is only indicated when the O<sub>2</sub> saturation falls below 90% (pO<sub>2</sub><70 mmHg). Monitor the oxygen saturation percentage to establish ongoing need for oxygen therapy.

##### Obstruction (stridor)

Often caused by compression of the trachea or the main bronchi by lymph nodes or mass.

###### Steroids

- prednisone 10-60 mg daily PO
- dexamethasone 1-8 mg 4 x daily (PO, IV or SC)

##### Pleural effusion

- thoracocentesis
- for recurrent effusions: insert chest tube to evacuate and perform pleurodesis by injecting powder of tetracycline or talc (retain chest tube with continuous suction for some days to assure good collage).

### **Pulmonary oedema**

- careful salt and fluid management
- appropriate cardiac medication
- diuretics: furosemide 20-240 mg PO, IV as needed
- morphine 2,5 - 5 mg SC.

### **Pneumothorax**

- chest tube.

### **4.3.2. Severe respiratory distress causing anxiety and restlessness, and no reversible causes of dyspnoea identified.**

For opioid naïve

- Morphine 2,5-15 mg PO, SC every hour if necessary.
- For persons already taking opioids, increase the dose of the same opioid by 25-100% every 4 hours.
- For associated anxiety, diazepam 5-10 mg 4 x daily PO.

For extreme distress

- Same doses, but IV.
- Dose of morphine as above combined with 0,4 -0,6 mg of atropine in the same syringe SC. May be repeated after 5-10 minutes.

### **4.4 Last hours of life**

- Respiratory failure.
- Oxygen may prolong suffering rather than improve the quality of life and may not be appropriate.
- Provide support for those at the bedside, particularly if the dyspnoea is perceived as being distressing.
- Focus on treating the sense of shortness of breath, clearing or reducing secretions (morphine). Avoid atropine at this stage because of CNS and cardio-respiratory stimulation.
- Cheyne-Stokes breathing is one of the cardinal signs that death is approaching; this respiration is not distressing for the patient.

## 5 NECESSARY DRUGS AND EQUIPMENT

Level A	Level B	Level C
<b>DRUGS</b>		
Amoxicillin	Albendazole / Ivermectin	Albendazole / Ivermectin
Codeine 30 mg	Amoxicillin	Amoxicillin
Senna	Amoxy-clavulanic acid	Amoxy-clavulanic acid
TMP/SMX	Chloramphenicol	Chloramphenicol
	(Clindamycin)	Clindamycin
	Codeine 30 mg	Codeine 30 mg
	Diazepam	Dexamethasone
	Doxycycline	Diazepam
	(Flu)cloxacillin	Doxycycline
	Minocycline	(Flu)cloxacillin
	Morphine	Itraconazole
	Praziquantel	Minocycline
	Prednisolone	Morphine
	(Quinolones)	Praziquantel
	Salbutamol 2,5 mg	Prednisolone
	Senna	Quinolones
	TB drugs	Salbutamol 2,5 mg
	TMP/SMX	Senna
		TB drugs
	Aminophylline IV	TMP/SMX
	Atropine 0,5 mg/ml	
	Benzylpenicillin	Amikacin
	Ceftriaxone	Aminophylline IV
	Epinephrine 1:1000	Amphotericin B
	Fortified penicillin procaine	Atropine 0,5 mg/ml
	Morphine SC,IV	Benzylpenicillin
		Ceftriaxone
		Clindamycin IV
		Epinephrine 1:1000
		Fortified penicillin procaine
		Morphine SC,IV
		TMP/SMX IV
<b>LABORATORY AND MEDICAL EQUIPMENT</b>		
	ESR, HgB, WBC count	(Blood culture)
	Fresh examination	Cotton-blue or Wright's stain
	Gram stain, AFB	ESR, complete blood count (CBC)
	Microscope	Fresh examination
		Gram stain, AFB
	Oxygen	Liver function tests
	Nebuliser (salbutamol)	Microscope
	LN aspiration for AFB	PCP staining
		Pleural fluid: cell count Differential count, protein



Level A	Level B	Level C
		(Bronchoscopy + BAL)
		Chest tube + Pleurevac
		LN aspiration and/or biopsy: AFB, histology
		Nebuliser (hypertonic saline and salbutamol)
		Oxygen
		X-ray

## 6 LABORATORY TECHNIQUES

### 6.1 Direct smear examination for TB: Ziehl-Neelsen Method

An excellent review about sputum examination for TB has recently been published by the IUATLD<sup>19</sup> (strongly recommended reading).

The method of choice for sputum smear microscopy is the Ziehl-Neelsen (ZN) staining technique. Cold staining procedures such as the Kinyoun are not recommended because they have low sensitivity in paucibacillary samples and the staining fades rapidly. A binocular light microscope with objective x40 and x100 is required. Fluorescence microscopy, which is recommended when the daily workload exceeds 50 specimens, has no place in most of the situations in which MSF is working. The advantage of this method is that it can screen smears quickly under low magnification. It is important to re-check fluorochrome stain positive smears using ZN stain. In this way, +/- 80 smears a day can be examined.

- 100 high power fields (there are about 100 microscopic fields in a 2 cm long smear) must be read before declaring the slide to be negative.
- The reading should be stopped when 10 or more AFB are observed in less than one length). When a drop of immersion oil is put onto the smear slide, this should never be touched with the oil applicator to avoid transfer of AFB from one smear to another.
- A microscopist should take at least 10 minutes to examine 100 fields, and one microscopist should not be expected to process and read more than 25 sputum specimens a day.

Several concentration methods have been tested to increase the sensitivity. They are cumbersome and not superior to a well-prepared and stained Ziehl Neelsen. The most important factor is the quality of the carbol fuchsin. Slide reporting is done in a standardised way.

#### Standard method of reporting according to IUATLD.

AFB counts	Reporting
No AFB in at least 100 fields	0/negative
1-9 AFB in 100 fields	Actual AFB counts**
10-99 AFB in 100 fields	+
1-10 AFB per field in at least 50 fields	++
>10 AFB per field in at least 20 fields	+++

Ideally, 2 sputum samples out of 3 should be positive. If only 1 sputum smear is positive, an abnormal chest X-ray is a necessary criterion for the diagnosis of sputum smear-positive pulmonary TB.<sup>3</sup>

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\*\* The finding of 1-3 AFB on 100 fields does not correlate with positive TB cultures. It is better to make a new smear from the same sputum sample.

Sensitivity: sputum smear microscopy for tubercle bacilli is positive when there are at least 10.000 organisms present per 1 ml of sputum. The likelihood of a positive sputum smear decreases as the degree of immunosuppression deteriorates, because there is less cavitory pulmonary TB, and more extra-pulmonary TB.

### Preparation of ZN reagents

(The most important factor in this staining is the quality of the carbol fuchsin.)

#### Ziehl's carbol fuchsin (Ziehl's solution)

A. **solution A:** 3% fuchsin alcoholic stock solution.

- basic fuchsin.....3 g
- 95% alcohol.....up to 100 ml

B. **solution B:** Aqueous phenol solution

- phenol crystals.....5 g
- distilled water, if possible.....up to 90 ml

- To prepare the 0,3% Ziehl's carbol fuchsin working solution, mix 10 ml of solution A with 90 ml of solution B.
- Add together and mix.
- Let the stain stand for several days to allow all components to go into solution.

#### Decolourising agents

Acid-alcohol (decolourise)

- ethanol.....97 ml
- concentrated (35%) HCl..... 3 ml

Add the HCl slowly to the ethanol.

#### Counterstaining

- methylene blue.....0,3 g
- distilled water.....100 ml

### Smearing

- Put the identification number of the sputum on the frosted part of the slide with a pencil, never with a marking pen.
- It is recommended to standardise the size of the smear (20 mm by 10 mm) so that 100 visual fields can be automatically screened to obtain a negative result.
- Before flame-sterilisation, remove the adherent sputum from the used wire loop by moving it up and down in the washing bottle.
- Neither fixed nor unfixed slides should be left on the table without cover because they may serve as a cause of infection to other people and also because they may be damaged by accidental breakage.
  1. Select a small portion of sputum. (Select the most purulent, most bloody, most mucoid, if such is present.)

2. Spread one loopful of purulent particles **EVENLY** to a size of approximately 20 mm by 10 mm.
3. Dry it at completely room temperature (+/-30 minutes).
4. Fix it by passing through the flame (smear side up) 5 times, taking about 4 seconds each time. **DO NOT OVERHEAT. DO NOT** heat-fix moist slides.

### Staining

- Observe the quality and the quantity of the reagents before use. If they are not adequate and sufficient to use, prepare new ones.
- Place the fixed smear slides on the staining bridge. Never use the staining jar for staining so that no material can be transferred from one smear to another (this could cause false positive slides).
- Cover the whole surface of the slide (not only the smear) with filtered 0,3% **Ziehl's carbolfuchsin solution.**
- Flame the slide (flooded with Ziehl's solution) to steaming. Never boil it and never allow it to dry out. Heating slides from underneath can be done with the flame of a Bunsen burner, an alcohol lamp or an alcohol soaked cotton swab.
- Keep slides covered with hot, steaming carbolfuchsin for 5 minutes by re-flaming as required.
- Rinse slides gently with water to remove excess carbolfuchsin.
- **Decolourise with acid-alcohol**, until no more stain comes off (3 minutes)
- Gently wash away the acid-alcohol with water.
- **Counterstain with 0,1% methylene blue solution for 1 minute.**
- Rinse slides with water.
- Drain water off the slides; allow them to dry.

### Ziehl-Neelsen:

- staining for 5 minutes
- decolourising for 3 minutes
- counterstaining for 1 minute.

## 6.2 Staining methods for *Pneumocystis carinii*.

From: Bailey W.R. and Scott E.G. *Diagnostic bacteriology*, and Ash L.R. and Orihel T.C. *Parasites: a guide to laboratory procedures and identification*.

- Induced sputum: sputum obtained after the inhalation of hypertonic saline for approximately 10-20 minutes. Up till now there has not been very much experience with this method in developing countries.
- Some use an ultrasonic nebuliser with 3% NaCl solutions for 20 minutes. The equipment needs to be decontaminated (washed and soaked in glutaraldehyde overnight) at the end of each session. It is therefore time-consuming. It is also important to perform sputum induction in a well-ventilated room, or even out of doors, in order to reduce the risk of transmission.
- Alternative method: specimens are collected by allowing the patient to breathe aerosolised droplets of a solution containing 15% NaCl and 10%

glycerine for approximately 10 minutes or until a strong cough reflex is initiated. The lower respiratory secretions obtained in this way appear watery, resembling saliva, although they often contain material directly from the alveolar spaces. The sensitivity of this method ranges from 55%-92%.

### Method of preparing slides

- A. For tissue (transbronchial biopsy): make touch preparations on clear slides; allow the smears to dry.
- B. For BAL: centrifuge for at least 10 minutes at 3000 rpm, or 15 minutes at 2000 rpm. Pour off supernatant in a recipient. Prepare several slides from the sediment. Allow the smears to dry. If thick consistency, treat the BAL with an equal amount Sputolysine® (Behring diagnostics) (diluted 1/10 in H<sup>2</sup>O). Mix and allow to stand for 30 minutes. Centrifuge.
- C. For induced sputum: if thin and watery, simply select smears (choose mucoid-appearing flakes) or centrifuge 10 minutes at 3000 rpm. Prepare slides from the sediment. If thick and mucus-like, combine with equal amount of Sputolysine®, mix and allow standing for 30 minutes. Centrifuge for at least for 10 minutes at 3000 rpm. Pour off supernatant. Prepare slides from sediment.

### Staining

Several different stains are available. The best choice is a staining for the cell walls (e.g. Toluidine-blue-O-stain or Gram-Weigert) and a staining for the parasite (e.g. May-Grünwald-Giemsa or methanol Giemsa)

#### A. Modified Toluidine blue O staining procedure

##### Reagents

1. Glacial acetic acid.
2. Sulphuric acid, concentrated.
3. Toluidine blue O (52% dye content-Roboz Surgical Instrument Co.).
4. Hydrochloric acid, concentrated.
5. 100% Ethyl alcohol.
6. Xylene or Xyless.

##### Prepared reagents

1. Sulphating reagent.
  - a) Using a fume hood, pour 45 ml glacial acetic acid into a Coplin jar that has been placed in a plastic tub filled with cool tap water (temperature not below 10°C).
  - b) Using a glass pipette, carefully add, without splashing, 15 ml concentrated sulphuric acid to the acetic acid in the jar and mix gently.
  - c) Apply petroleum jelly to the lid of the Coplin jar and seal. When kept at room temperature, this solution can be kept and used for 1 week.

2. Toluidine blue O stain
  - a) Dissolve 0,3 g toluidine blue O in 60 ml distilled water; add 2 ml concentrated hydrochloric acid and 140 ml 100% ethyl alcohol.
  - b) Store the staining solution at room temperature. It can be used for up to one year.

### Procedure

1. Once dry, stain the slides. Note: Always stain a known positive control slide with slides from each patient's specimen.
2. Place the slides in sulphating reagent for 10 minutes. Mix the reagent with a stirring rod when the slides are first placed into the solution and mix again after 5 minutes.
3. Transfer the slides to another Coplin jar and wash gently in cold running tap water for 5 minutes. Drain the water from the slides.
4. Place the slides in toluidine blue O stain for 3 minutes.
5. Drain excess stain from the slides by touching the edges to a paper towel and dip into 95% ethyl alcohol for 10 seconds to remove most of the blue dye.
6. Dip the slides into 100% ethyl alcohol for 10 seconds for further decolourising.
7. Dip the slides into two changes of xylene for 10 seconds per change. A substitute for xylene that may be used is Xyless, a less hazardous clearing agent.
8. Drain excess xylene and, while the slides are moist, mount them with permount or other mounting medium and a cover glass.
9. Examine the slides using 40 x objectives (screening). Afterwards use 100-immersion oil objective to confirm.

### Comments

Cysts of *P. carinii* will appear rounded, approximately 5 µm in diameter and stain reddish violet; the outlines of the cysts are distinct and the cysts contents stain uniformly. Little background material will be seen. The cysts often appear cup-shaped and may occur singly or in clusters. Non-budding yeast cells may stain similarly, but usual they are more oval in shape. To avoid misdiagnosis when only single organisms are seen in specimens that also contain yeast cells, the slide should be searched until a cluster of characteristic *P. carinii* cysts is found.

## B. Methanol Giemsa staining of the trophozoites.<sup>††</sup>

### Reagents

- Giemsa solution
- buffer with pH 7.2
- methanol.

### Procedure

1. Allow the slides with the thin smears to air-dry.
2. Fix the smears in methanol 100% for 3 minutes. Allow to dry.
3. Stain for 1 hour in Giemsa, 4% diluted in buffered water at pH 7.2. This means 5 drops of Giemsa solution added to 4 ml buffer.
4. Pour off the Giemsa and rinse carefully with water.
5. Allow to dry.
6. Examine with x 100 objective, under oil immersion.

Trophozoites are the free-floating forms of *Pneumocystis*. They are pleomorphic, 2-5  $\mu$  in size. They tend to form clusters and resemble platelets. Internal structures of the cysts can be visualised and free Trophozoites (the cyst wall will not stain). They look a bit like *P.falciparum* trophozoites.

### 6.3 Staining method for *Penicillium Marneffe*.

Cotton-blue provides an easy staining method for fungal elements in clinical material and culture.

### Composition

- |                   |        |
|-------------------|--------|
| - Cotton-blue     | 0,05 g |
| - phenol          | 20 g   |
| - lactic acid     | 20 g   |
| - glycerol        | 40 g   |
| - distilled water | 20 ml  |

Dissolve in a warm water bath. Cotton-blue should be added last.

### Procedure

Mix the material to be examined with a drop of the stain and cover with a cover glass.

*Penicillium* will resemble basophilic elliptical yeast-like organisms with central septation.

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<sup>††</sup> Especially in inexperienced hands, it is good to combine two types of staining, one for the cysts and one for the Trophozoites. This will increase the accuracy of the laboratory diagnosis.

#### 6.4 Nocardia in pus or sputum.

*Nocardia asteroides* stains weakly acid fast in Ziehl-Neelsen. The best stain to visualise Nocardia species is Gram stain. They appear as beaded, branching and filamentous Gram-positive organisms. Sputum collection should be the same as for tuberculosis (3 samples). Because the samples contain a lot of cellular material, the diagnostic yield is increased if the sample is first treated with a same amount of NaOH (10%-20%). The reading is much clearer still if the mixture is heated during 20 minutes at 45-56°C.

They resemble blue thin mycelium threads.

#### 6.5 Paragonimus in sputum.

The eggs of the lung flukes are found in stools and sputum. The sputum should be examined by direct microscopy, using the **objective x 10**. Very mucoid specimens are easier to examine if they are first incubated in 2-3 times their volume of a potassium or sodium hydroxide (10%) solution for 1 hour. The deposit produced after centrifugation for 3 minutes at 1500 rpm is then examined in the usual way. Masses of eggs are often contained in the brown specks sometimes visible in the sputum. Take this part for direct examination.



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Part of this section is based on documents from the MSF AIDS programme in Nairobi.<sup>1,2</sup>

## **1 INTRODUCTION**

The reported incidence of neurological abnormalities on clinical examination varies greatly, from 16% to 72% among hospitalised AIDS patients.<sup>3</sup> A wide range of neurological manifestations is reported: cognitive defects, focal deficits such as hemiplegia and acute peripheral facial palsy, painful feet syndrome, encephalopathy, etc. Some of these manifestations are directly caused by HIV itself; others are the result of OI caused by different pathogens.

Focal signs include seizures, any sort of paralysis, cranial nerve lesions, and visual disturbance.

Visual impairment in PLWH/A is mostly due to CMV retinitis. This condition can affect both eyes and lead to progressive loss of vision. Catastrophic vision loss may occur in patients with cryptococcal and tuberculous meningitis due to severe intracranial hypertension.

Meningitis in PLWH/A can have different causes: early in the course of the infection, it is due to HIV itself; later on to cryptococcal meningitis, TB meningitis, bacterial meningitis (meningococcal and pneumococcal).

The most accurate data on the aetiology of neurological disease in Africa come from autopsy studies in Ivory Coast. Cerebral toxoplasmosis was the third most common cause of death in HIV-infected people, accounting for 10% of deaths.<sup>3</sup>

Neurological HIV-related pathologies in autopsy studies in Ivory Coast show:

- cerebral toxoplasmosis: 15%
- tuberculous meningitis: 8%
- purulent meningitis: 5%
- cryptococcal meningitis: 2%.

In Rwanda/Congo, cryptococcal meningitis seems to be more frequent than tuberculous meningitis (Colebunders, ITM: personal communication).

In Southeast Asia, fungal infections (cryptococcal meningitis and penicilliosis) are more frequent than in other regions, affecting up to 38% of patients hospitalised at Bamranaradura hospital, Bangkok, between 1993 and 1996.<sup>4</sup> In the home-based care programmes in Thailand, 15% to 20% of patients are admitted with a diagnosis of cryptococcal meningitis (MSF-Thailand). In 1999, Preah Norodom Sihanouk hospital in Phnom Penh reported that 14% of admissions were attributable to cryptococcal meningitis (>800 admissions in 1999).<sup>5</sup>

MSF-Thailand identified cerebral vascular disease as an important cause of hemiplegia (26%) (undiagnosed toxoplasmosis? PML?) in AIDS patients, second only in frequency to toxoplasmosis (33%).<sup>6</sup>

## **2 CONDITIONS CAUSED BY HIV ITSELF**

### **2.1 Acute aseptic meningitis**

Early-stage acute aseptic meningitis associated with high viral load. This condition resolves spontaneously and does not require treatment.

### **2.2 Mononeuropathy and polyneuropathy**

The most common type seen is a distal, predominantly sensory neuropathy. It can be caused by HIV itself or by other viral infections such as Herpes zoster and CMV. Sometimes it is due to nutritional deficiencies responding to vitamin B. In severe forms, the painful paraesthesias and burning can prevent patients from walking despite intact motor function. It should be differentiated from syphilis and isoniazid (INH) toxicity, which can also cause painful neuropathies and myelopathies. Generalised motor weakness, with inability to walk, can be due to severe hypokalaemia. Low potassium is frequently encountered in AIDS patients with chronic diarrhoea and during treatment with amphotericin B. Antiretroviral drugs, especially nucleoside analogues are frequently responsible for peripheral neuropathy (ddC 25%, D4T 23%, ddI 13%).

If no obvious cause is found (INH, syphilis, etc.), treatment with vitamin B complex is given in association with painkillers. If the pain is neuropathic and severe, carbamazepine can be effective (see: *Palliative care* section).

### **2.3 HIV encephalopathy**

AIDS dementia complex is a condition observed relatively late in the course of HIV infection, when immunosuppression is more severe. It is a diagnosis of exclusion. The CSF is usually normal, although 20% of cases may have a mild mononuclear pleocytosis (<50 WBC/mm<sup>3</sup>) with slightly increased protein content (<200 mg/dl). The initial manifestations are loss of memory and

content (<200 mg/dl). The initial manifestations are loss of memory and strange behaviour. These will later be associated with various degrees of incontinence and gait disturbances with ataxia. In very advanced stages, patients may become completely demented with associated mutism and even paraplegia.

When available, AZT is an effective treatment for HIV-associated dementia. With 600-1000 mg of AZT daily, at least 50% of the patients will improve after 6 to 8 weeks.<sup>7</sup>

### 3 OPPORTUNISTIC INFECTIONS INVOLVING THE BRAIN

The differential diagnosis includes the following pathogens:

**Protozoal infection:** *Toxoplasma gondii*  
**Mycobacterial infection:** *M. tuberculosis*  
**Fungal infection:** *Cryptococcus neoformans*, *Candida* species (rare)  
**Viral infection:** Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, JC virus (slow virus causing progressive multifocal leukoencephalopathy (PML)).

Since neurological involvement in AIDS patients can present in so many different ways and since some of the conditions can be treated, early diagnosis is important. This is true for TB meningitis, *Toxoplasma* brain abscess and cryptococcal meningitis. The threshold for performing an LP should therefore be kept very low in AIDS patients who have headache. Even in the presence of papilloedema, an LP seems to carry no excessive risk in TB meningitis or toxoplasmosis, and is even indicated for treating intracranial hypertension in the case of cryptococcal meningitis.

#### 3.1 *Cryptococcus neoformans*

*Cryptococcus neoformans* is the most common life-threatening fungal infection in patients with AIDS. It is the first cause of meningitis in patients with AIDS in Africa and Asia. It occurs most often in HIV-positive patients with CD4 <50. In this group of AIDS patients, 90% of those infected with *Cryptococcus neoformans* will present with meningitis. The onset is insidious, fever and headache being the only symptoms. Neck stiffness can be absent, and thus prolonged headache and fever, behavioural changes and confusion justify a lumbar puncture even without clear meningeal signs.

##### 3.1.1 *Diagnosis*

By lumbar puncture: increased opening pressure, sometimes only slightly elevated WBC count (predominantly lymphocytes). Even in the presence of papilloedema, an LP seems to carry no excessive risk.

Staining is easy: India ink and direct microscopic examination: positive in most cases. (82%-85%)<sup>8,9</sup>

Cryptococcal Ag on CSF (latex agglutination): this test has a sensitivity of 92%, but is expensive to perform.

### **3.1.2 Treatment**

#### **3.1.2.1 Primary treatment and maintenance therapy**

Several combinations of treatment have been studied in clinical trials. The best survival at 2 months is reached with the combination amphotericin B and fluconazole, together with regular spinal taps to decrease intracranial hypertension.

Treatment according to WHO guidelines<sup>9,12</sup>

- **First choice:** amphotericin B (IV) 0,7 mg/kg daily + flucytosine 100 mg/kg daily (2 weeks) followed by fluconazole 400 mg once daily for 8 weeks, reduced to 200 mg once daily as a maintenance therapy to be taken for life.
- **Second choice:** amphotericin B (IV) 0,7 mg/kg daily + flucytosine 100 mg/kg daily (2 weeks) followed by itraconazole 200 mg 2 x daily for 8 weeks.
- **Third choice:** fluconazole oral throughout (400 mg once daily for 8 weeks, followed by 200 mg once daily)
- **Fourth choice:** amphotericin B IV throughout.

#### Comments

Even in the US with the current treatment regimens, there is a high rate of acute mortality during initial therapy (10%-25%). Often there is a sudden deterioration and catastrophic visual loss in patients with elevated intracranial pressure. Spinal taps removing 30 ml of spinal fluid daily and the use of acetazolamide, as long as the pressure is elevated, seem to be adequate measures to reduce early mortality.<sup>9,11</sup> There is no place for corticosteroids as adjuvant therapy in cryptococcal meningitis.

Sometimes the only effective therapy to reduce the severe headache is to lower intracranial pressure by repeated spinal taps.

**MSF has good experience with a slightly different scheme in Bangkok using the first choice, but without flucytosine in the first two weeks.** This scheme was used in the US in an AIDS clinical trials group<sup>9</sup> with no difference in clinical response at 2 weeks between amphotericin B alone or combined with flucytosine. The rate of CSF sterilisation was higher, however, with the combination regimen than with amphotericin B alone.

**We recommend for all MSF missions the combination of amphotericin B for 2 weeks, followed by fluconazole 400 mg daily for 8 weeks, followed by maintenance therapy with fluconazole 200 mg daily.** In patients with less severe disease, oral fluconazole treatment alone may be sufficient.

Of course, without ARV therapy, the gain in survival is limited (a few months up to 15 months?). But with correct management of intracranial hypertension, severe headache can be treated and loss of vision can be prevented. This means a lot in terms of quality of life.

In AIDS patients, the response to treatment is often poor and there is a high risk of recurrent disease if no maintenance therapy is taken.<sup>10</sup> To improve treatment outcome, an early diagnosis of cryptococcal meningitis is required by doing an LP early in the course of the disease. Untreated, the disease runs a slowly progressive and ultimately fatal course. A study in Zimbabwe showed that untreated, the median survival is 14 days after diagnosis<sup>8</sup>; however, 22% of patients without treatment survived more than 30 days. Clinical features that predicted a rapid deterioration following admission (death within 3 days) in their study were lethargy and obtundation (GCS <13) at admission and hyponatremia.

Other risk factors for poor prognosis in cryptococcal meningitis are:

- high titre of cryptococcal Ag in CSF (>1: 1024)
- low WBC count in CSF (<20 cells/mm<sup>3</sup>)
- high opening pressures.

The decision to treat or not to treat a patient with cryptococcal meningitis depends on clinical judgement and financial considerations. In a patient who has already had several OI and who is highly dependent and suffering, the clinical decision might be to give symptomatic treatment only.

### 3.1.2.2 Adverse effects of amphotericin B

Infusion-related reactions such as nausea and vomiting are common with amphotericin B. They usually occur between 15 minutes and 3 hours following the start of the infusion. Drug-induced fever, chills and headache are also seen. These symptoms can be prevented by premedication with 1 g of paracetamol and 25 mg of promethazine. For severe chills and rigors, pethidine 25 mg IM or IV is frequently prescribed. The severity of the reactions tends to decrease with subsequent doses of amphotericin B. Some clinicians prefer to start with a lower dose (0,3 mg/kg). Severe hypokalaemia can occur during treatment with amphotericin B due to a potassium wasting nephropathy. In some patients, this leads to severe muscle weakness. Replacement with oral KCl is indicated. Prehydration with 1 litre normal saline can help reduce the incidence of nephrotoxicity. Close medical supervision is required throughout treatment. Safe use in pregnancy has not been established.

### 3.1.2.3 Primary prevention

A study in the US<sup>13</sup> comparing weekly versus daily fluconazole for the *primary* prevention of fungal infections showed a similar efficacy with a weekly 400 mg fluconazole in the prevention of cryptococcal meningitis as with a daily schedule. It would be interesting to evaluate the effect of this weekly schedule as chronic suppressive therapy (secondary prevention). There are concerns, however, that primary prevention of cryptococcosis could promote azole-resistant *Candida* species.

## **3.2 Toxoplasma encephalitis or brain abscess**

Toxoplasmosis was a common CNS infection in patients with advanced HIV disease in Europe and the USA in the early years of the epidemic. Between 20% and 47% of HIV-infected patients with serologic evidence of *Toxoplasma gondii* infection will develop symptomatic disease. In Southeast Asia, toxoplasmosis appears to be infrequently reported (1% to 2%). This can be due either to the limited diagnostic capacity or to a real low incidence of Toxoplasma encephalitis. A serologic study on pregnant women and blood donors in Cambodia showed a low percentage of seropositivity for *Toxoplasma gondii* (13,1%).<sup>14</sup> This makes cerebral toxoplasmosis an unlikely diagnosis in an HIV-positive patient in Cambodia.

*Toxoplasma gondii*, a protozoan parasite of mammals, is transmitted when oocysts are ingested, either via excretion by household pets or their presence in undercooked meat. Invasive forms enter the bloodstream to reach the brain, heart and lungs where they form cystic aggregates that remain latent, but subject to reactivation throughout the life of the host. In many communities, the majority of people will have been infected by early childhood, but otherwise healthy persons do not develop clinically evident disease.

### **3.2.1 Pathogenesis**

Primary infection may result in focal necrotizing encephalitis and occasionally chorioretinitis and pneumonitis as a result of the unrestrained multiplication of tachyzoites. Reactivation of latent bradyzoites produces focal neurological signs mainly in patients with CD4<100. Hemiparesis, cognitive disorders, seizures and other signs suggestive of an intracerebral space-occupying lesion tend to develop subacutely over several weeks, and they are sometimes accompanied by symptoms of a diffuse encephalopathy.

### **3.2.2 Symptoms**

Symptoms are variable, but fever is present in about 50% of patients and headache, which may be very prominent, is present in 50%-70% of patients. 50% of patients have hemiplegia or hemiparesis. 30% have seizures.<sup>15</sup> Meningeal irritation is infrequent.

### **3.2.3 Diagnosis**

CSF findings are non-specific or normal. A CT scan is not absolutely necessary to make the diagnosis of Toxoplasma brain abscess. In many countries, *Toxoplasma gondii* is the most common cause of focal brain disease in HIV patients. It is therefore worth treating any HIV-positive patient presenting with headache, fever and focal neurological signs, and who has normal CSF findings, for toxoplasmosis. If the diagnosis of toxoplasmosis is correct, the patient should improve within 7 days. Response to empirical therapy is currently being considered as a diagnostic criterion. If possible, Toxoplasma antibody



(IgG) can be useful, because the negative predictive value is high. In other words, Toxoplasma brain abscess is less likely if the Toxoplasma serology is negative.

### **3.2.4 Treatment<sup>12</sup>**

#### **3.2.4.1 Primary therapy**

##### **First choice: sulfadiazine and pyrimethamine and folinic acid for 6-8 wks.**

- pyrimethamine 100 mg loading dose, followed by 50 mg daily
- sulfadiazine 1-2g 4 x daily (100 mg/kg daily)
- folinic acid 10 mg daily.\*

Sulfadiazine and pyrimethamine is the treatment of choice for HIV-positive patients suspected of having acute toxoplasmosis (including children and seriously ill pregnant women). Both drugs are cheap and penetrate into the cerebrospinal fluid in therapeutically active concentrations. The relatively high doses used can, however, lead to toxicities, so careful monitoring is important. Leukopenia, thrombocytopenia and rash are common. Folinic acid, which counteracts the blockade of folate metabolism in mammalian cells without affecting antiprotozoal activity, should be administered regularly to reduce the risk of myelosuppression. Patients should be advised to maintain a high fluid intake and urine output to prevent the development of sulfadiazine induced crystalluria, and to watch for signs of 'gravel' (sulfadiazine crystals) in their urine.

Many Thai hospitals omit folinic acid and use a lower dose of pyrimethamine.<sup>6</sup>

##### **Second choice: high dose TMP/SMX (10/50 mg/kg daily) for 4 weeks.**

In many European countries, sulfadiazine is not a registered drug. Several European studies have shown that, high dose TMP/SMX 10/50 mg/kg daily PO or IV, divided over 2 doses for 4 weeks, followed by a lifelong maintenance of 1 DS (960 mg) TMP/SMX daily (or Fansidar® 2 tablets weekly) is effective in the treatment of Toxoplasma encephalitis, and has fewer side effects than the combination sulfadiazine/ pyrimethamine.<sup>15-17</sup>

In this regard, it is interesting to know that MSF-Nairobi has successfully treated cases of CT-proven Toxoplasma brain abscess with Fansidar® 2 tablets daily. The same experience is shared in Peru.

##### **Third choice: clindamycin and pyrimethamine and folinic acid for 6-8 wks.**

- clindamycin 600 mg 3 x daily
- pyrimethamine 100 mg daily loading dose followed by 50 mg daily
- folinic acid 10 mg daily.

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\* It is important to remember that folic acid counteracts the anti-protozoal activity of pyrimethamine and is not a good alternative for the expensive folinic acid.

### 3.2.4.2 Other measures

In case of intracranial hypertension: papilloedema, vomiting: corticosteroids: prednisolone 40 mg 4 x daily or dexamethasone 4 mg 4 x daily.

Anti-epileptic treatment in case of seizures: phenytoine 100 mg 2-3 x daily (after a loading dose of 15 mg/kg daily the first day).

Primary treatment should be continued for 4 (TMP/SMX) to 6 (sulfadiazine, clindamycin) weeks. After this, the doses are reduced and patients should remain on this maintenance therapy for life.

### 3.2.4.3 Maintenance therapy

- **TMP/SMX: 1DS daily.**
- dapson 200 mg weekly or 50 mg daily + pyrimethamine 75 mg weekly + (folinic acid 25 mg weekly)<sup>†</sup>
- sulfadiazine 500 mg 2 tablets 2 x daily + pyrimethamine 25 mg daily + (folinic acid 25 mg weekly)
- Fansidar® 1-2 tab weekly (sulfadoxine 500 mg + pyrimethamine 25 mg).

### 3.2.4.4 Primary prophylaxis

The risk of transmission can be reduced if meat is adequately cooked and if vegetables and fruit are washed carefully before they are eaten. In HIV-positive patients with CD4<100 and *T. gondii* antibody positive, prophylaxis with either **TMP/SMX** or dapson and pyrimethamine at doses used for the prevention of PCP, have been shown to reduce the incidence of toxoplasmosis.

- TMP/SMX: 1DS daily.
- dapson 200 mg weekly or 50 mg daily + pyrimethamine 75 mg weekly + folinic acid 25 mg weekly
- Fansidar® 1 tab weekly (sulfadoxine 500 mg + pyrimethamine 25 mg).

## 3.3 **Tuberculous meningitis**

Up to 10% of AIDS patients who present with TB will show involvement of the meninges. This results from rupture of a cerebral tuberculoma or is blood-borne.

### 3.3.1 **Symptoms**

- Gradual onset of headache and decreased consciousness, low-grade fever.
- Neck stiffness and positive Kernig's sign.
- Cranial nerve palsies result from exsudate around the base of the brain.

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<sup>†</sup>Note that of the commercial antimalarial drugs, Maloprim® contains dapson 100 mg/pyrimethamine 12,5 mg and Daraprim® contains pyrimethamine 25 mg.

### **3.3.2 Diagnosis**

- Lumbar puncture is mostly safe in tuberculous meningitis.
- CSF may look cloudy. WBC: 500/mm<sup>3</sup>; lymphocytes (early in the course: granulocytes).
- High protein level (40 mg/dl-100 mg/dl).
- Low glucose level (<20 mg/dl).
  
- CSF microscopy only seldom shows AFB. You can increase the diagnostic pick-up rate by the following:
  - examine the deposit after centrifugation of a 10 ml CSF sample
  - examine the deposit for at least half an hour before reporting it as negative
  - examine several CSF samples obtained over a few days.
  
- Always exclude cryptococcal meningitis by CSF microscopy (Indian ink stain).

### **3.3.3 Differential diagnosis of TB meningitis on CSF findings**

See next page.

### **3.3.4 Treatment**

Whenever available, the national TB programme protocols should be used.

See *Respiratory Problems*, chapter 6: section 2.1 for the WHO-recommended TB treatment regimens.<sup>18, 19</sup>

A 7-month continuation phase with daily isoniazid and rifampicin (7HR) is recommended for category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs. In case of severe neurological signs (cranial nerve lesions, drowsiness, coma) the use of steroids (prednisone 1 mg/kg for 2-4 weeks, then tapered off over 4-6 weeks) is good clinical practice. Patients treated with steroids have more rapid symptomatic relief and less neurological sequelae.<sup>20</sup>

CSF ABNORMALITIES						
Disease	Appearance	Opening pressure	WBC/mm <sup>3</sup>	Protein	Glucose	Microscopy/other tests
Tuberculous meningitis	Opalescent	I	25-1000 mainly L	45-500	10-45	AFB (25% sensitivity)
Cryptococcal meningitis	C	I	I but <800 L> PMN	I but <500	Slightly decreased	Positive India ink staining Cryptococcal Ag: sensitivity 92%
Bacterial meningitis	O or P	I	25-10,000 mainly PMN	50-1500	0-45	Bacteria on Gram stain: 60-90% sensitivity
Viral meningitis	N or O	N	20-300 L>PMN	Increased	Normal	
Neuro-syphilis	N	N	10-150 mononuclear	50-300	Normal	Usually high VDRL
Late stage trypanosomiasis			Elevated (L>PMN)	Increased	Decreased	Motile trypanosomes
Toxoplasmosis	N	I	N	N	N	
PML	N	N	N	N	N	
HIV encephalopathy	N	N	<50	I but < 200	N	Abnormalities in the CSF are present in 20% of patients

Differential diagnosis of tuberculous meningitis<sup>18</sup>

Key: I: increased, O: opalescent, P: pus, C: clear, N: normal, PMN: granulocytes, L: lymphocytes

### 3.4 Cytomegalovirus (CMV)

50% of PLWH/A with active CMV disease, will have eye involvement or CMV retinitis. Other neurological manifestations include myelopathy and encephalitis. Induction therapy with IV ganciclovir effectively treats retinitis in 70%-90% of patients. Lifelong maintenance therapy is necessary. Severe bone marrow suppression can occur. The drug is expensive and beyond the reach of most developing countries.

### 3.5 Syphilis

Tertiary syphilis involving the brain and spinal cord used to be common before the availability of antibiotics. In PLWH/A, syphilis can occur even in people who had previously a complete course of antibiotics, and it can occur without a rise in VDRL or RPR. If clinical suspicion is high and serology is negative, the VDRL should be rechecked after dilution of the sample (to rule out the prozone effect = false negative tests due to excessive presence of antigen). Although serum VDRL has a high sensitivity (90%) and low specificity, this trend is reversed on the CSF sample. CSF VDRL has high specificity but low sensitivity. A positive VDRL on CSF confirms the diagnosis of neuro-syphilis. All the classical presentations of neuro-syphilis are seen again: tabes dorsalis, gumma (meningo-vascular disease), etc.

#### Treatment of neuro-syphilis

- Peni G 12-24 MIU daily for 14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks. Check VDRL again at 3, 6, 12 and 24 months. If VDRL fails to decline: repeat treatment.
- Alternative: penicillin procaine IM 2,4 MIU daily plus probenecid PO 500 mg 4 x daily for 10-14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks.

### 3.6 Progressive multifocal leukoencephalopathy

This is a viral opportunistic brain infection caused by the JC virus. It occurs in up to 4% of patients with advanced AIDS. CSF is typically normal. Patients have hemiparesis, cortical blindness, dysarthria, hemianopsia, cerebellar ataxia, dementia, but they remain alert and rarely have seizures. CT scan shows single or multiple hypo-dense lesions. Rapid clinical progression is common and death usually occurs within 6 months of diagnosis. Specific antiviral therapy (cytarabine, acyclovir, alpha-interferon) does not alter the prognosis. AZT-naïve patients with PML seem to have a prolonged survival when started on AZT.<sup>21</sup>

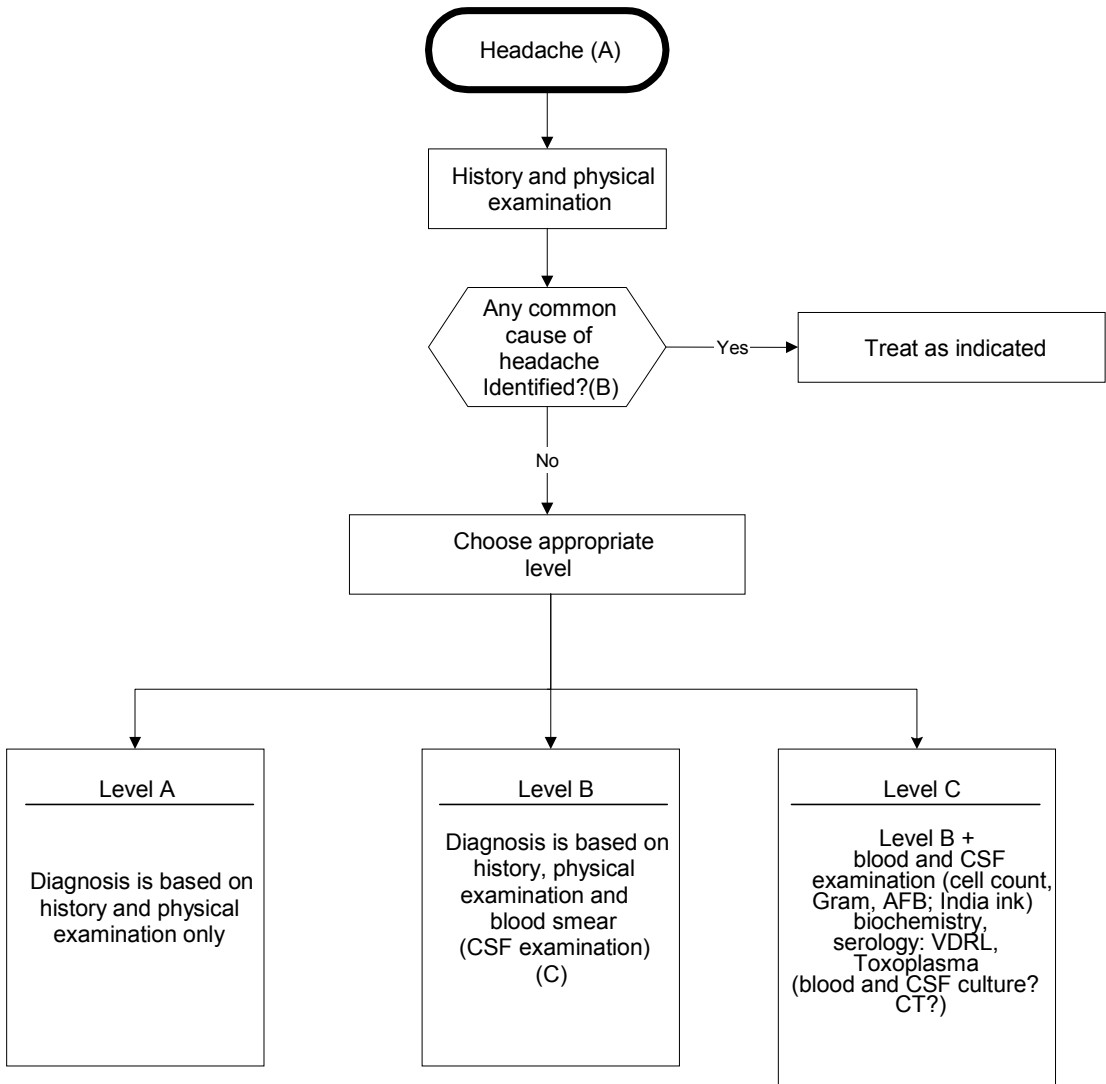
### **3.7 Malignancies**

If a mass lesion/focal lesion of the brain in an AIDS patient does not respond to empirical treatment against toxoplasmosis, lymphoma is another possible diagnosis. The CNS is a frequent location of lymphomas in AIDS patients. Intensive chemotherapy is often not possible because of haematological toxicity; and prognosis is extremely poor. Kaposi's sarcoma of the brain occurs rarely and specific diagnosis is difficult and out of reach of most settings in which MSF works.

# 4 CLINICAL MANAGEMENT OF HEADACHE

## Headache

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## **Annotations headache**

(A) Headache in a patient with symptomatic HIV infection, often persistent and severe and rapidly increasing or not responding to common drugs used for pain relief. It can be with or without fever.

### ***Infections***

- Tuberculous meningitis
- Cryptococcal meningitis
- Toxoplasma meningo encephalitis
- Neuro-syphilis
- CMV encephalitis
- HIV meningitis
- PML
- HIV encephalopathy.

### ***Malignancy***

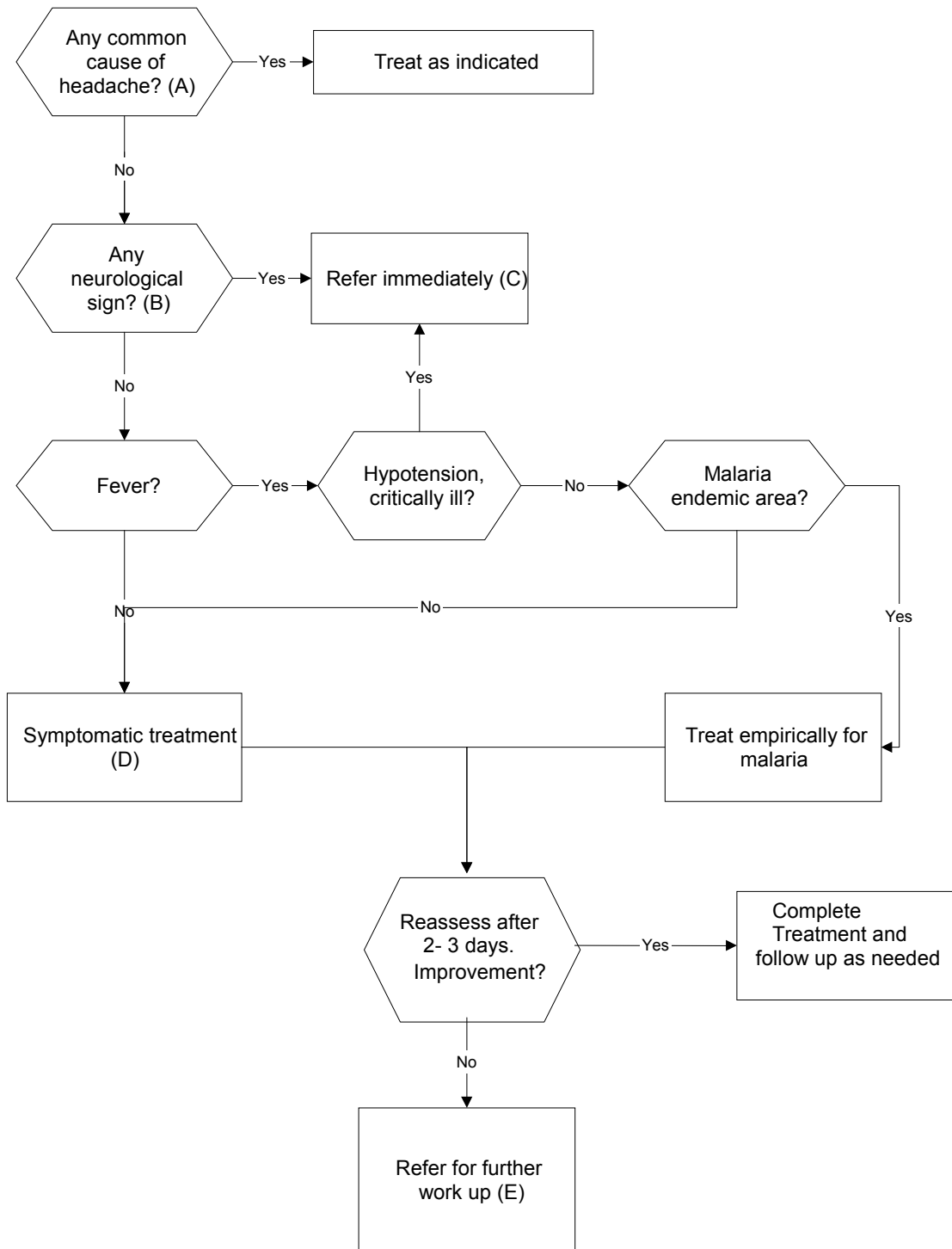
- Lymphoma; Kaposi's sarcoma

(B) Causes of headache not related to HIV infection: **migraine, toothache, hypertension**, etc. should be identified and treated. Other causes, such as tension headache, may be produced by anxiety related to the diagnosis of HIV. See *headache (2) level C for more details*.

**Sinusitis** is a frequent HIV-related cause of headache and should be treated as usual. Infectious diseases prevalent in the region concerned that can lead to headache, e.g. **malaria, trypanosomiasis, typhoid fever, dengue fever, yellow fever, rickettsiosis**, etc. should also be considered and treated, if possible.

(C) In some health centres, the health-care worker might be able to perform a lumbar puncture. If this is not the case, whenever meningitis is suspected, the patient should be referred. In most district hospitals, a lumbar puncture is possible and it is useful to identify those conditions that can be treated at level B before considering referral to a higher level.





## Annotations headache (level A)

(A) Causes of headache not related to HIV infection: **migraine, toothache, hypertension**, etc. should be identified and treated. Other causes, such as tension headache, may be produced by anxiety related to the diagnosis of HIV. See *headache (2) level C* for more details.

**Sinusitis** is a frequent HIV-related cause of headache and should be treated as usual. Infectious diseases prevalent in the region concerned that can lead to headache, e.g. **malaria, trypanosomiasis, typhoid fever, dengue fever, yellow fever, rickettsiosis**, etc. should also be considered and treated, if possible.

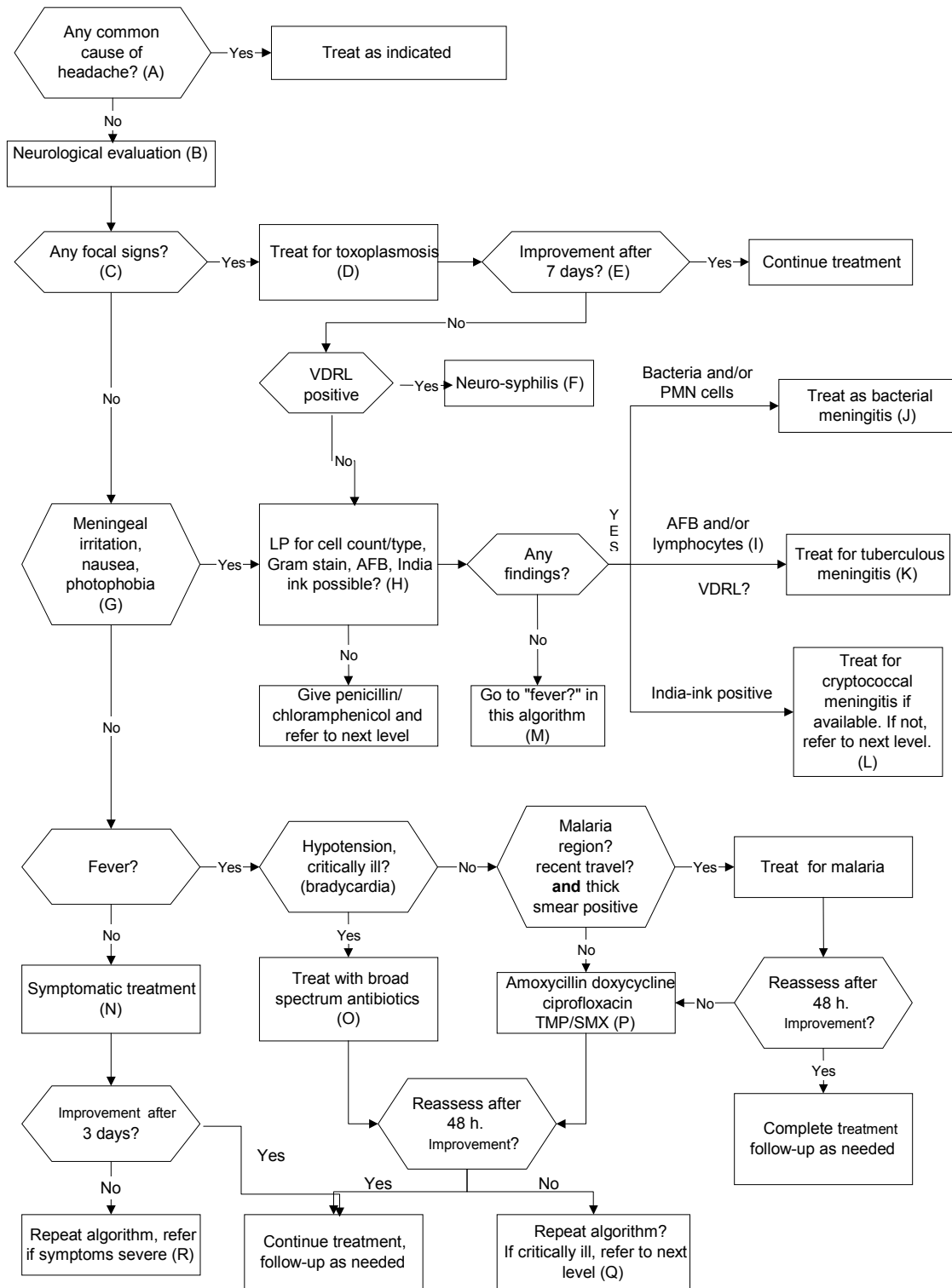
(B) These include:

1. Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, vomiting, high blood pressure and bradycardia in the presence of fever).
2. Seizures.
3. Focal neurological deficits: paresis, cranial nerve palsies, movement disorders, ataxia, aphasia.
4. Changes in mental state; including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment, dementia.

(C) Wherever possible, further evaluation of headache, particularly in a patient with symptomatic HIV infection showing neurological signs, should be pursued to identify treatable conditions. Cerebral malaria can lead to mental changes. In areas where malaria is endemic, empirical treatment may be indicated.

(D) As in patients without HIV-infection. Start with a simple analgesic like paracetamol; if necessary use compound analgesics containing narcotics. In palliative treatment, optimal pain relief is essential (see: *Palliative care* at the end of this section).

(E) Many cases of cryptococcal meningitis do not have neck stiffness. Cryptococcal meningitis may present with fever and headache only.



## **Annotations headache (level B)**

(A) See *annotation (A) level A*.

(B) Neurological evaluation. This includes:

1. Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, high blood pressure and bradycardia in the presence of fever)
2. Seizures.
3. Focal neurological deficits: paresis, cranial nerve palsies, movement disorders, ataxia, aphasia.
4. Changes in mental state; including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment, dementia.

(C) Focal signs: hemiparesis, cranial nerve palsies, seizures, ataxia, aphasia.

If toxoplasmosis is a frequent problem in your region it is justified to start empirical treatment against *Toxoplasma gondii* immediately.

However:

- In patients who have isolated hemiplegia, without fever or signs of raised intracranial pressure, a few days of observation could be incorporated into the algorithm at this level. Symptoms due to a cerebro-vascular accident (CVA) tend to improve spontaneously. If this is the case, start treatment with low dose aspirin 1 week after the onset of symptoms.
- Toxoplasma brain abscess is rarely seen in Southeast Asia and serological epidemiological data from Cambodia and Vietnam show that only 10% of people have antibodies against toxoplasmosis. In these low prevalence areas, an observation period is certainly indicated in a stable patient.
- Cranial nerve lesions are often seen in TB meningitis and this is a frequent problem in HIV patients in developing countries. Especially in the presence of meningeal irritation, do not hesitate to do an LP. If the CSF is normal and focal neurological signs persist, the diagnosis of toxoplasmosis becomes more likely.

(D) Treatment consists of TMP-SMX (see: *Introduction* section) or, if available, the combination therapy with sulfadiazine and pyrimethamine. The latter is more toxic and requires the addition of folinic acid. Therefore the treatment of choice at level B is TMP-SMX.

(E) Toxoplasmosis usually responds well to treatment and this response can be used to support the diagnosis. Primary therapy should be maintained for 4 weeks for TMP-SMX and for 6 weeks for sulfadiazine/pyrimethamine. If the response is good, lifelong chronic suppressive therapy is advised: TMP-SMX 960 mg daily, or pyrimethamine 25 mg daily and sulfadiazine 2-4 g daily, or Fansidar® 1-2 tab weekly. If there is no response after 7 days, a diagnosis of cerebral toxoplasmosis is unlikely. Check VDRL or RPR.

(F) Treatment of neuro-syphilis: Peni G 12-24 MIU daily for 14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks. Check VDRL again at 3, 6, 12 and 24 months. If VDRL fails to decline, repeat treatment.

Alternative: penicillin procaine IM 2,4 MIU daily plus probenecid PO 500 mg 4 x daily for 10-14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks.

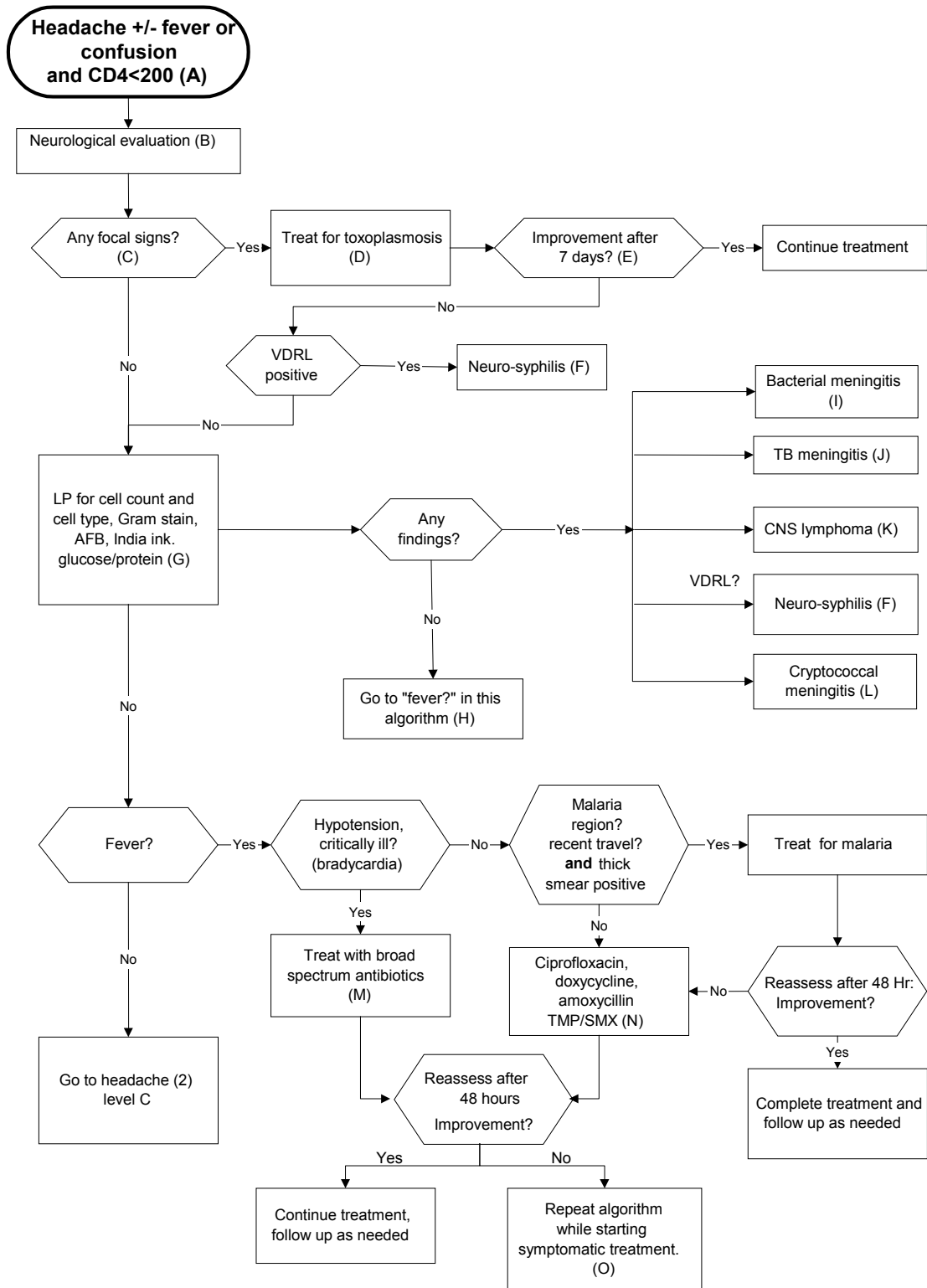
- (G) If your patient has signs of advanced HIV disease, an LP should be performed in the presence of headache and unexplained fever, or confusion, even when there are no signs of meningeal irritation. In most textbooks, it is advised to do a fundoscopy before an LP is performed. However, this examination is not available everywhere and most physicians feel uncomfortable about diagnosing papilloedema. Moreover, studies comparing CT scan and fundoscopy have shown that there is a latency of 24 hours before the onset of papilloedema and the presence of signs of raised intracranial pressure on CT scan. MSF experience in Thailand has shown that LP seldom causes problems, not even in patients with focal signs. In cryptococcal meningitis, raised intracranial pressure is caused by an alteration of reabsorption of CSF and not by a mass effect. Papilloedema is frequently present and is an indication to perform repeated spinal taps to decrease the intracranial pressure, to reduce complications and to improve survival.
- (H) At level B, a CSF examination should consist of determining cell count, cell type, Gram stain, AFB stain and India ink to detect diseases that can be treated at level B. If this is not possible, the patient should be referred to level C. Start treatment with benzylpenicillin 4 MIU IV, or chloramphenicol 1 g IV, before referral.
- (I) When the CSF contains lymphocytes and India ink stain is negative, the differential diagnosis between viral and tuberculous meningitis is sometimes difficult. The onset of headache in viral meningitis is more rapid, while TB meningitis tends to have a protracted slow onset over several weeks. Biochemistry of the CSF is helpful, if available. A VDRL should also be done to exclude neuro-syphilis because this can also present with mononuclear pleocytosis in the CSF. Neuro-syphilis is seldom seen, but VDRL serology is an easy and sensitive test. VDRL on CSF is very specific and confirms the diagnosis of neuro-syphilis.

If biochemistry is not available, try to find other clinical and laboratory signs that point in the direction of tuberculous meningitis: evidence of pulmonary or extra-pulmonary TB (pericardial effusion, pleural effusion), miliary TB? Cranial nerve palsies are particularly suggestive of tuberculous meningitis.

- (J) Benzylpenicillin 12-24 million IU daily by IV injections divided into 4 doses, or chloramphenicol 2-4 g daily by IV injection in 4 divided doses. Treat for a minimum of 7 days or for 5 days after the patient becomes afebrile. If no improvement, refer to a hospital where ceftriaxone is available. (If there is data available for your region confirming a problem of penicillin-resistant *Streptococcus pneumoniae*, the first-line treatment for bacterial meningitis should be ceftriaxone or chloramphenicol).

- (K) Short-course chemotherapy containing rifampicin and INH. In TB meningitis, a 7-month continuation phase with daily rifampicin and INH is recommended. Always associate with pyridoxine 10-20 mg daily or 250 mg weekly. Do not use thioacetazone in patients with suspected/known HIV infection. In severe cases, add prednisolone 1 mg/kg daily for 2-4 weeks, then gradually taper off the dose.
- (L) Cryptococcal meningitis: see *Introduction* for possible treatment regimens
- (M) If the result of the CSF is normal, the next step is to exclude febrile conditions that can present with headache and signs of meningeal irritation such as malaria, typhoid fever, scrub typhus, etc.
- (N) Symptomatic treatment: paracetamol, NSAID, see stepwise analgesia. (*Palliative care*). If symptoms worsen despite treatment, reassess the patient and consider referral. In case of signs of gait disturbance, behavioural changes, dementia, ataxia in the presence of a normal CSF, the diagnosis of PML and HIV encephalopathy or HIV dementia is possible in advanced AIDS. If available, treatment with AZT 600 mg-1200 mg daily may help in 50% of patients. If OI can be excluded with reasonable certainty and the patient cannot easily be referred, go to algorithm *level C headache (2)* for further management
- (O) The most frequent bacterial infections that can lead to septicaemias in HIV patients in Africa are *S.pneumoniae*, non-typhi salmonella infections, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. Give broad-spectrum antibiotics: chloramphenicol 4 g daily IV in 4 divided doses, or ciprofloxacin 2 g 3 x daily IV + gentamycin 4 mg/kg IV once daily. (Depending on sensitivity of salmonella for beta-lactams in your area, for these severe infections it is justified to use ceftriaxone 2 g IV or ciprofloxacin 400 mg 2 x daily IV (750 mg 2 x daily PO). Continue PO as soon as possible.
- (P) A patient presenting with headache and fever, but not severely ill. The choice of the antibiotic depends on prior treatment and on other symptoms. In the case of abdominal pain, treat as typhoid fever (ciprofloxacin, ofloxacin, amoxicillin). Doxycycline would cover rickettsial diseases and staphylococcal infections, and also has an anti-malaria effect. If the patient did not yet take antibiotics, co-trimoxazole is a broad-spectrum antibiotic that can be started on an empirical base and that also has some anti-malaria effect.
- (Q) Fever that continues despite broad-spectrum antibiotics raises the possibility of blood-borne infection with *M. tuberculosis* or invasive fungal infections (*P. marneffe* in Southeast Asia). Refer the patient to a higher level for further work-up. If no LP was done until now, do this first. Cryptococcal meningitis can present with fever and headache, or even headache alone.
- (R) Cryptococcal meningitis can present as severe headache, without fever. Depending on the availability of treatment at level B or C, it may be wise to do an LP before referral.

Headache (1)



## **Annotations headache (1) (level C)**

(A) At this level, the HIV stage of disease should be considered if there is clinical or laboratory evidence (e.g. low lymphocyte count, CD4<200) The pre-test probability of an OI is so high that this is the most probable cause of headache, even in the absence of fever. The *headache (1)* algorithm is to ensure that OI are excluded before symptomatic treatment is offered.

(B) Neurological evaluation

- Evidence of meningeal irritation or raised intracranial pressure (neck stiffness, high blood pressure and bradycardia in the presence of fever).
- Seizures.
- Focal neurological deficits: paresis, cranial nerve palsies, movement disorders, ataxia, aphasia.
- Changes in mental state; including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment, dementia.

(C) Focal signs

- Hemiparesis, cranial nerve palsies, seizures, ataxia, aphasia.
- If toxoplasmosis is a frequent problem in your region, it is justifiable to start empirical treatment against *Toxoplasma gondii* immediately.

However:

- Toxoplasma brain abscess is rarely seen in Southeast Asia.
- Focal signs are also present in TB meningitis. Cranial nerve lesions are particularly suggestive of TB meningitis. Tuberculosis is a frequent problem in HIV patients in developing countries and about 10% of the cases has meningeal involvement. Especially in the presence of meningeal irritation, do not hesitate to do an LP. If the CSF is normal and focal neurological signs persist, the diagnosis of toxoplasmosis becomes more likely.
- In patients who have isolated hemiplegia, without fever or signs of raised intracranial pressure, a few days of observation could be incorporated into the algorithm at this level. Symptoms due to a CVA tend to occur abruptly and improve spontaneously. If this is the case, start treatment with low-dose aspirin 1 week after the onset of symptoms. If not, start toxoplasmosis treatment after 1 week's observation.
- Progressive weakness, monoparesis, or hemiparesis accompanied by cognitive deterioration is suggestive of PML. AZT, if available, may be beneficial in such patients.

(D) Treatment consists of combination therapy with sulfadiazine and pyrimethamine, or with TMP-SMX (see above).

(E) Toxoplasmosis usually responds well to treatment and this response can be used to support the diagnosis. Primary therapy should be maintained for 6 weeks (4 weeks for TMP-SMX). If the response is good, lifelong chronic suppressive therapy is advised: pyrimethamine 25 mg daily and sulfadiazine 2-4 g daily, or TMP-SMX 960 mg daily, or Fansidar® 1-2 tab



weekly. If there is no response after 7 days, a diagnosis of cerebral toxoplasmosis is unlikely. Check VDRL or RPR.

- (F) Treatment of neuro-syphilis: Peni G 12-24 MIU daily for 14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks. Check VDRL again at 3, 6 and 12 months. If VDRL fails to decline: repeat treatment.

Alternative: penicillin procaine IM 2,4 MIU daily plus probenecid PO 500 mg 4 x daily for 10-14 days, followed by benzathine penicillin 2,4 MIU once weekly for 3 weeks.

- (G) The threshold for doing an LP should be very low in patients with headache and low CD4 counts. Examination of CSF at level C includes: opening pressure (normally: 7-18 cmH<sub>2</sub>O), cell count and cell type, glucose and protein level, Gram stain, India ink, AFB. Normal CSF has a protein content of 15-45 mg/dl, a glucose content of 45-80 mg/dl, and a cell count less than 5 cells/mm<sup>3</sup> (see table: CSF DD of TB meningitis in the *Introduction*). In toxoplasmosis, the CSF is usually normal.

- (H) If the result of the CSF is normal, the next step is to exclude febrile conditions that can present with headache and signs of meningeal irritation such as malaria, typhoid fever, scrub typhus, etc.

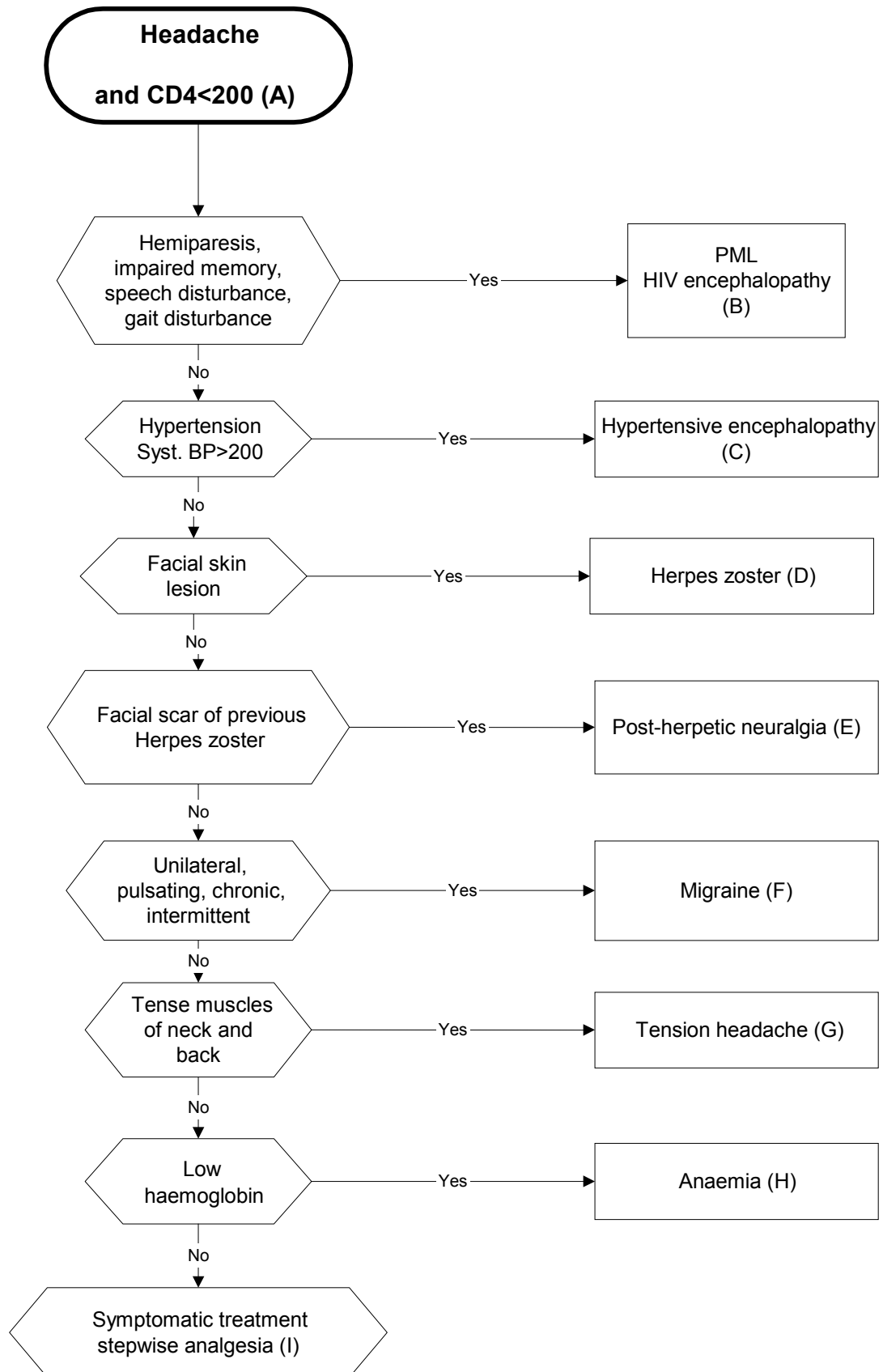
- (I) Elevated WBC count in the CSF with predominant neutrophils is suggestive of bacterial meningitis. Glucose in CSF is low and protein high. Sometimes the Gram stain shows Gram-positive or Gram-negative bacteria; this will orient the choice of the antibiotic. For empirical therapy, the first choice in bacterial meningitis is ceftriaxone 2g IV 2 x daily. When ceftriaxone is not available: benzylpenicillin 12-24 MIU daily by IV injections divided into 4 doses, or chloramphenicol 4 g daily by IV injection in 4 divided doses. Treat for a minimum of 7 days or for 5 days after the patient becomes afebrile. If there is a high percentage of penicillin-resistant *Streptococcus pneumoniae*, use chloramphenicol.

- (J) In the presence of a lymphocytic pleocytosis in the CSF, the differential diagnosis between viral meningitis and TB meningitis is facilitated by the duration of the history, the biochemistry of the CSF and the presence of other signs or symptoms of TB (see *annotation (I) in level B*). For TB meningitis, a short-course chemotherapy containing rifampicin and INH with a 7-month continuation phase with daily rifampicin and INH is recommended. Always associate with pyridoxine 10-20 mg daily or 250 mg weekly. Thioacetazone should not be used in patients with suspected/known HIV infection. In severe cases, add prednisolone 1 mg/kg daily for 2-4 weeks, then gradually taper off the dose. Neuro-syphilis can also present with lymphocytic pleocytosis in CSF. VDRL on CSF is a specific test.

- (K) CNS lymphoma: non-Hodgkin lymphoma is one of the most common malignancies associated with HIV-infection. The response to treatment is poor and the mortality high.

- (L) Cryptococcal meningitis: see: *Introduction* section for different treatment options.
- (M) The most frequent bacterial infections that can lead to septicaemias in HIV patients in developing countries are *S.pneumoniae*, non typhi salmonella infections, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. If possible, take blood cultures to document the cause of septicaemia and to obtain information on antimicrobial sensitivity of the different pathogens in your situation. Chloramphenicol 4 g daily IV in 4 divided doses, or ciprofloxacin 2 g 3 x daily IV + gentamycin 4 mg/kg once daily IV or ofloxacin 400 mg 2 x daily or ciprofloxacin 500 mg 2 x daily, or ceftriaxone 2 gr IV once daily, if available. Continue PO as soon as possible.
- (N) A patient presenting with headache and fever, but not severely ill. The choice of antibiotic depends on prior treatment and on other symptoms. In the case of abdominal pain, treat as for typhoid fever (ciprofloxacin, ofloxacin, amoxicillin). Doxycycline would cover rickettsial diseases and staphylococcal infections. It also has an anti-malaria effect. If the patient did not yet take antibiotics, co-trimoxazole is a broad-spectrum antibiotic that can be started on an empirical basis and has some anti-malaria effect as well.
- (O) Fever and headache that continue despite broad-spectrum antibiotics raises the possibility of blood-borne infection with *M.tuberculosis* or invasive fungal infections (*P.marneffeii* in Southeast Asia). Re-examine the patient and see if there are other associated signs that may offer diagnostic clues: skin (TB, mycosis, Kaposi's sarcoma), lymph nodes (TB, lymphoma etc.), abnormal chest X-ray, abscesses (staphylococcal, Nocardia, TB, etc).

**Headache (2)**



### **Annotations headache (2) (level C)**

- (A) At this point an opportunistic CNS infection has become unlikely at level C. Levels A and B may want to use this part for the treatment of common causes of headache. Ideally, an opportunistic infection should have been excluded first by referring the patient to the appropriate level.
- (B) In patients with low CD4 count, hemiplegia or cognitive deterioration can be due to HIV encephalopathy and PML. Some of those patients respond to treatment with AZT.
- (C) Nifedipine 10 mg SL, followed by maintenance anti-hypertensive drugs.
- (D) Herpes zoster on head and face: Gentian violet or polyvidone 10% 2 x daily, Vitamin B complex 3 x daily for 2 weeks. Acyclovir 800 mg 5 x daily for 7 days. Provide stepwise analgesia and associate carbamazepine for two weeks if pain not controlled.
- (E) Post-herpetic neuralgia: provide stepwise analgesia (see below), combined with carbamazepine or clomipramine (see below).
- (F) NSAID. In case of frequent attacks: low dose beta-blocking agent as prevention (atenolol 25 mg daily, propranolol 10 mg 3 x daily).
- (G) Make sure that CSF examination is normal. Diazepam at bedtime, massage of back and neck muscles.
- (H) In patients with low CD4 count anaemia is almost invariably present. Always consider OI first before ascribing headache to anaemia.
- (I) See stepwise analgesia in *Palliative care*.

## 5 SYMPTOMATIC AND PALLIATIVE CARE<sup>22</sup>

WHO has published an excellent document on cancer pain relief.<sup>23</sup> This booklet should be available in all MSF missions involved in clinical care.

### 5.1 Headache

#### Aetiology

Always exclude treatable condition by following the algorithms. If symptomatic treatment, try to give doses that relieve all pain as much as possible.

1. Provide stepwise analgesia (see below).
2. NSAID may reduce meningismus.
3. Corticosteroids may reduce oedema around space occupying lesions. They also have an anti-emetic effect. (1 mg dexamethasone = 7 mg prednisolone).
  - prednisone 10-80 mg once daily
  - dexamethasone 1-8 mg 4 x daily.
4. Chiropractic manipulation may relieve headache of cervical or muskuloskeletal origin.
5. Massage therapy.
6. Relaxation therapy.

#### Provide stepwise analgesia

Step	Type of drug	Recommended drug	Maximum dose
1. Mild pain	Non - opioid	Aspirin PO Paracetamol PO, NSAID Indometacin 25 mg 4 x daily (or ibuprofen 400 mg 4 x daily)	4 g daily in 4-6 doses 6 g daily in 4-6 doses 200 mg daily  3 g daily
2. Moderate pain	Weak opioid	Add a weak opioid Codeine phosphate 30 mg Tramadol 50-100 mg 2-4 x daily	240 mg daily in 4-6 doses 400 mg daily
3. Severe pain	Strong opioid	Replace the weak opioid with a strong opioid Morphine every 4 hours <sup>†</sup> Pethidine Buprenorphine: 0,3 mg 3 x daily	No maximum  1 mg every 8 hours

<sup>†</sup> The initial dose depends on what the patient took before. Sometimes 5 mg every 4 hours is enough to control the pain. Increase the dose stepwise: 5,10,15,20,30,40,50,60,100 mg. Over 100 mg increase in steps of 20-30 mg. If supplemental doses are necessary, give 50% of the dose after 2 hours.

## Dosing

- Use the least invasive route of administration, oral if possible.
- Provide "around-the-clock-dosing" for constant pain at rest. Never provide pain relief only when the patient asks for it (PRN dosing) in palliative care. It takes time before the patient receives the medication and before it is absorbed and effective.
- Provide breakthrough dosing for intermittent pain, e.g. while moving.
- Add recurring breakthrough doses to the routine dose; do not hesitate to give enough.
- Consider continuous parenteral infusion, preferably sc, only when the person:
  - is unable to swallow
  - has intractable nausea
  - has severe diarrhoea
  - has too much medication to swallow.
- When changing the route of administration from PO to parenteral, decrease the dose by 50%.
- If a patient is on continuous infusion, provide breakthrough dosing by adding 1/2 of a normal hourly dose every 30 minutes.
- Respect maximum dosing for NSAID, paracetamol and codeine. There is no maximum standard dose for morphine.

## Side effects

Anticipate and educate about potential side effects: constipation, nausea, dry mouth, sedation, confusion, urinary retention, twitches/jerks, myoclonus.

## Adjuvant drugs

1. To treat adverse effects of analgesics:

- nausea/vomiting (opioid-induced): anti-emetic: haloperidol, chlorpromazine, metoclopramide.
- constipation: in PLWH/A who suffer from untreatable chronic diarrhoea, this side effect is sometimes desired. If there is a problem of constipation, laxatives: Senna tablets 2 x daily is a good starting dose.

2. To enhance pain relief:

- Corticosteroids: they are useful for relieving pain associated with nerve compression or spinal cord compression, and headache from raised intracranial pressure.

3. To treat concomitant psychological disturbances such as insomnia, depression:

- psychotropic drugs: some have an analgesic effect (clomipramine for neuropathic pain); others counteract side effects (haloperidol for opioid induced vomiting). For other patients, an anxiolytic drug such as diazepam is necessary. Diazepam is also useful for muscle spasms.

## 5.2 Neuropathic pain

### Causes

- Direct involvement of the nerve by CMV or HIV
- Post herpetic neuralgia
- Isoniazid, certain chemotherapy (vincristine)
- Kaposi's sarcoma
- Lymphoma
- Squamous cell carcinoma.

There are several types of pain.

- 1. Pain due to nerve compression:** irritation that may evolve into nerve damage. Sharp pain, stabbing, "shooting electrical feeling", e.g. trigeminal neuralgia. There is usually a normal cutaneous sensation. Provide stepwise analgesia and associate carbamazepine: The starting dose is 100 mg 2 x daily. This can be increased slowly, at a rate of 200 mg every few days. Sometimes nerve compression pain only responds when corticosteroids are added. However, these should be given with caution in HIV patients because of additional immunosuppression. **In terminal AIDS care, there should be no hesitation about using corticosteroids.**
- 2. Pain due to nerve damage:** infiltration, e.g. tumour invasion. Burning, tingling, pins and needles. Altered skin sensation: hyperalgesia (skin is painful on light touch, e.g. patient cannot support bed sheets) or hypoalgesia, numbness. Provide stepwise analgesia and associate TCA's (tricyclic antidepressants). TCA's enhance the analgesic effect of opioids. clomipramine: a dose as low as 10 mg may be appropriate for some patients, but most can take 25-50 mg. The dose can be gradually increased (every 3-4 days), as rapidly as can be tolerated in terms of postural hypotension, sedation and dry mouth. The total daily dose should be given at bedtime because of the sedative effect. Maximum dosage: 200 mg daily.
- 3. Neuropathic pain due to isoniazid:** in AIDS patients who receive antituberculous treatment, pyridoxine should always be given to prevent INH neuropathy, in a dose of 10-50 mg daily. (If, despite this, neuropathy develops, the dose should be increased to 100 mg daily.)

## 6 NECESSARY DRUGS AND EQUIPMENT

Level A	Level B	Level C
<b>DRUGS</b>		
Antimalaria drugs	Acyclovir	Acyclovir
Aspirin	Amoxicillin	Amoxicillin
Metoclopramide	Antimalaria drugs	Amphotericin B
(Morphine or Pethidine or Buprenorphine)	Aspirin	Antimalaria drugs
Paracetamol	Carbamazepine	Aspirin
Senna	Chloramphenicol	Carbamazepine
	Clomipramine	Chloramphenicol
	Codeine phosphate	Chlorpromazine
	Diazepam	Clomipramine
	Doxycycline	Codeine phosphate
	Ethambutol	(Dapsone)
	Fluconazole	Dexamethasone
	Indometacin	Diazepam
	INH	Doxycycline
	Metoclopramide	Ethambutol
	(Morphine or Pethidine or Buprenorphine)	Fluconazole
	Nifedipine SL	(Folinic acid)
	Paracetamol	Haloperidol
	Phenytoin	Indometacin
	Prednisolone	INH
	Pyrazinamide	Metoclopramide
	Pyridoxine	Morphine or Pethidine or Buprenorphine
	(Quinolones)	Nifedipine SL
	Rifampicin	Paracetamol
	Senna	Phenytoin
	TMP-SMX	Prednisolone
	Vit B complex	Pyrazinamide
		Pyridoxine
	Benzathine penicillin	(Pyrimethamine)
	Benzylpenicillin	Quinolones
	(Ceftriaxone)	Rifampicin
	Streptomycin	Senna
		(Sulfadiazine)
		Sulphadoxine-pyrimethamine (Fansidar®)
		TMP-SMX
		Tramadol
		Vit B complex
		Benzathine penicillin
		Benzylpenicillin
		Ceftriaxone



Level A	Level B	Level C
		Streptomycin
		TMP-SMX (IV)
LABORATORY AND MEDICAL EQUIPMENT		
	Complete blood count (CBC)	Complete blood count (CBC)
	CSF: cell type/count Gram stain, AFB, India Ink	CSF: cell type/count Gram stain, AFB, India ink + glucose and protein
	Malaria smear	Malaria smear
	Microscope	Microscope
	Sputum AFB	Sputum AFB
	VDRL	VDRL/Toxoplasma serology
		Blood culture
		CSF culture
		Liver and renal function Electrolytes
	Fundoscopy	Fundoscopy
	X-ray	X-ray

### Comments

In the MSF drug list, oral morphine is not available. Because pain is a frequent problem in AIDS care, and because we want to promote home care (in one way or another) as much as possible, oral morphine should be available at level C and, sometimes, at level B when confronted with a large number of AIDS patients. The prescription and the dose adjustment should be supervised/authorised by a medical doctor.

The sustained release form (MS-Contin®) is not appropriate for AIDS patients because of malabsorption problems due to HIV enteropathy and frequent diarrhoea.

Buprenorphine: sublingual form is useful in patients who cannot swallow.

Flucytosine is not listed, as it is not perceived as essential.

Sulfadiazine and pyrimethamine: can be replaced by TMP-SMX for the treatment of Toxoplasma brain abscess.

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**1 INTRODUCTION**

Chronic diarrhoea is a very frequent and frustrating problem in PLWH/A, of whom at least 50% experience it at some time during the evolution of the disease. It is often accompanied by nausea, weight loss, abdominal cramps and dehydration. There is often an intermittent watery diarrhoea, without blood or mucus. In one-third to two-thirds of cases, no cause is identified.

In areas with a high prevalence of HIV infection, chronic diarrhoea is almost invariably due to symptomatic HIV infection. Whenever possible, the cause of the diarrhoea should be established and specific treatment provided. Failing this, management is symptomatic. A high energy and protein intake reduces the degree of muscle wasting. The use of anti-diarrhoeal agents such as codeine phosphate is justified when symptomatic relief is a major consideration.

Prevention consists of: attention to personal hygiene (hand-washing), drinking boiled water, and eating only thoroughly cooked meat and vegetables.

**2 OPPORTUNISTIC INFECTIONS AS CAUSE OF DIARRHOEA IN AIDS PATIENTS<sup>1-3</sup>**

An infectious agent can be identified in about 50% of patients with AIDS-associated diarrhoea.<sup>4</sup> The differential diagnosis includes the following pathogens:

**Bacterial infection:** *Campylobacter*, *Shigella*, and *Salmonella* species  
**Protozoal infection:** *Cryptosporidium* species, *Giardia lamblia*, *Isospora belli*, *Entamoeba histolytica*, *Microsporidium* species  
**Toxin induced:** *E. Coli* and *Clostridium difficile*  
**Mycobacterial infection:** *M. avium* complex, *M. tuberculosis*  
**Helminthic infection:** *Strongyloides stercoralis*  
**Fungal infection:** *Candida* species (seldom a cause of diarrhoea)  
**Viral infection:** Cytomegalovirus, Herpes simplex virus

These conditions should be differentiated with:

**AIDS enteropathy:** direct cytopathic effect of HIV disease.

**Non-infectious disorders:** Kaposi's sarcoma, lymphoma

## 2.1 Bacterial gastroenteritis

Invasive bacterial pathogens such as *Campylobacter*, *Shigella* and *Salmonella* species can cause severe and prolonged illness in PLWH/A.

**Salmonellosis** is a frequent cause of bacteraemia in PLWH/A. The only symptoms can be fever and general malaise, sometimes without GI symptoms. Treatment consists of: TMP/SMX 960 mg 2 x daily or chloramphenicol 250 mg 4 x daily for 3 weeks. In case of signs of sepsis, IV therapy is necessary. Shorter regimens are: ciprofloxacin 500 mg 2 x daily or ofloxacin 400 mg 2 x daily or ceftriaxone 2 g IV for 7-10 days. However, a lot of patients relapse after treatment and chronic maintenance therapy (TMP/SMX 1DD daily) is sometimes necessary.

**Shigella** infection usually manifests with high fever, abdominal pain and bloody diarrhoea. Treatment consists of TMP/SMX 960 mg 2 x daily for 5 days or amoxicillin 500 mg 3 x daily for 5 days. In many developing countries, however, resistance of *Shigella* (and *Salmonella*) to TMP/SMX and amoxicillin has increased. The antibiotic of choice has become ciprofloxacin 500 mg 2 x daily or norfloxacin 400 mg 2 x daily for 5 days, or nalidixic acid 1 g 4 x daily for 10 days.

**Campylobacter** enteritis is characterised by fever, bloody diarrhoea, abdominal pain and weight loss. After the diagnosis has been confirmed by stool culture, erythromycin (500 mg 2 x daily for 5 days) is the first choice treatment. Fluoroquinolones are also effective but resistance rates of 30%-50% have been reported in Spain, Greece and some developing countries.

It is clinically impossible to distinguish the different agents without stool culture. Therefore, if empiric therapy with TMP/SMX is not effective in patients with bacillary dysentery, fluoroquinolones can be tried, followed by a trial of erythromycin if symptoms of bloody diarrhoea persist.

## 2.2 Cryptosporidiosis

*Cryptosporidium parvum* is a small, obligate, intracellular protozoan that occurs widely in nature and causes disease in cattle and humans. Cryptosporidia are highly infectious and can be transmitted through water, food, animal-to-human and human-to-human contact. Because of cryptosporidia's ubiquity and ease of transmission, people with compromised immune systems should take special precautions to avoid exposure. It is recommended that people with HIV and a CD4<200 should boil tap water for at least one minute to reduce the risk of ingestion of the oocysts in potentially contaminated public drinking water.

Cryptosporidium is an important cause of debilitating watery diarrhoea and weight loss in HIV-infected patients. The small bowel is extensively colonised and invasion of the biliary tree occasionally results in stenosis and cholecystitis. In PLWH/A with CD4>200, cryptosporidiosis manifests as an acute self-limiting disease that does not require treatment. In patients with lower CD4 counts, it

may present as chronic diarrhoea or as fulminant disease with 20 or more stools a day. The organism can be easily detected in the stool by using a modified acid-fast stain.

Before the introduction of HAART, the diagnosis of cryptosporidiosis was associated with increased mortality. Median survival in the US was 200 days for HIV patients who had diarrhoea due to cryptosporidiosis.

The use of ARV is protective against cryptosporidiosis.<sup>5</sup> Therefore ARV may be the most effective therapy for this protozoan infection. Paromomycin (500 mg 4 x daily for 2 weeks; maintenance 500 mg 2 x daily), an orally poorly absorbed aminoglycoside, has been evaluated in small and uncontrolled studies. One clinical controlled trial, involving only 10 patients, showed a decrease in daily stool excretion and total oocysts excretion.<sup>6</sup>

### **2.3 *Isospora belli* infection**

*Isospora belli* infection presents in a way that is clinically indistinguishable from disease caused by *Cryptosporidium*. It may be detected in stools by the same techniques as those developed for *Cryptosporidium* species. *Isospora belli* oocysts are relatively big (20-30 µm) and can be easily identified in unstained wet preparations.

Most cases are readily treatable with a high dose of TMP/SMX (1DS = double strength = 800 mg sulfamethoxazole and 160 mg trimethoprim) 4 x daily for 10 days, followed by 1DS 2 x daily for 3 weeks, then chronic suppression with the same dose of TMP/SMX as used for PCP prophylaxis (1DS daily or 1DS 3 x weekly as tolerated). As with all HIV patients at clinical stages 2, 3 and 4, TMP/SMX prophylaxis is recommended. This will also provide protection against *Isospora belli*. In settings where primary prophylaxis with TMP-SMX is implemented, this is a rare parasite (the same is true for *Cyclospora*).

### **2.4 *Cyclospora***

*Cyclospora* infection also occurs in HIV-infected patients. It is rarely found in patients on TMP/SMX prophylaxis. *Cyclospora* also stains with modified acid-fast stain. It is important to distinguish the larger *Cyclospora* oocysts (8-9 µm) from the smaller cryptosporidium oocysts (5 µm) because the treatment is different. TMP-SMX 1DS 4 x daily for 10 days, followed by secondary prophylaxis with TMP/SMX.

### **2.5 Microsporidiosis**

The most common manifestation of intestinal microsporidiosis in PLWH/A is profuse, watery, non-bloody diarrhoea, sometimes accompanied by abdominal pain and cramping, nausea, vomiting and weight loss. Species of microsporidia have been linked with disseminated disease: cholangitis, keratoconjunctivitis,

hepatitis, peritonitis and infections of the lungs, muscles and brain. However, the presence of microsporidia does not always correlate with symptomatic disease. Diagnosis is made by modified trichrome stain to identify the spores in stool specimens.

Most of the microsporidial infections are not treatable. Only the *Encephalitozoon* species responds clinically (reduction in diarrhoea and weight gain) to Albendazole 400 mg 2 x daily for 2-4 weeks.<sup>7</sup> However, parasites are not cleared and long-term therapy is often needed. *Enterocytozoon bieneusi* does not respond to treatment.

## 2.6 Mycobacterium Avium Complex (MAC)

Organisms of the MAC comprise two closely related species: *M. avium* and *M. intracellulare*. The organism is ubiquitous in the environment and disseminated infection results from recent infection rather than reactivation of a previous infection. Infection is rare in patients with CD4>100. The most common findings at diagnosis are fever and severe anaemia (denoted by a haematocrit of <26 percent). More than 70% of patients have gastrointestinal or hepatobiliary symptoms: diarrhoea, abdominal pain, hepatomegaly, and increased alkaline phosphatase levels.

Disseminated MAC infection is most readily diagnosed by mycobacterial culture of blood or bone marrow. In developing countries, very little data is available about MAC incidence in HIV-infected people.

MAC infection occurs in patients with advanced disease, and the median survival after the initial diagnosis is around 3 months.<sup>8</sup> Treatment is expensive and often not very beneficial (azithromycin or clarithromycin + ethambutol + ciprofloxacin or clofazimine).

## 2.7 Clostridium difficile

*Clostridium difficile* may be underestimated as a cause of diarrhoea in AIDS patients in the tropics because of difficulty in making the diagnosis. In a study of causes of diarrhoea in Peruvian AIDS patients, *Clostridium difficile* was the most prevalent pathogen and it was associated with a significant increase in mortality. Frequent hospitalisation and exposure to antibiotics puts AIDS patients at high risk of infection with the toxin-producing strain of *C.difficile*.<sup>9</sup> Treatment is with metronidazole 500 mg x 3 daily for 7 days.

As in HIV-negative patients, 5%-30% of patients with *Clostridium-difficile*-associated diarrhoea experience relapse.



## 2.8 *Strongyloides stercoralis*

*S. stercoralis* can complete its life cycle entirely within the human host.<sup>10</sup> As a result, the burden of adult worms in infected humans can increase substantially through a cycle of auto-infection. In immunocompromised patients, it can cause overwhelming infection, especially when cell-mediated immunity is impaired. This serious complication is called strongyloides hyper-infection syndrome and has a high case-fatality rate.

Strongyloides infection should be suspected in patients who have serpiginous erythematous skin lesions (larva currens), diarrhoea, abdominal pain and cough. Full-blown hyper-infection syndrome has the characteristics of a Gram-negative sepsis, with ARDS\*, DIC† and secondary peritonitis. The chest radiograph reveals diffuse pulmonary infiltrates. Hyper-infection strongyloidiasis is generally associated with other conditions of depressed host cellular immunity. Disseminated strongyloidiasis and heavy worm loads can occur in patients with HIV, but the full-blown hyper-infection syndrome is less common.<sup>11,12</sup> The likelihood of developing the hyper-infection syndrome is also increased in patients taking high-dose steroids.

In uncomplicated strongyloidiasis, the sensitivity of a single stool examination to detect filariform larvae is low. In HIV patients, this is probably higher because of higher worm burdens. In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, broncho-alveolar lavage fluid, pleural fluid, peritoneal fluid and surgical drainage fluid.

Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days, and this drug is also considered by some as the drug of choice for the treatment of systemic strongyloidiasis.<sup>10</sup> An alternative treatment is albendazole 400 mg 2 x daily for 5 days. A maintenance therapy once a month is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).

## 2.9 AIDS enteropathy

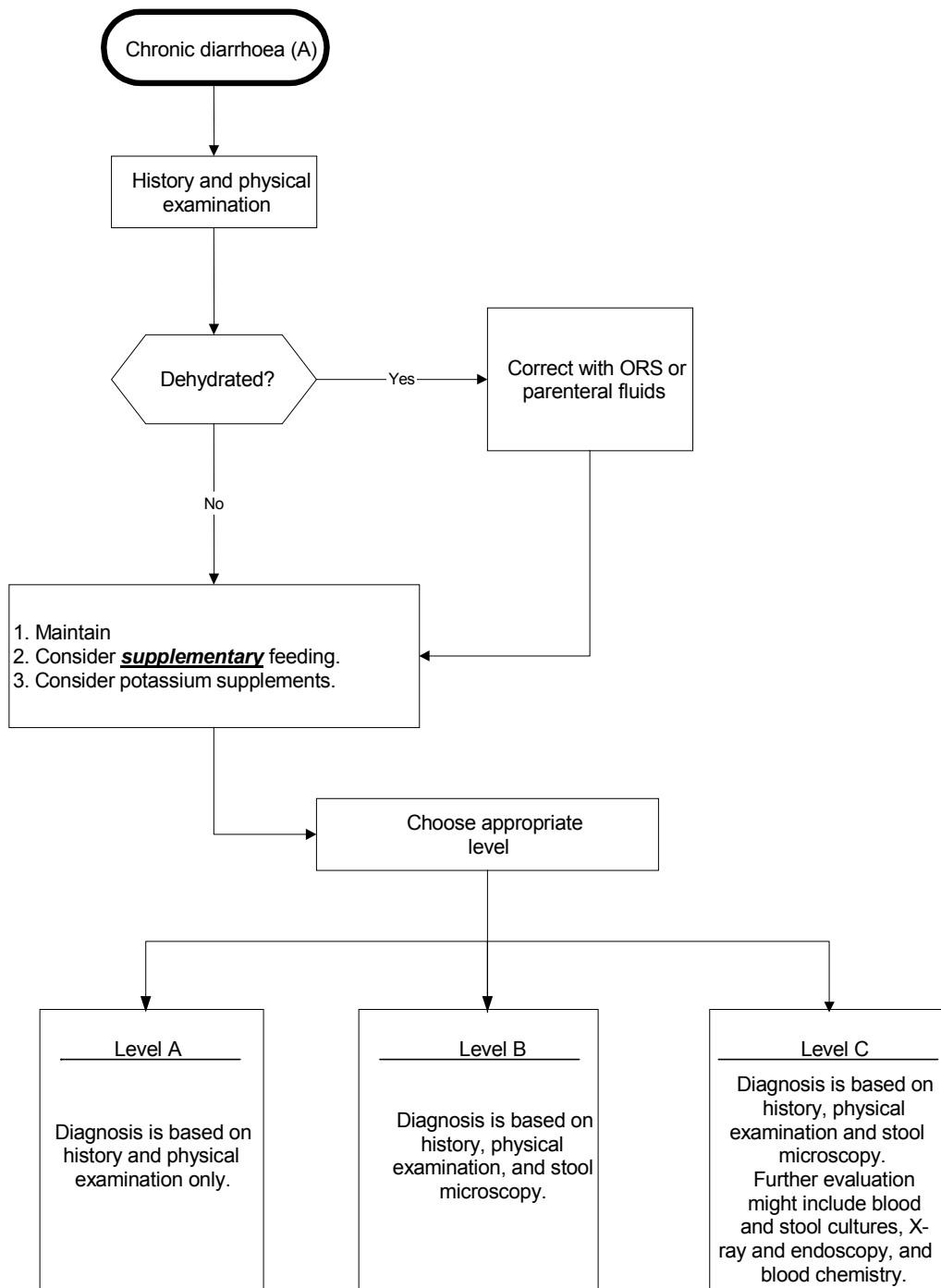
Patients can be identified with symptoms of diarrhoea and weight loss, but without any known parasite. Several hypotheses about the pathogenesis have been put forward. It may be due to unknown or undetected enteric pathogens or it might be a result of a direct mucosal HIV infection by the virus. A third suggestion is that bacterial overgrowth, possibly related to gastric hypo-acidity, may play a role.

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\* Acute respiratory distress syndrome

† Disseminated intravascular coagulation

### 3 CLINICAL MANAGEMENT OF DIARRHOEA



## **Annotations chronic diarrhoea**

(A) Definition: liquid stools 3 or more times daily, continuously or episodically for more than one month in a patient with HIV infection.

Aetiology is listed in the introduction.

It is important to obtain the following anamnesis data in a patient with diarrhoea:

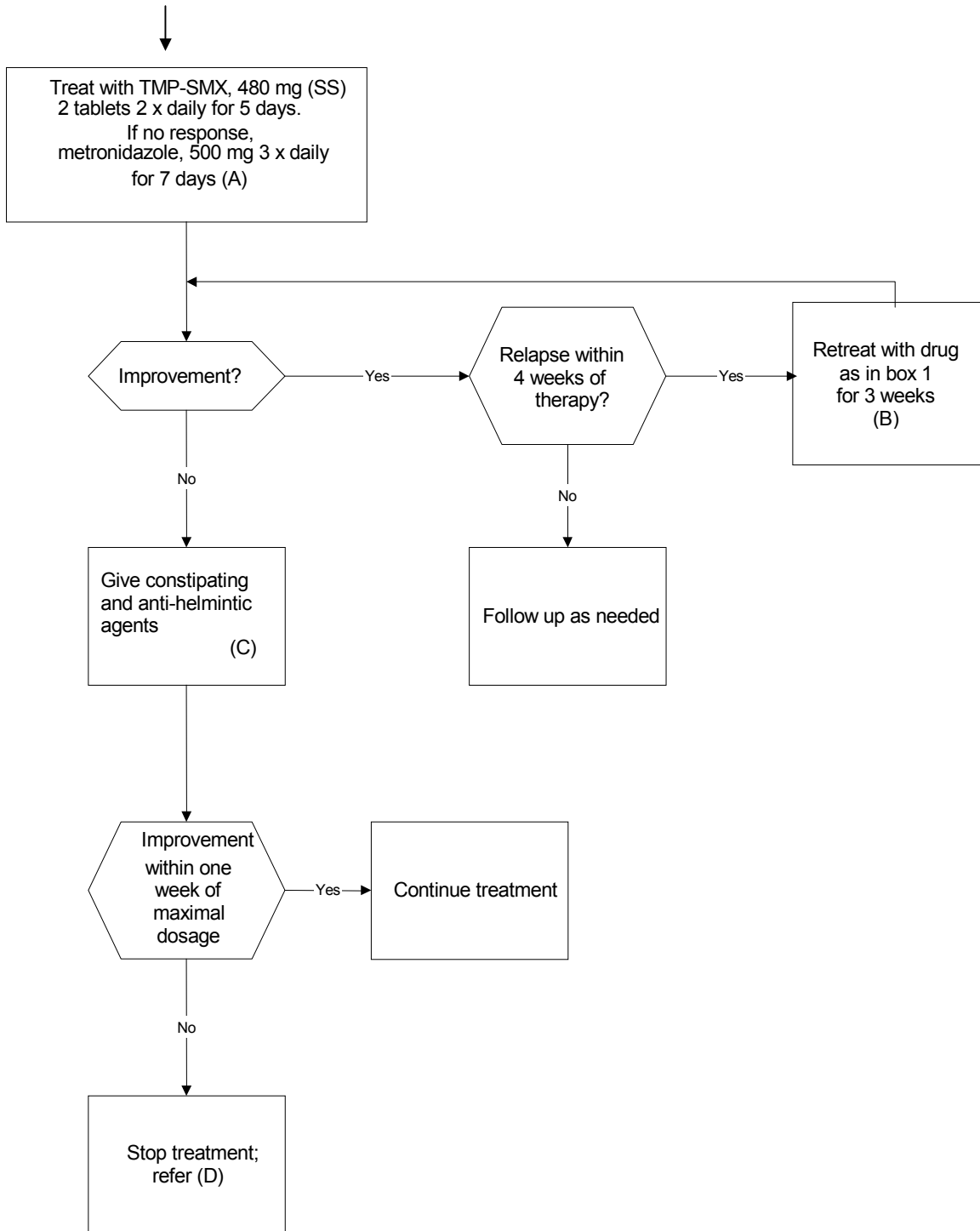
- fever
- blood or mucus in the stools
- drugs
- previous antibiotic use and hospitalisation.

A physical examination should assess the degree of hydration and the nutritional status.

Nutritional support is very important to avoid wasting. Try giving regular small meals as tolerated by the patient. At least 2500 kcal daily are needed.

At all levels of care, time must be taken to instruct the patient's family about how to handle soiled bed linen and the disposal of faeces. It may be necessary to give them appropriate material (gloves, buckets, etc.).

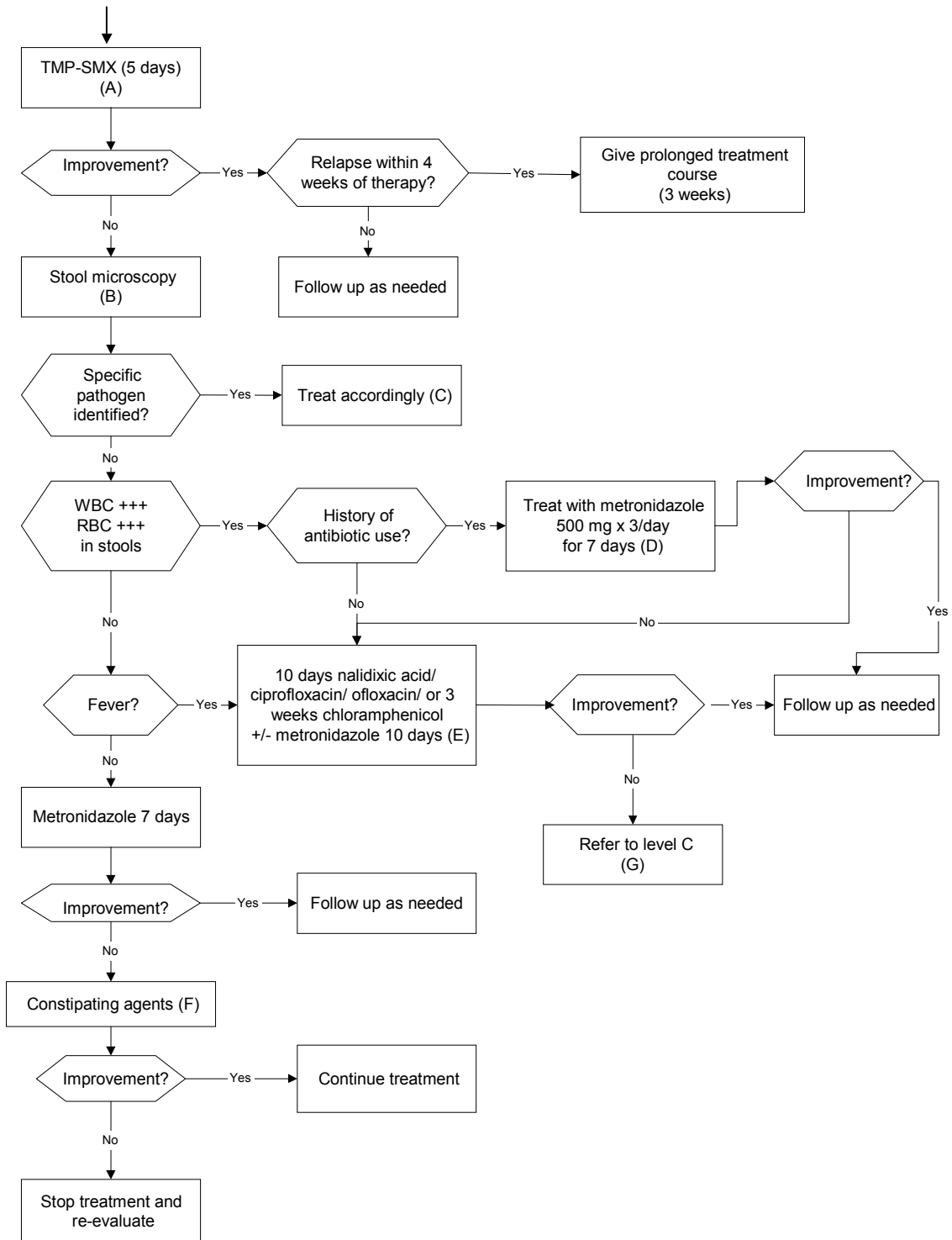
Continued from flowchart 1



### **Annotations chronic diarrhoea (level A)**

- (A) TMP-SMX. Any episode of diarrhoea in an AIDS patient lasting longer than 5 days is worth an empirical treatment with antibiotics, in association with ORS. If there is no response, a course of metronidazole should be given. Both drugs cover common bacterial infections, and bacterial overgrowth.
- (B) It is possible that the initial treatment was too short. A prolonged course of the therapy that was effective (3 weeks) is justified.
- (C) For example, loperamide, 4 mg initially, followed by a further 2 mg after each liquid stool. The maximum daily dose should not exceed 16 mg. An alternative is codeine phosphate 30-60 mg 3-6 x daily. Constipating agents should not be given to patients with bloody diarrhoea.  
An anti-helminthic drug should be given first (mebendazole 100 mg 3 x daily for 7 days is partially effective against strongyloidiasis. Albendazole 400 mg daily for 3 days is a broader spectrum anti-helminthic but not often available at home-care level).
- (D) When diarrhoea is disabling, refer to a centre with better care facilities.

Continued from flowchart 1



### **Annotations chronic diarrhoea (level B)**

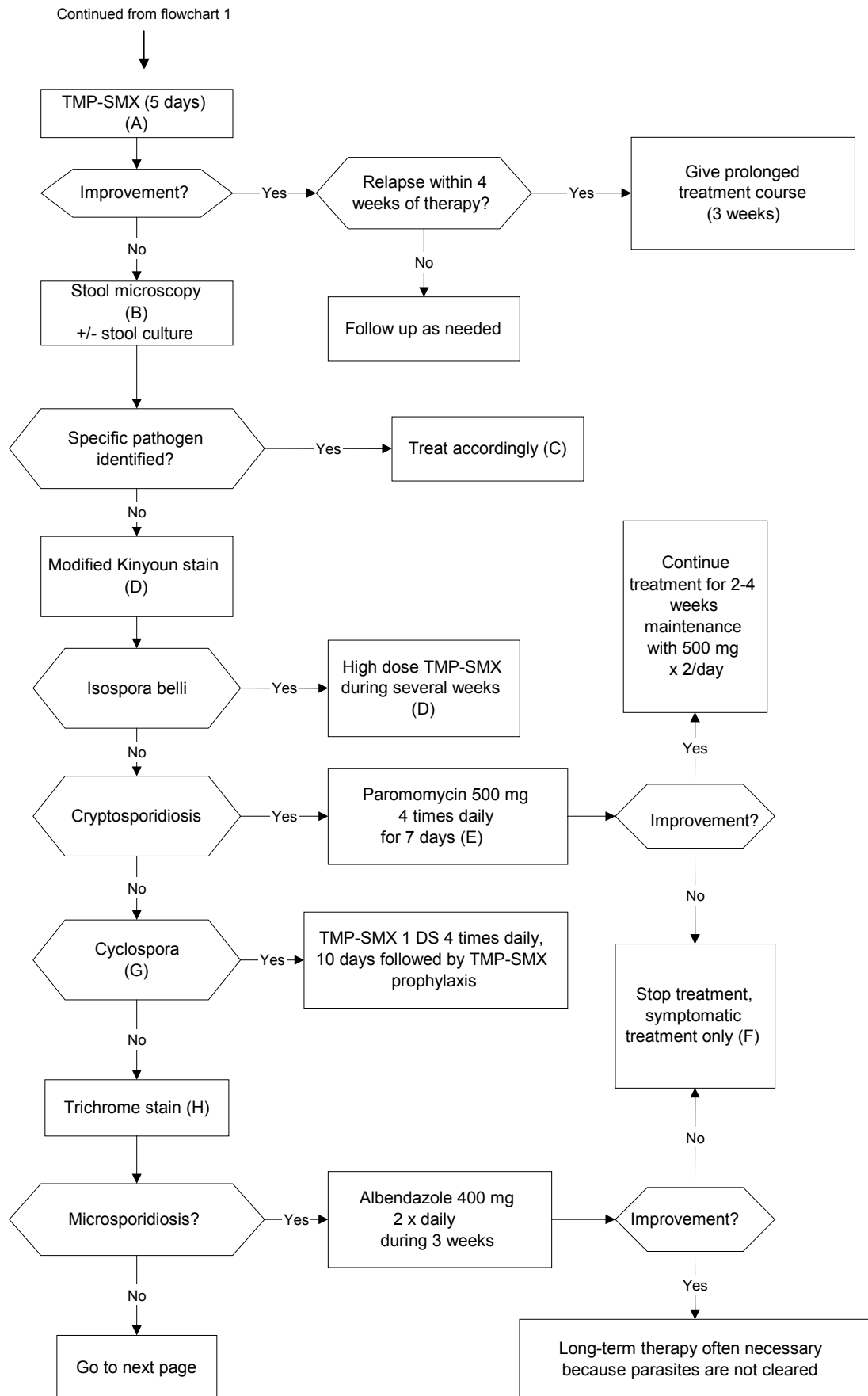
- (A) If the patient was not yet treated, a trial with antibiotics is justified, always associated with ORS and feeding instructions. Avoid repeating a treatment that brought no improvement. If the patient has already received a treatment for this episode of diarrhoea without success, a stool examination should be performed for the detection of specific pathogens. Three stool samples may increase the diagnostic yield of parasites.
- (B) A fresh stool examination (direct and after concentration) and a lugol stained wet mount is necessary at this level.
- (C) In the case of a helminthic infection, treat accordingly. Strongyloidiasis can be successfully treated with ivermectin 12 mg daily for 3 days. An alternative treatment is Albendazole 400 mg 2 x daily for 5 days. A once-monthly maintenance therapy is necessary (albendazole 400 mg or ivermectin 6 mg once monthly). Trophozoites of *Entamoeba histolytica* should be treated with metronidazole 750 mg 3 x daily for 10 days followed by a contact-amoebicide: diloxanide furoate (Furamide®) 500 mg 3 x daily for 10 days or paromomycin 500 mg 3 x daily for 7 days. (In some countries Intetrix® is still available: 1 caps. 4 x daily for 10 days). *Giardia lamblia* is treated with metronidazole 750 mg 3 x daily for 5 days. *Isospora belli* is treated with higher than usual TMP-SMX: 1DS 4 x daily for 10 days followed by 1 DS 2 x daily for 3 weeks. Single doses are not recommended in HIV patients because of unreliable gastric absorption.
- (D) As in HIV-negative patients, 5%-30% of patients with *Clostridium*-associated diarrhoea relapse. The treatment with metronidazole should be repeated.<sup>9</sup>
- (E) In a long-lasting or severe diarrhoea with fever, a combination of metronidazole with an antibiotic effective on the local strains of bacterial enteric pathogens is warranted. Empiric therapy with quinolones is most likely to be effective: nalidixic acid 1 g 4 x daily for 10 days or ciprofloxacin 500 mg 2 x daily for 10 days or ofloxacin 400 mg 2 x daily for 10 days. Although chloramphenicol has become unacceptable for use in certain countries, it remains a valuable drug for severe Gram-negative infections, and it is more readily available at level B. If there is no response, bacterial resistance or the presence of a parasite not responding to metronidazole must be considered. As this point, a course of erythromycin might be tried in a dose of 500 mg 2 x daily for 5 days for *Campylobacter* dysentery.
- (F) E.g. loperamide 4 mg initially, followed by a further 2 mg after each liquid stool. The maximum daily dose should not exceed 16 mg. An alternative is codeine phosphate 30-60 mg 3-6 x daily. Constipating agents should not be given to patients with bloody diarrhoea.

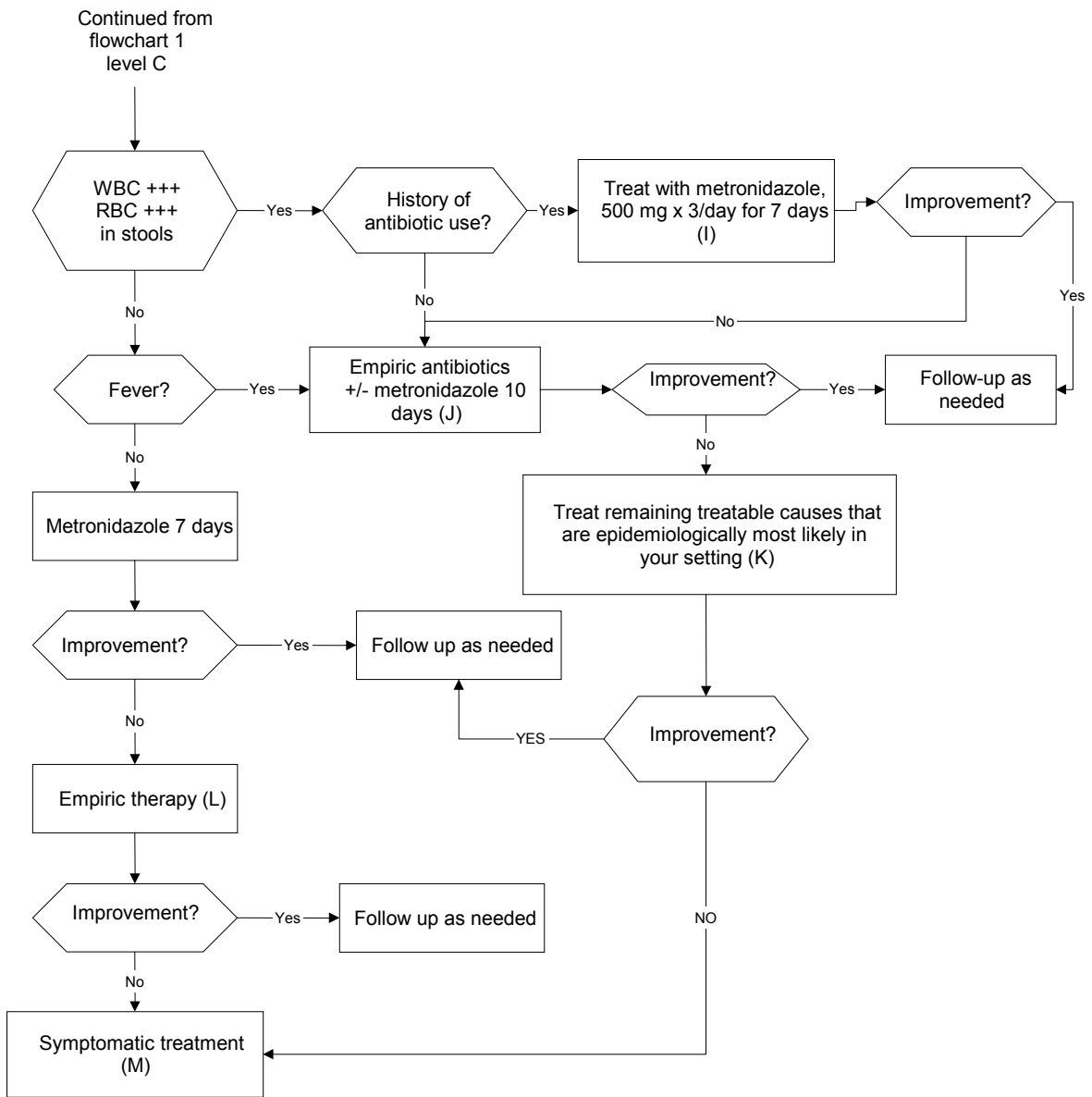
(G) At level C, special stains or stool cultures could be performed to identify remaining treatable conditions. If referral is not possible (low geographical or financial accessibility), a treatment trial for remaining treatable causes should be started.

- Resistant bacteria: it is important to obtain information on prevailing resistance patterns in your region. E.g. in Nairobi, most of the salmonellae and shigellae are resistant to co-trimoxazole, amoxicillin and chloramphenicol. However, they remain sensitive to quinolones and nalidixic acid.<sup>13</sup>
- *Isospora belli*: a parasite sometimes encountered, will respond to higher than usual doses of CTX (1DS 4 x daily for 10 days followed by 1 DS 2 x daily for 3 weeks) This infection is less likely to occur, however, in patients who are on TMP-SMX prophylaxis.
- Albendazole will be effective on strongyloides and may have an effect on microsporidia.



# Chronic diarrhoea (1)





### **Annotations chronic diarrhoea (level C)**

(A) A trial of antibiotics is only justified if we are dealing with a new case of diarrhoea. Always consider previous treatment in order to avoid re-running the same algorithms every time without success. If your patient is referred from level B, and has reached the point that referral was necessary, start immediately with the stool examination.

(B) *Stool microscopy*: fresh examination and after concentration. Multiple stool samples may be necessary.<sup>5</sup>

*Stool culture*: if available, will be useful to detect resistant enteropathogens. Systematic stool culture at this level may also help in orienting empiric therapy at the lower levels of care.

(C) See annotation C level B.

(D) *Cryptosporidium* and *Isospora belli* are identified in the stool with use of a modified acid-fast stain (see: *Laboratory* section at the end of this chapter). *Isospora* cysts are much larger than those attributable to *Cryptosporidium* species (20-30  $\mu\text{m}$  vs. 4-6  $\mu\text{m}$ ). The distinction between them is important because *Isospora belli* usually responds well to high dose TMP-SMX (1DS 4 x daily for 10 days, followed by 1DS 2 x daily for 3 weeks, then chronic suppression with 1DS a day (PCP prophylaxis dose).

(E) There is no good treatment for cryptosporidiosis. Often symptomatic control with anti-diarrhoeal agents is the only recourse. Sometimes there is a partial response with paromomycin (500 mg 4 x daily). If there is a response, treatment should be continued for 2-4 weeks, after which it is often necessary to maintain the patient on suppressive therapy with paromomycin 500 mg 2 x daily.

(F) Loperamide or codeine phosphate. For symptomatic treatment see: *Palliative Care* section. Treatment is often not successful, especially for cryptosporidiosis and microsporidiosis. Do not continue an ineffective treatment. Switch to symptomatic treatment.

(G) On rare occasions, *Cyclospora*, another protozoa, can be detected on the stains for *Cryptosporidium*. The *Cyclospora* oocysts are a little bit bigger (8-9  $\mu\text{m}$ ) than cryptosporidium oocysts (5  $\mu\text{m}$ ). *Cyclospora* can be treated with TMP-SMX 1DS 4 x daily for 10 days, followed by secondary prophylaxis with TMP-SMX.

(H) *Microsporidia*: Thin smears of unconcentrated stool-formaline suspension or of duodenal aspirates stained with Weber's modified trichrome method.

(I) Frequent hospitalisation of AIDS patients and exposure to antibiotics puts them at high risk of infection with the toxin-producing strain of *Clostridium difficile*.<sup>9</sup> 5%-30% of patients with *Clostridium*-associated diarrhoea relapse. The same treatment with metronidazole should be repeated.

- (J) When no specific pathogens are identified, or when stool culture is not available, empiric antibiotherapy is justified. For watery diarrhoea: high dose TMP-SMX for isosporiasis; for dysenteric stools (WBC + RBC): nalidixic acid, or another quinolone (ciprofloxacin or ofloxacin) for resistant shigellae and salmonellae. If not yet treated with metronidazole, it can be added at this point; giardiasis and amoebiasis are then treated as well.
- (K) In case of non-response, bacterial resistance or the presence of a parasite not responding to metronidazole must be considered. A trial with albendazole (Microsporidium and strongyloidiasis) or a higher-than-usual dose of TMP-SMX (*Isospora belli*) can be tried. The choice will depend on the existing epidemiology of gastro-intestinal pathogens in the region where you are working.
- (L) See annotation (J). Giardiasis should have responded. If *Campylobacter* was diagnosed from stool culture, the first choice treatment is now erythromycin 500 mg 2 x daily for 5-10 days.
- (M) Once this flowchart has been followed through without result, we remain with untreatable conditions: CMV, *Cryptosporidium*, atypical *Mycobacteria*, etc. Continue with palliative care.

## 4 SYMPTOMATIC AND PALLIATIVE CARE<sup>14</sup>

### 4.1 Diarrhoea

At all levels of care, we must take time to instruct the patient's family in how to handle soiled bed linen and the disposal of faeces. It may be necessary to give them appropriate material (gloves, buckets, etc.).

- Maintain adequate hydration.
- Assure ready access to a bathroom or toilet.
- Use devices for incontinence (protective bed coverings, clothes, sheets, nappies, etc.) to prevent soiling.
- Keep the peri-anal region dry. If fissures or ulcers develop, use sitz baths to improve hygiene and cover the lesions with zinc oxide ointment.
- Deodorise.
- Maintain dignity and privacy while toileting.
- Maintain good peri-anal care.

### 4.2 Transient diarrhoea

This can be managed by:

- Actapulgite: 2 tablespoons PRN (when needed), (in combination with furazolidone in home-care project in Nairobi).
- Aluminium antacids: 15-30 ml PO 6 x daily PRN.
- Bismuth salts: 15-30 ml 2-4 x daily.

### 4.3 Cramping

If cramping is a problem, foods that may cause gas or cramps should be avoided: beans, cabbage, cauliflower, highly spiced foods, sweet or carbonated drinks. Increase bulk by providing fibres.

### 4.4 Peristalsis

This can be reduced by:

- Diphenoxylate (Lomotil®): 2,5-5 mg 4-6 x daily, max 20 mg/24hr.
- Loperamide (Imodium®) 4 mg PO first dose followed by 2 mg-4 mg after each unformed stool (max 16 mg daily).
- Codeine 30-60 mg 3-6 x daily. Maximum dose = 200-300 mg in a day.
- Strong opioids: morphine
  - for opioid-naïve: morphine 5-10 mg PO, SC every 4 hours
  - for those already receiving opioids: increase the dose by 25%-50%, or add codeine.

## 5 NECESSARY DRUGS AND EQUIPMENT

level A	level B	level C
	<b>DRUGS</b>	
Actapulgit ( +/- furazolidone)	Actapulgit ( +/- furazolidone)	Actapulgit ( +/- furazolidone)
Aluminium hydroxide	Albendazole	Albendazole
Codeine phosphate	Aluminium hydroxide	Aluminium hydroxide
Loperamide	Chloramphenicol	Chloramphenicol
Mebendazole	Codeine phosphate	Codeine phosphate
Metronidazole	Contact amoebicide paromomycin or diloxanide furoate	Contact amoebicide paromomycin or diloxanide furoate
Morphine (medical prescription)	Erythromycin	Erythromycin
ORS	Ivermectin	Ivermectin
TMP-SMX	Loperamide	Loperamide
Zinc oxide ointment	Mebendazole	Mebendazole
	Metronidazole	Metronidazole
	Morphine (medical prescription)	Morphine (medical prescription)
	ORS	ORS
	Quinolones (ciprofloxacin or ofloxacin or nalidixic acid)	Quinolones (ciprofloxacin or ofloxacin or nalidixic acid)
	TMP-SMX	TMP-SMX
	Zinc oxide ointment	Zinc oxide ointment
	Parenteral fluid: normal saline with KCL Ringer Lactate	Parenteral fluid: normal saline with KCL Ringer Lactate
	<b>LABORATORY</b>	
	Stool microscopy: fresh and lugol wet mount	Blood chemistry (electrolytes)
		Formol-ether concentration method
		Modified Kinyoun stain
		Stool microscopy: fresh and lugol wet mount
		Trichrome stain

## 6 LABORATORY TECHNIQUES<sup>‡</sup>

### 6.1 Level B

- *Stool microscopy*: multiple stool samples may be necessary.<sup>5</sup> Examine the stools fresh and after concentration (the formol ether concentration technique is most frequently used).

### 6.2 Level C

- *Modified acid-fast stain*: Formaline specimens are concentrated by the formaline-ethyl acetate procedure. Formaline-treated concentrated stool sediment is coloured with modified Kinyoun (carbol fuchsin) staining. *Cryptosporidium* cysts stain pink and are small (5 µm). *Cyclospora* are a little bigger (8-9 µm) and *Isospora belli* oocysts are very big (20-30 µm).
- *Weber's modified trichrome method*: for the detection of microsporidia. Thin smears of unconcentrated stool-formaline suspension or of duodenal aspirates are stained (100 oil immersion fields should be examined). Against a blue or green counter stain, the microsporidia spores stain pink with a clear posterior vacuole and a pink diagonal stripe within the spore. Spores are small, 1-3 µm x 1,5 - 4 µm.
- *Stool culture*.

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<sup>‡</sup> Techniques are described in detail in 'District Laboratory Practice in Tropical Countries' Part 1. Monica Cheesbrough. Tropical Health Technology. Cambridge University Press 1998.

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# HIV 9. LYMPHADENOPATHY

## 1 INTRODUCTION

Swelling of lymph nodes is a frequently encountered symptom in HIV-positive patients. It is important to carry out a careful history and physical examination. The cause of lymphadenopathy often becomes obvious. In more complicated cases, laboratory tests and a lymph node biopsy may be necessary to establish a definite diagnosis.

## 2 OPPORTUNISTIC INFECTIONS

The differential diagnosis includes the following aetiologies:

**HIV-related:** persistent generalised lymphadenopathy (PGL)  
**Opportunistic infections:** tuberculous lymphadenitis, CMV, toxoplasmosis, infections with *Nocardia* species, fungal infections (histoplasmosis, penicilliosis, cryptococcosis, etc.)  
**Reactive Lymphadenopathy:** pyomyositis, pyogenic skin infections, ear, nose and throat (ENT) infections  
**STI:** syphilis, inguinal lymphadenopathy due to donovanosis, chancroid or lymphogranuloma venereum (see: STI guidelines produced by WHO or MSF)  
**Malignancies:** lymphoma, Kaposi's sarcoma.

These aetiologies should be differentiated with others causes of lymphadenopathies, such as: carcinomatous metastases, brucellosis, visceral leishmaniasis (kala azar), sarcoidosis, trypanosomiasis, rickettsial disease, infectious mononucleosis and drug reactions (e.g. phenytoin hypersensitivity).

### 2.1 Persistent generalised lymphadenopathy (PGL)

PGL is a feature of HIV infection that develops in up to 50% of HIV-infected individuals. Up to one-third do not have any other symptom on presentation (WHO clinical stage 1). There is no specific treatment. The diagnostic criteria for PGL are as follows:

Lymph nodes larger than 1,5 cm in diameter, in 2 or more extra-inguinal sites, of 3 or more months duration.

The nodes are non-tender, symmetrical, and often involve the posterior cervical, axillary, occipital and epitrochlear nodes. PGL may slowly regress during the course of HIV infection and may disappear before the onset of AIDS. In populations with a high HIV prevalence, PGL is the commonest cause of lymphadenopathy. In HIV-positive patients, PGL is a clinical diagnosis. No further examinations are necessary, unless there are features of another disease.

On levels B and C: patients with generalised lymphadenopathy should have a CBC and a chest X-ray, before accepting the diagnosis of PGL.

### **Features of lymph nodes that indicate further investigation:<sup>1</sup>**

- large (>4 cm diameter) or rapidly growing lymph nodes
- asymmetrical lymphadenopathy
- tender/ painful lymph nodes not associated with a local infection
- matted/fluctuant lymph nodes
- obvious constitutional symptoms (fever, night sweats, weight loss)
- hilar or mediastinal lymphadenopathy on chest X-ray
- suspicion of pulmonary TB
- evidence of abscesses (cutaneous, pulmonary, etc).

## **2.2 Tuberculous lymphadenopathy**

This is one of the commonest forms of extra-pulmonary TB in HIV patients. The lymph nodes most commonly involved are the cervical nodes. The usual course of lymph node disease is as follows:

Firm, discrete nodes → fluctuant nodes matted together → skin breakdown, abscesses, chronic sinuses → healing with scarring.

Fluctuant cervical nodes that develop over weeks to months without significant inflammation or tenderness suggest infection with *M.tuberculosis*, atypical mycobacteria or cat scratch disease (*Bartonella henselae*).

In severe immunocompromised patients, tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis. In HIV patients there is a high rate of positive smears for acid-fast bacilli on fine-needle aspirates of the involved lymph nodes. In smear-negative pulmonary TB it is worthwhile aspirating extra-thoracic lymph nodes to confirm the diagnosis of TB (80% positive). Miliary TB is an important consideration in patients with generalised lymphadenopathy.

Treatment should be started following the national TB guidelines. For further details, see: *Respiratory Problems*, chapter 6: section 2.1.

## **2.3 Nocardiosis**

While nocardiosis is a rare cause of lymphadenitis in immune-competent patients, the diagnosis should be considered in HIV-infected patients with chronic lymphadenopathy and abscesses (skin, pulmonary, etc.). The organism

may stain weakly on acid-fast staining. However, they are morphologically different, from the Koch bacilli because of their long branching thread-like filaments. Nocardia organisms are easily recognised on Gram stain. The recommended treatment for Nocardia is TMP/SMX 10/50 mg/kg 2 x daily or minocycline 100 mg 2 x daily combined with amikacin 15-25 mg/kg daily or ceftriaxone 2 g daily combined with amikacin. The use of aminoglycosides should be limited to 2 weeks. See also *Respiratory Problems*, chapter 6, section 2.2.

## 2.4 Fungal infections (*histoplasmosis, penicilliosis, cryptococcosis*)

Disseminated fungal infections can present with fever and lymphadenopathy. There are often skin lesions (*Penicillium Marneffeii*, *Cryptococcus Neoformans*) or lung lesions (*Histoplasma Capsulatum*) also. Biopsy for histology and culture of skin lesions or lymph nodes often reveals the diagnosis.

Initial treatment for *histoplasmosis* and *penicilliosis* is amphotericin B for moderate-to-severe cases, and oral itraconazole for mild cases. Itraconazole 200 mg daily is the preferred lifelong maintenance therapy. If itraconazole is not available, use ketoconazole 400 mg daily. For *cryptococcosis*, 2 weeks amphotericin B (IV) 0,7 mg/kg daily followed by fluconazole 400 mg once a day for 8-10 weeks. After that, maintenance therapy consists of fluconazole 200 mg once a day.

## 2.5 Secondary syphilis

Generalised painless lymphadenopathy occurs in 90% of patients with secondary syphilis. Other classic manifestations are maculo-papular, papular or pustular rash on the entire body, especially on palms and soles. These are locations that strongly suggest the diagnosis. (See: *Skin Lesions*, chapter 12: section 3.1.2.) Highly infectious lesions may also develop on mucous membranes (lips, mouth, pharynx, vulva, glans penis). These lesions, mucous patches, are silvery grey superficial erosions with a red halo, that are not painful unless there is a secondary infection. About 40% of patients will have CNS involvement during this stage, with headache and meningismus. The CSF shows increased protein and lymphocytic pleocytosis. 1%-2% will develop acute aseptic meningitis.

Although there is some doubt about treatment efficacy in HIV patients, the CDC recommends the same treatment for primary and secondary syphilis as in HIV-negative subjects: benzathine penicillin 2,4 MIU IM single dose. In case of penicillin allergy:

- doxycycline 100 mg PO 2 x daily for 21 days, or
- ceftriaxone 1 g IM/IV daily for 14 days

PLWH/A often have high VDRL/RPR levels, and delayed regression to non-reactive levels, after apparently adequate treatment. If, however, the VDRL titres do not decline by two or more dilutions after 6 months, an LP should be performed and patients evaluated for re-treatment.<sup>2,3</sup>

## **2.6 Lymphoma and Kaposi's sarcoma (KS)**

The diagnosis is confirmed by histopathology. Treatment with chemotherapy is expensive and offers no survival benefit in the case of lymphoma. Give palliative care. Kaposi's sarcoma often presents with characteristic skin lesions (see: *Skin Lesions*, chapter 12: section 3.8). Lesions can be found in the oral cavity, the gastro-intestinal tract and the respiratory tract as well. There is no known curative treatment for KS. The major goal of treatment is palliation. This palliation should not be achieved at the expense of injury to an immune system that is already severely compromised. Treatment with HAART will cause a regression in size of the existing KS lesions.

## **2.7 Visceral leishmaniasis (kala azar)**

This is a frequent co-infection in HIV-positive IV drug users in the Mediterranean countries and in HIV patients in Somalia and Sudan, with problematic treatment because of frequent relapses after interruption of treatment. In countries where there is a combined problem of IV drug users, HIV infection and visceral leishmaniasis, this diagnosis should be considered in every HIV patient with fever. In Spain, Italy and Portugal, 17% of HIV-positive patients who present with fever have visceral leishmaniasis.

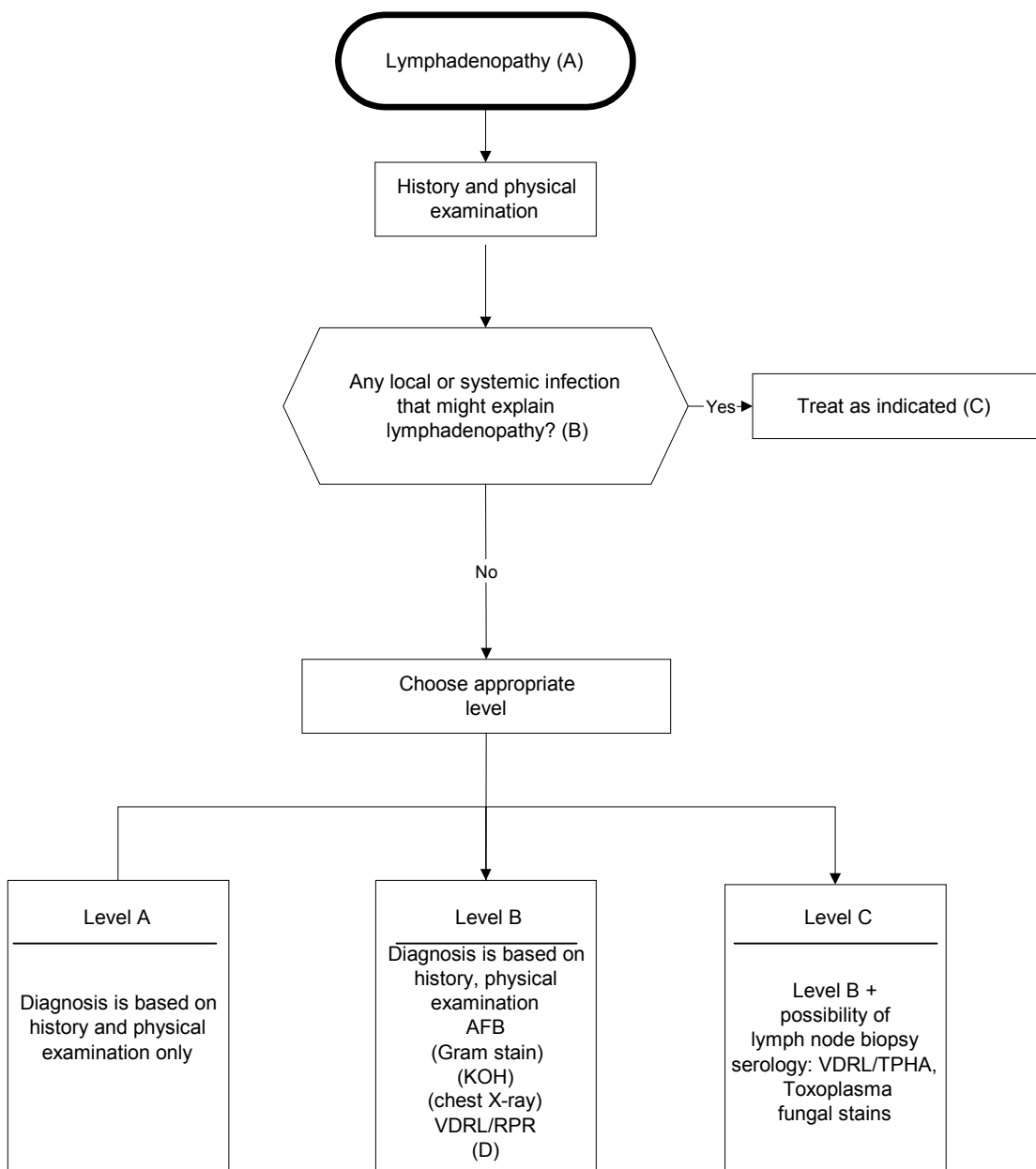
### 3 CLINICAL MANAGEMENT OF LYMPHADENOPATHY

PGL is very frequent in HIV patients, but other treatable conditions need to be excluded. Therefore the algorithms try to identify those lymph nodes that need further investigation.

Syphilis, although not very frequent, is considered in most algorithms as the first condition to treat. Penicillin is a widely available antibiotic and it is therefore good to consider this diagnosis before undertaking more invasive tests like biopsies.

#### Lymphadenopathy

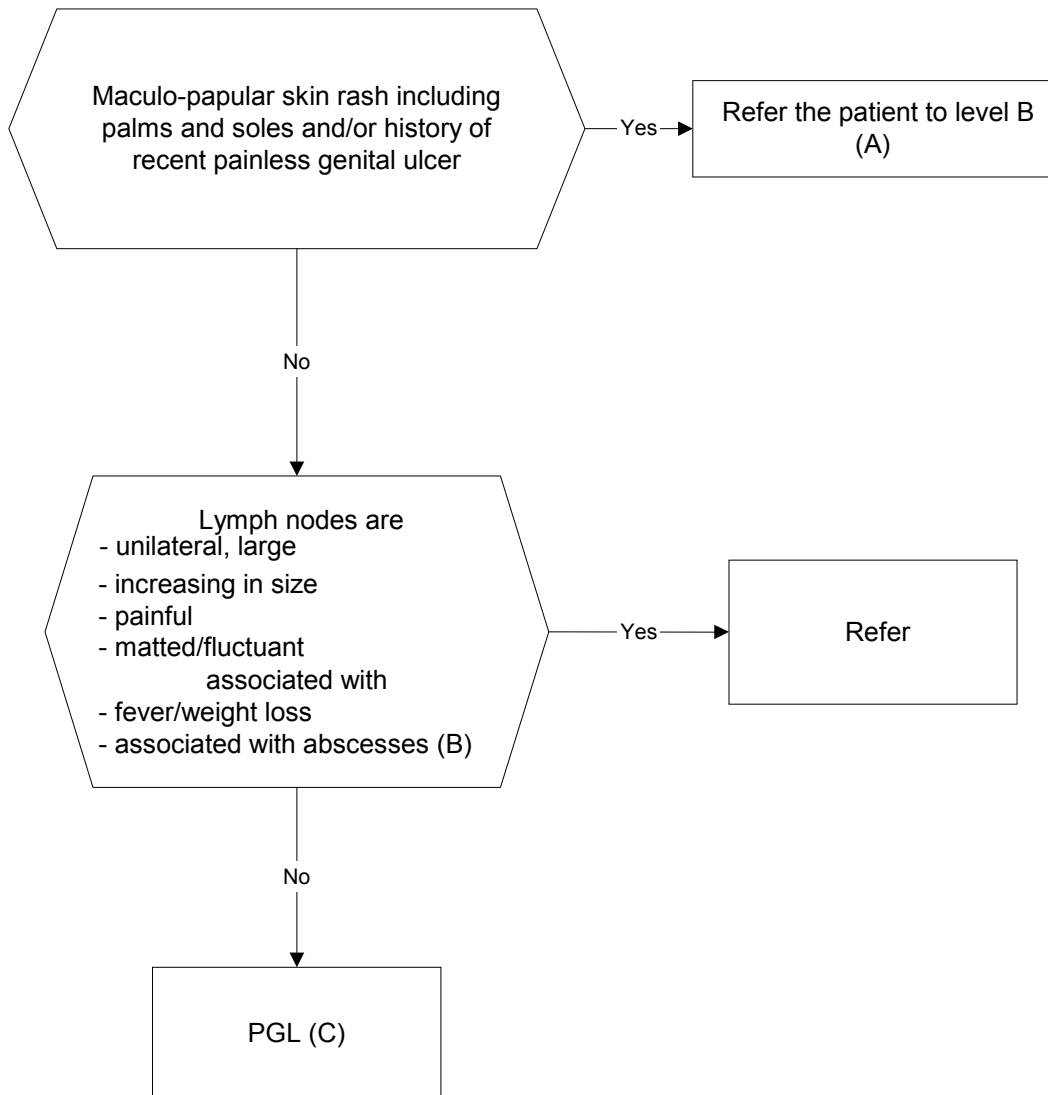
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## **Annotations lymphadenopathy**

- (A) Any lymph node swelling in a PLWH/A. For possible causes, see *Introduction*.
- (B) In early HIV, upper respiratory tract infections are common, and painful cervical lymph nodes are often reactive lymph nodes in the drainage area of ENT infections. Any pyogenic infection can cause regional lymphadenopathy. Many infectious diseases that are prevalent in tropical countries also need to be considered: sleeping sickness in Africa, rickettsial diseases after tick bite or epidemic louse-borne-typhus, bubonic plague, brucellosis, visceral leishmaniasis.
- (C) From the history and the physical examination, try to narrow down the different diagnostic possibilities. Cervical lymphadenitis that has developed from a pharyngeal or periodontal focus responds well to penicillin treatment, e.g. penicillin V 500 mg 4 x daily, or amoxicillin 500 mg -1 g 3 x daily. Pyogenic lymphadenitis and complicated skin infections usually originate from staphylococcal or streptococcal infections. In these cases, the preferred treatment is a penicillinase-resistant penicillin such as flucloxacillin. In the more acutely-ill patient, IV antibiotics are preferred (penicillinase-resistant penicillin such as cloxacillin, flucloxacillin or a first generation cephalosporine like cefazoline). If there is no improvement, surgical drainage or aspiration to detect other pathogens is necessary (tuberculosis, nocardiosis, etc.).
- (D) Health centres with medical doctors, or district hospitals that see a lot of HIV patients, should include simple staining techniques such as KOH and Gram stain to broaden their diagnostic capacities. Stains for AFB are a priority when a microscope is available, and when quality control is feasible. If no chest X-ray is available, referral to the next level or request for an X-ray in another facility should be considered, depending on what is financially or geographically acceptable for the patient.

# Lymphadenopathy



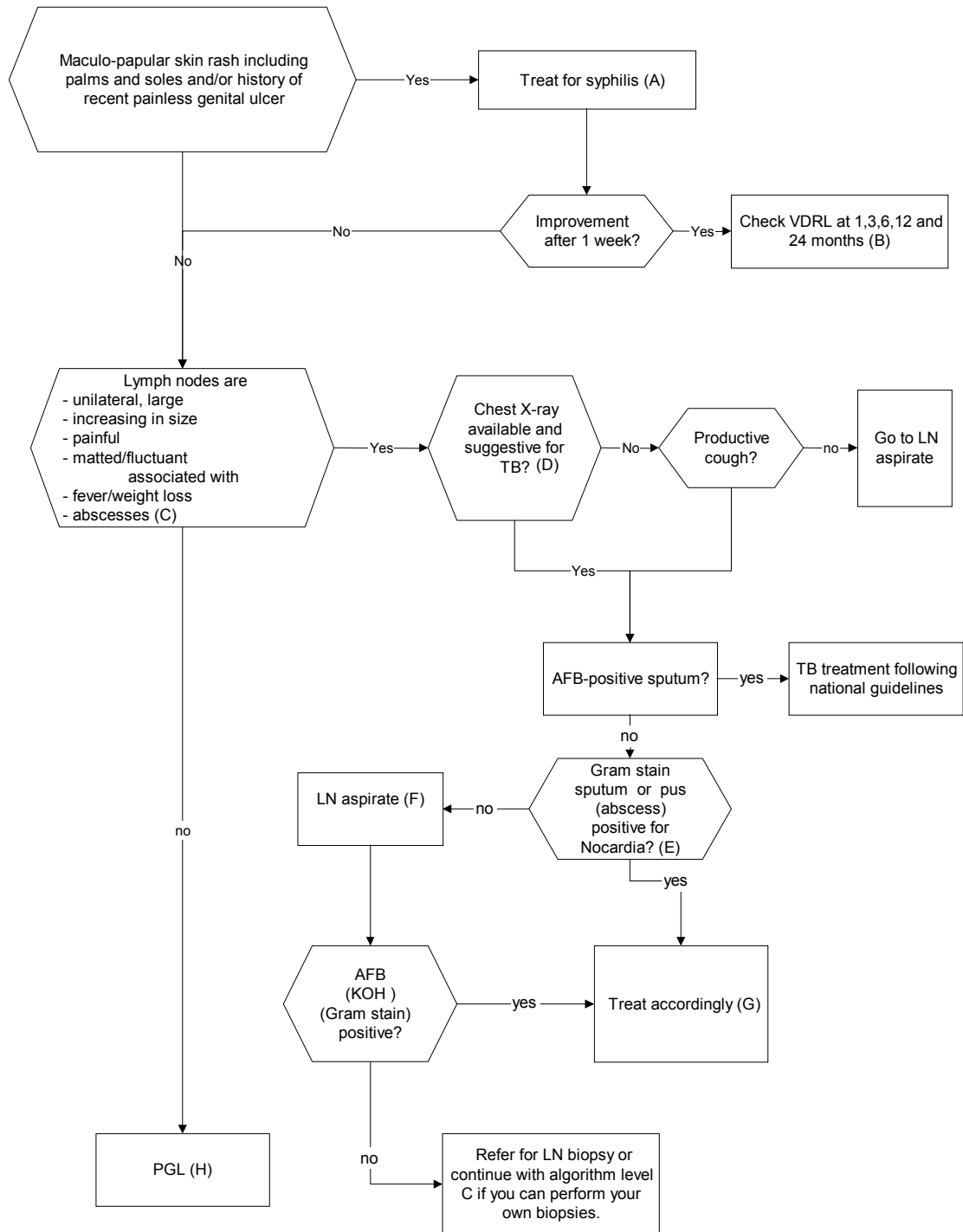
## **Annotations Lymphadenopathy (level A)**

- (A) This symptom set suggests secondary syphilis. In HIV-infected patients the response to treatment needs to be closely monitored by following up the VDRL/RPR. The patient should therefore be referred to level B for treatment and lab tests.
- (B) At level A, the health care worker has to look for features of lymph nodes that indicate further investigation:<sup>1</sup>
- large (>4 cm diameter) or rapidly growing lymph nodes
  - asymmetrical lymphadenopathy
  - tender/ painful lymph nodes not associated with a local infection
  - matted/fluctuant lymph nodes
  - obvious constitutional symptoms (fever, night sweats, weight loss)
  - (hilar or mediastinal lymphadenopathy on chest X ray)
  - suspicion of pulmonary TB
  - evidence of abscesses (cutaneous, pulmonary, etc).
- (C) Persistent generalised lymphadenopathy. In an asymptomatic patient no further investigation or treatment is necessary. The patient should be reassured. However, the patient should be asked to come back whenever constitutional symptoms develop, or the lymph nodes tend to increase in size. In that case, referral to level B for further evaluation will be necessary.



# Lymphadenopathy

**LEVEL B**



## **Annotations Lymphadenopathy (level B)**

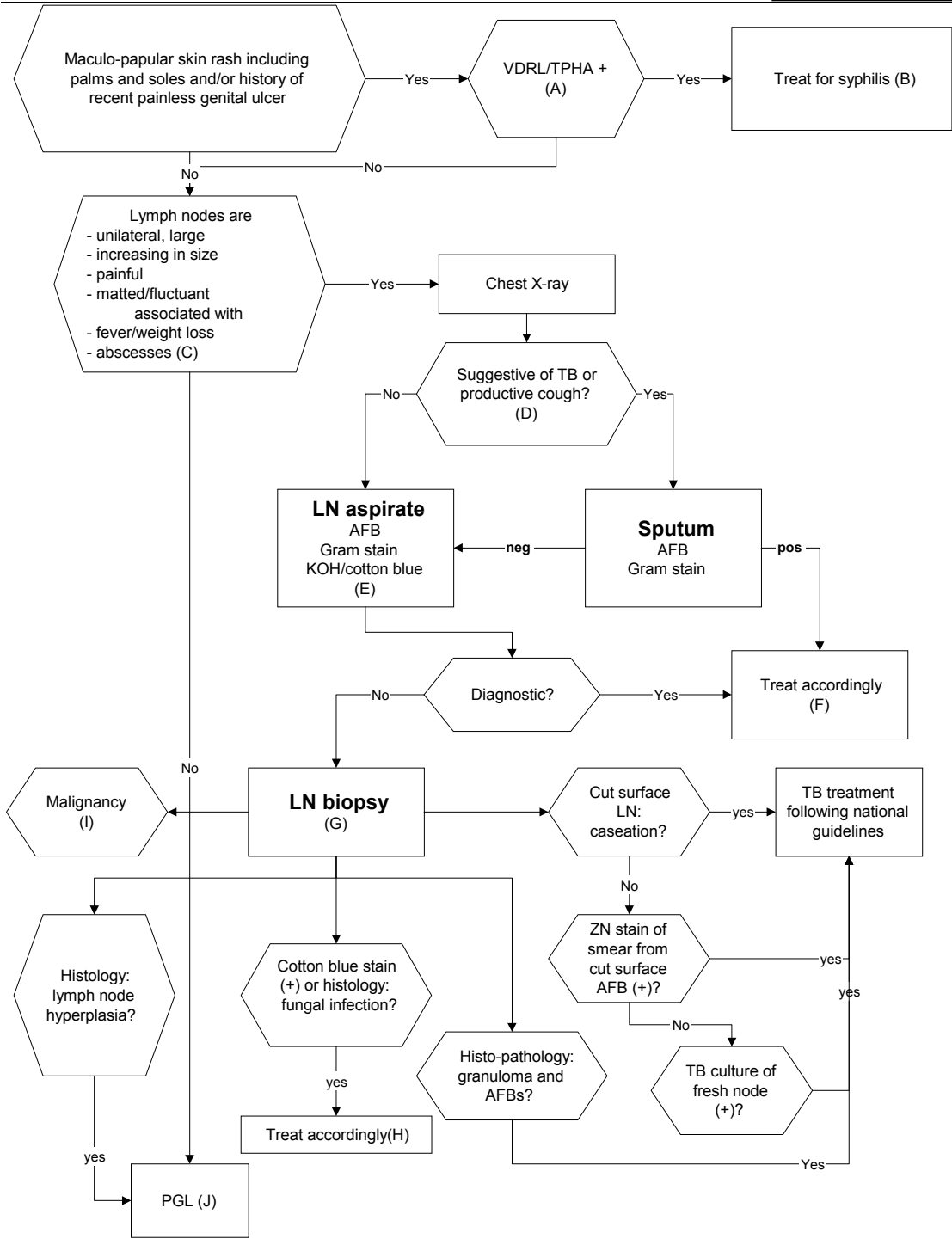
- (A) The CDC recommends the same treatment for primary and secondary syphilis in PLWH/A as in people who are HIV-negative. Benzathine penicillin 2,4 MIU IM, single dose. In case of penicillin allergy, doxycycline 100 mg 2 x daily for 21 days, or ceftriaxone 2 g IM/IV for 14 days.
- (B) Although there is a clinical improvement, the VDRL decline is often delayed. Repeat VDRL test after 3, 6, 12 and 24 months. At 6 months, a two-or-more-fold decrease in titre dilution should have occurred. If not, the patient has to be considered for re-treatment, and an LP performed. In case of neuro-syphilis, treat with benzathine penicillin 2,4 MIU IM weekly for 3 weeks. Earlier relapses of muco-cutaneous disease can occur, and are usually accompanied by a sharp rise in VDRL. In that case, the patient needs to be re-treated.
- (C) Lymph nodes that need investigation include<sup>1</sup>:
- large (>4 cm diameter) or rapidly growing lymph nodes
  - asymmetrical lymphadenopathy
  - tender/ painful lymph nodes not associated with a local infection
  - matted/fluctuant lymph nodes
  - obvious constitutional symptoms (fever, night sweats, weight loss)
  - hilar or mediastinal lymphadenopathy on chest X ray
  - suspicion of pulmonary TB
  - evidence of abscesses (cutaneous, pulmonary, etc).
- (D) When it is impossible to obtain the results of a chest X-ray, or the chest X-ray is *not suggestive* of TB, but the patient has productive cough, it is useful to do a sputum acid-fast stain. If there is no sputum production, go to lymph node aspirate (see F). If the sputum is positive for AFB, give your patient TB treatment according to national guidelines.
- (E) A chest X-ray suggestive of TB may not be TB at all. Try to gather as much evidence as possible before starting a treatment trial (see: *Respiratory Problems*, chapter 6: section 2.1). Nocardia may present with upper lobe cavitory lung disease and lymphadenopathy. Therefore do a Gram stain of sputum and/or of pus obtained from a subcutaneous abscess. If the Gram stain shows Gram-positive, long, branching, thread-like filaments, the diagnosis of Nocardia infection is very likely. Treatment consists of TMP/SMX 10/50 mg/kg 2 x daily for 6 weeks to 6 months (see: *Introduction* section).
- (F) Do a fine needle aspirate (19G needle) without anaesthesia, of lymph nodes and stain the material for AFB and Gram stain (and KOH).
- (G) In patients with fluctuant nodes or with fistula and sinuses, pus may be stained for AFB at an earlier stage. If you can do a Gram stain, you will be able to detect pyogenic lymphadenitis and Nocardia infections. KOH preparation may allow you to find hyphae and yeast cells in systemic

mycosis. Most of the deep mycosis require tissue diagnosis and special stains. An easy staining method for deep fungal infections is Cotton-blue stain (see: *Respiratory Problems*, chapter 6: section 6.3). For the treatment of the different pathologies, see *Introduction* section.

(H)PGL: if, however, the patient develops systemic symptoms or the lymph nodes increase in size, a re-evaluation should be made.

# Lymphadenopathy

**LEVEL C**



### **Annotations Lymphadenopathy (level C)**

- (A) In PLWH/A, VDRL/RPR can be false positive. TPHA is a confirmatory test. If the patient has symptoms of secondary syphilis, but the VDRL/RPR is negative, repeat the VDRL after dilution of the serum (prozone effect, see: *Neurological Disorders*, chapter 7: section 3.5). Repeat the VDRL test after 3, 6, 12 and 24 months. If the VDRL fails to decline, re-treat the patient.
- (B) CDC recommends the same treatment for primary and secondary syphilis in PLWH/A as in people who are HIV-negative. Benzathine penicillin 2,4 MIU IM, single dose. In case of penicillin allergy, doxycycline 100 mg 2 x daily for 21 days, or ceftriaxone 2 g IV for 14 days.
- (C) Lymph nodes that require further investigation: see annotation C, level B.
- (D) A chest X-ray suggestive of TB may not be TB at all (see: *Respiratory Problems*, chapter 6: section 2.1). Try to gather as much evidence as possible before starting a treatment trial. In case of an abnormal X-ray, the next logical step is a sputum exam for AFB and a Gram stain of sputum. But even in a patient with a normal chest X-ray who presents with productive cough, a sputum exam for AFB and a Gram stain are worthwhile.
- (E) If the patient has a chest X-ray compatible with TB, but remains smear-negative, and does not respond to antibiotics, a fine needle aspirate of extra thoracic lymph nodes is a sensitive method to confirm the diagnosis. In patients with normal chest X-rays but with fluctuant nodes or with fistula and sinuses, it is probably more effective to stain pus immediately for AFB and do a Gram stain and Cotton-blue stain (or KOH).
- (F) - Nocardia: high dose TMP/SMX.  
- TB: TB treatment.  
- Fungal infection: amphotericin B + fluconazole or itraconazole / ketoconazole (see *Introduction* section).
- (G) If after a LN aspirate, an X-ray and a sputum exam, a diagnosis is still not possible, a lymph node biopsy is justified. In case of skin lesions, it is useful to do a skin biopsy as well. Always make touch preparations of the cut surface to stain it for bacteria, fungi and AFB. Histology will also yield the diagnosis of **malignancies**.
- (H) Cryptococcosis: amphotericin B + fluconazole.  
Histoplasmosis and penicilliosis: amphotericin B + itraconazole/ ketoconazole.
- (I) Lymphoma and Kaposi's sarcoma are the most frequent malignancies encountered in PLWH/A. Provide palliative care.
- (J) In the asymptomatic patient no treatment is required.

#### 4 NECESSARY DRUGS AND EQUIPMENT

Level A	Level B	Level C
<b>DRUGS</b>		
Amoxicillin	Amoxicillin	Amoxicillin
Penicillin V	Doxycycline	Doxycycline
	(Flu)cloxacillin	(Flu)cloxacillin
	Penicillin V	Penicillin V
	TB medication	TB medication
	TMP/SMX	TMP/SMX
	Benzathine penicillin	Benzathine penicillin
	(Ceftriaxone)	Ceftriaxone
<b>LABORATORY AND MEDICAL EQUIPMENT</b>		
	AFB stain	AFB stain
	Gram stain	Cotton blue stain
	KOH	Gram stain
	LN aspiration	KOH
	LN biopsy)	LN aspiration
	VDRL or RPR	LN biopsy
		TB culture
		Toxoplasma serology
		VDRL or RPR/TPHA
	(Chest X-ray)	Chest X-ray

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*An excellent review with good photographic illustrations of the most common oral manifestations in PLWH/A was published in 1996 in the Annals of Internal Medicine.*<sup>1</sup>

## **1 INTRODUCTION**

Many different conditions involving the oral cavity are encountered in patients with AIDS. An examination of the mouth needs to be part of the physical examination of every patient suspected of HIV infection, even in the absence of complaints. In practice, people often present with another complaint and it is the presence of oral thrush that raises the suspicion of HIV infection. Sometimes oral lesions are debilitating because they interfere with correct feeding and increase the risk of weight loss.

## **2 OPPORTUNISTIC INFECTIONS AND OTHER DISORDERS**

The differential diagnosis includes the following pathogens:

<p><b>Bacterial infection:</b> anaerobic infections causing necrotising gingivitis <b>Fungal infection:</b> <i>Candida albicans</i> <b>Viral infection:</b> Epstein-Barr virus, Herpes simplex virus.</p>
---

These conditions should be differentiated with:

**Non-infectious disorders:** aphtous ulcers.

### **2.1 Oral hairy leukoplakia**

This condition is neither dangerous nor painful. It presents as non-removable whitish plaques with vertical folds, mostly on the lateral surface of the tongue, and is caused by the Epstein-Barr Virus (EBV). It does not require any treatment. However it is a sign of immune suppression and heralds a poor prognosis.

## 2.2 Oral thrush and oesophageal candidiasis

*Candida albicans* is an endogenous yeast. In healthy individuals it dwells predominantly in the gastrointestinal tract, sometimes in the respiratory tract. It can be pathogenic in immunocompromised patients. Oral candidiasis is frequently the first indication of immune impairment in HIV-infected patients. It is often used as an indicator disease for starting TMP-SMX prophylaxis. It is characterised by white sloughs covering areas of superficial ulceration on the gums, palate and tongue, which contain many yeast organisms and are readily detached. In severe cases, these lesions extend into the lower pharynx and oesophagus to cause dysphagia, nausea and epigastric pain. Recurrent episodes of oral candidiasis usually occur in patients with  $CD4 < 300$ .<sup>2</sup>

Over 60% of patients with  $CD4 < 100$  will develop oropharyngeal candidiasis each year.

Oesophageal candidiasis will develop in 10%-20% of AIDS patients.<sup>3</sup>

Oropharyngeal candidiasis may present atypically with erythematous lesions, with atrophic ulcers or as angular cheilitis with localised disease at the corners of the mouth. Before starting a trial with antifungal drugs, it is useful in these atypical presentations to demonstrate the presence of budding yeasts and pseudohyphae in mouth scrapings (Gram stain or potassium hydroxide (KOH)), in order to avoid sequential drug trials and raise the suspicion of resistant candida infections. Indeed, if only yeast cells are found without pseudohyphae, this is an indication of *colonisation* of the oral cavity rather than *infection*.

Continuous use of antifungals should be avoided, except in patients that were treated for systemic fungal infections and patients with severe and recurrent oropharyngeal candidiasis.

### 2.2.1 Topical antifungal therapy

Topical therapy requires contact for a sufficient time (20-30 minutes) between the drug and the oral mucosa and sufficient saliva to dissolve the medication. Treatment with only topical agents becomes less effective once disease progresses.

**Nystatin:** one tablet 500,000 IU 4 x daily; tablets should be sucked and retained in the mouth for as long as possible. Therapy should be continued for at least 48 hours after symptoms have resolved. Suspension is less effective because of shorter contact time with the oral mucosa.

**Gentian violet:** local application of Gentian Violet 1% aqueous solution 2 x daily for 1 week is effective. However the acceptability of this treatment may be low in adults.

**Miconazole oral gel:** Miconazole oral gel (60 mg 4 x daily) has similar efficacy to ketoconazole for the treatment of oropharyngeal candidiasis, without hepatotoxicity and without interaction with antiretroviral drugs and rifampicin. However, this gel is rather expensive and therefore not a first choice.

**Miconazole gum patch** has recently been proposed in generic form for the treatment of oral thrush (once daily for 7 days). Case reports also mention its efficacy in treating oesophageal thrush. Its low price (US\$1 per week) makes it an interesting alternative. However, this drug is not yet widely registered.

### **2.2.2 Systemic therapy**

Where no improvement is seen after 7 days of a topical treatment, a switch should be made to a systemic antifungal therapy.

For **oesophageal candidiasis**, however, **always use a systemic treatment!** (For more details, go to *Odynophagia and Dysphagia*, chapter 11: section 2.1.)

First choice treatment: if cheap generic fluconazole is available or if fluconazole is given free of charge, as in South Africa, this is the preferred systemic therapy for oesophageal candidiasis and for oropharyngeal candidiasis that does not respond to topical antifungal therapy.

**Fluconazole:** 200 mg as an initial loading dose followed by 100 mg daily until symptoms have resolved. Doses of up to 400 mg daily have been used in resistant cases. Fluconazole is preferred to ketokonazole and itraconazole, the former being hepato-toxic and the latter more expensive. Both are also contra-indicated in patients on TB treatment (INH, rifampicin).

If fluconazole is not available (expensive!):

**Ketoconazole\***: 200 mg - 400 mg daily until remission is obtained. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of ketoconazole, and ketoconazole is thought to inhibit the absorption of rifampicin. Treatment should be withdrawn in case of evidence of severe hepatocellular damage.

**Itraconazole:** Doses start at 100 mg 2 x daily and can be increased to a maximum of 400 mg daily, for 10-14 days. The capsules should be taken with food or an acid drink (e.g. coke,) to increase their bioavailability. Drugs that increase the pH of the stomach (i.e. antacids, H<sub>2</sub> blockers) can lead to decreased itraconazole absorption. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of itraconazole, and itraconazole is thought to inhibit the absorption of rifampicin.

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\* In the 1999 WHO MEDL (Model Essential Drug List), ketoconazole was replaced by fluconazole, which has a better therapeutic profile and less hepatotoxicity.

### 2.3 Necrotising gingivitis

This is an inflammation of the gums that can become very extensive and necrotic and lead to tooth loss. It is caused by bacteria of the oral flora and thus responds frequently to oral hygiene, antiseptic mouth washes and antibiotics effective against anaerobic infections:

- metronidazole 500 mg, 3 x daily for 7 days, or
- penicillin V 500 mg, 4 x daily for 7 days.

### 2.4 Herpes simplex stomatitis

Herpes simplex virus 1 and 2 (HSV) are common in HIV-positive patients, often appearing among the earlier infections associated with HIV infection. For some, HSV remains asymptomatic or causes only occasional outbreaks. For others, in the presence of severe immuno-deficiency, HSV muco-cutaneous lesions may persist or continue to enlarge, exposing the patient to extreme pain and the risk of secondary infection.

Treatment consists of topical antiseptics to avoid secondary infection and oral acyclovir: start with 200 mg 5 x daily. If no response, increase the dose to 400 mg 5 x daily for 1 week.

### 2.5 Kaposi's sarcoma (KS)

KS can involve the oral cavity, and is then considered to be an aggressive form of KS. Lesions can stay stable for a long time, however. They appear as red or purple maculae or nodules. Sometimes they are painful and interfere with food intake and speech. They respond to chemotherapy (vincristine), but this is not easily available in developing countries. (See also *Skin Lesions*, chapter 12)

### 2.6 Aphthous ulcers

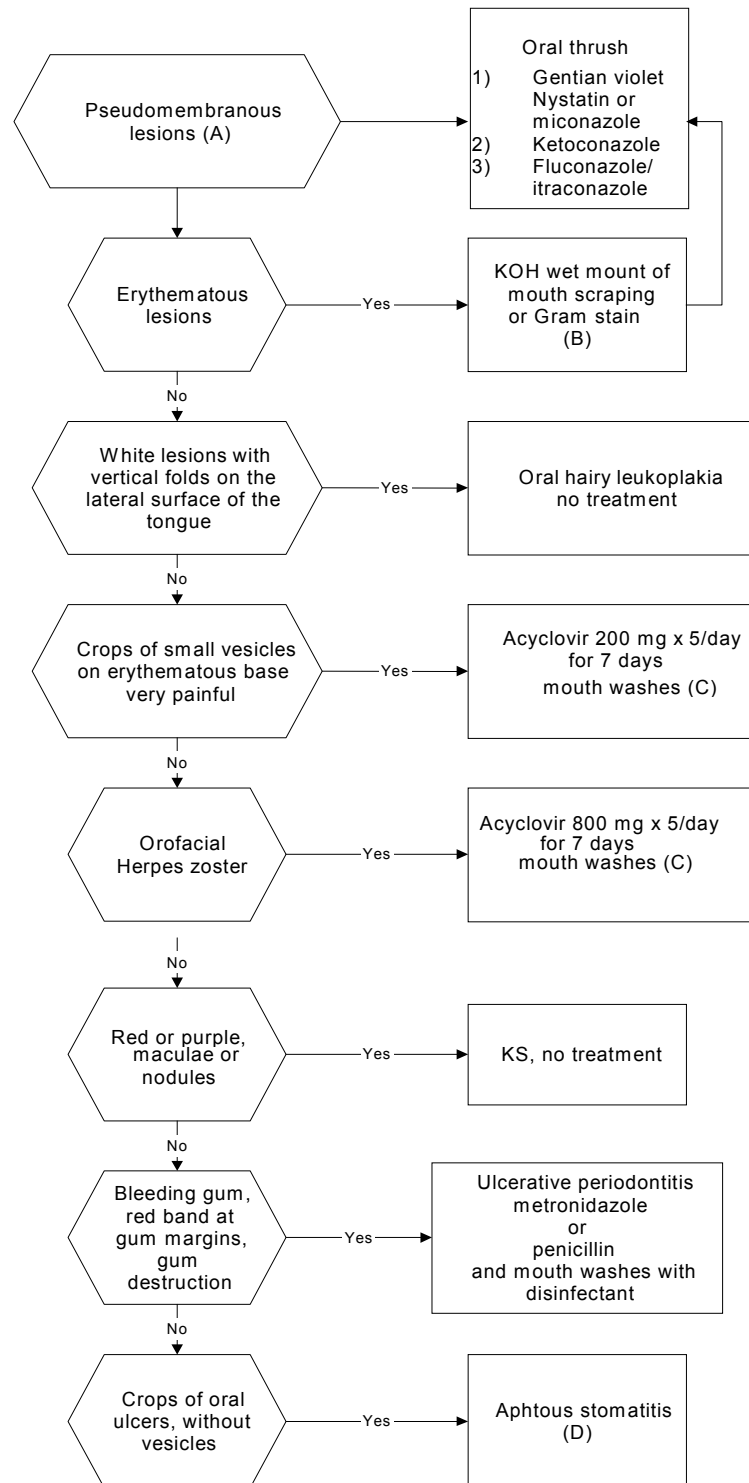
This condition, involving any part of oral mucosa, can lead to painful giant lesions. Steroids are very effective for deep ulcers of unknown origin (1 week prednisolone 40 mg daily). However, avoid long-term use of steroids in HIV patients because of the additional immune suppression they cause. Herpes simplex should be excluded. Treatment with painkillers and topical use of antiseptics can be helpful.

As an alternative for large ulcers, a suspension of 1 tablet tetracycline 250 mg dissolved in 15 cc of water can be tried. This should be kept in the mouth for a few minutes while gargling; the suspension is preferably not swallowed. Bartlett<sup>5</sup> gives a composition of a solution that can be gargled and swallowed 4 x daily:

- 1 mg hydrocortisone
- nystatin 84000 IU
- tetracycline 84 mg
- 5 ml of viscous lidocaine.

### 3 CLINICAL MANAGEMENT OF ORAL LESIONS

There is no distinction between levels of care here. Treatment options are often very limited. Most of the recommended treatments are expensive. Although not immediately life-threatening, mouth problems can significantly hamper quality of life. Efforts should be directed at decreasing pain. Particular attention should be paid to the need for appropriate fluid and food intake.



## **Annotations Oral lesions**

- (A) The clinical diagnosis of oral candidiasis is often obvious. A treatment with topical antifungals can be started without further investigation. Recurrences are frequent. When the patient has pain or difficulty when swallowing, oesophageal candidiasis is likely. In that case, start with systemic treatment.
- (B) In case of doubtful lesions (erythematous without white sloughs), take a sample of mouth scrapings and make a KOH wet mount or stain it with Gram stain. A lot of yeast cells and pseudohyphae can be found in mouth scrapings of patients with oral thrush. If only yeast cells are found without pseudohyphae, this is an indication of *colonisation* of the oral cavity rather than *infection*.
- (C) When acyclovir is not available, provide sufficient painkilling and use antiseptic mouthwashes to prevent secondary bacterial infection.
- (D) Mouth washes, topical steroids, oral steroids when severe, suspension with tetracycline and steroids, etc. (See *Introduction* section).

## **4 SYMPTOMATIC AND PALLIATIVE CARE**

### **4.1 Mouth care in general**

*Avoid dry mucous membranes*

- Use baking soda mouth wash every hour: 1 teaspoon baking soda, 1 teaspoon salt, 250 cc lukewarm water.
- Apply mouthwash with sponge swabs.
- Avoid commercial mouthwashes.

### **4.2 Pain**

#### **4.2.1 Analgesics**

- Provide stepwise analgesia (see *Neurological Disorders*, chapter 7: section 5).
- NSAID may be particular helpful.

#### **4.2.2 Anaesthesia**

- Lidocaine mouth gel.

## 5 NECESSARY DRUGS AND EQUIPMENT

Level A	Level B	Level C
<b>TOPICAL DRUGS</b>		
Baking soda	Baking soda	Baking soda
Gentian violet	Gentian violet	Gentian violet
Local anaesthetic gel	Local anaesthetic gel	Local anaesthetic gel
Nystatin/miconazole oral gel (or gum patch)	Nystatin/miconazole oral gel (or gum patch)	Nystatin/miconazole oral gel (or gum patch)
<b>ORAL DRUGS</b>		
Codeine	Acyclovir	Acyclovir
NSAID	Codeine	Codeine
Paracetamol	Fluconazole/itraconazole	Fluconazole/itraconazole
	(Ketoconazole)	(Ketoconazole)
	Metronidazole	Metronidazole
	Morphine	Morphine
	NSAID	NSAID's
	Paracetamol	Paracetamol
	Penicillin V	Penicillin V
	Prednisolone	Prednisolone
	Tetracycline	Tetracycline
<b>LABORATORY</b>		
	Microscope	Microscope
	KOH wet mount of mouth scrapings	KOH wet mount of mouth scrapings
	Gram stain of mouth scrapings	Gram stain of mouth scrapings



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The HIV logo consists of a white, wavy-edged shape resembling a flag or a piece of paper, with the letters 'HIV' written in bold, black, sans-serif font inside it.

# 11. ODYNOPHAGIA AND DYSPHAGIA

*Pain (odynophagia) or difficulty (dysphagia) when swallowing*

## 1 INTRODUCTION

Oesophageal complaints are common in HIV-infected patients, occurring in at least one-third of patients at some point during the course of disease. The incidence is higher in patients with CD4<200. It is an important problem in AIDS patients because it interferes with adequate nutrition and considerably decreases quality of life.

## 2 OPPORTUNISTIC INFECTIONS AND OTHER DISORDERS

The causes of dysphagia or odynophagia are multiple. Infections most commonly involved in oesophageal disease are:

**Fungal infection:** *Candida albicans* (50-70%)

**Viral infection:** CMV (10-20%), Herpes simplex (2-5%), EBV.

Other possible causes of dysphagia/odynophagia are:

aphthous ulcers (10-20%), neurological deficits due to PML, HIV encephalopathy and Toxoplasma brain abscess, cachexia and malignancies (KS, lymphoma).

All these conditions should be differentiated with gastro-oesophageal reflux (heartburn, hyperacidity), hiatus hernia, intake of irritants (e.g. alcohol and spicy foods), stress and cachexia. It is therefore important to identify the treatable causes.

### 2.1 *Candida* oesophagitis

*Candida* oesophagitis is the most common cause of dysphagia in AIDS patients. In two prospective studies, *Candida* oesophagitis was detected by endoscopy in up to 64% of symptomatic patients. The presence of oral thrush has a high positive and negative predictive value for the diagnosis of *Candida* oesophagitis (resp. 90% and 82%), but the absence of oral thrush does not completely exclude the diagnosis.<sup>1</sup> Patients complain of dysphagia and retrosternal pain. Odynophagia is less severe than in CMV oesophagitis.

Barium-meal studies are not sufficient to distinguish candida oesophagitis from malignancy or viral infection, and should be avoided. Definitive diagnosis of oesophageal candidiasis requires the demonstration of tissue invasive mycelia on endoscopic biopsy. However, presumptive diagnosis and empiric therapy is acceptable, especially when oral thrush is present. Treatment consists of **systemic** antifungal drugs.

First choice treatment: if cheap generic fluconazole is available or if fluconazole is given free of charge, as in South Africa, this is the preferred systemic therapy for oesophageal candidiasis and for oropharyngeal candidiasis that does not respond to topical antifungal therapy.

**Fluconazole:** 200 mg as an initial loading dose followed by 100 mg daily until symptoms have resolved. Doses of up to 400 mg daily have been used in resistant cases. Fluconazole is preferred to ketoconazole and itraconazole, the former being hepato-toxic and the latter more expensive. Both are also contra-indicated in patients on TB treatment (INH, rifampicin).

If fluconazole is not available (expensive!):

**Ketoconazole\*:** 200 mg-400 mg daily until remission is obtained. Concurrent rifampicin therapy should be avoided. Rifampicin induces the metabolism of ketoconazole, and ketoconazole is thought to inhibit the absorption of rifampicin. Treatment should be withdrawn in case of evidence of severe hepatocellular damage.

**Itraconazole:** Doses start at 100 mg 2 x daily and can be increased to a maximum of 400 mg daily, for 10-14 days. The capsules should be taken with food or an acid drink (e.g. coke,) to increase their bioavailability. Drugs that increase the pH of the stomach (i.e. antacids, H2 blockers) can lead to decreased itraconazole absorption. Concurrent rifampicin therapy should be avoided: rifampicin induces the metabolism of itraconazole, and itraconazole is thought to inhibit the absorption of rifampicin.

## 2.2 CMV oesophagitis

The most frequent clinical manifestation of CMV disease is retinitis followed by gastrointestinal symptoms. CMV oesophagitis presents with odynophagia. Clinically it cannot be distinguished from candida oesophagitis. CMV infection should be considered in patients with oesophageal symptoms that do not respond to empiric antifungal therapy.

On endoscopic examination CMV oesophageal ulcers are usually single or few in number, large and deep.<sup>2</sup> Often they are located in the lower third of the oesophagus. Most oesophageal ulcers are due to CMV infection (45%), the other main cause being aphthous ulcers (40%). In the presence of fever, CMV infection is more likely than aphthous lesions. The two antiviral drugs that are

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\* In the 1999 WHO MEDL (Model Essential Drug List), ketoconazole was replaced by fluconazole, which has a better therapeutic profile and less hepatotoxicity.

currently approved for treatment of CMV infection are ganciclovir and foscarnet. Both drugs are expensive and beyond the reach of most developing countries. Therefore palliative care is often the only treatment available (see: *Symptomatic and Palliative Care section*).

### **2.3 Herpes simplex oesophagitis**

This is a more rare cause of viral oesophagitis in AIDS patients. Patients present with retro-sternal pain and odynophagia. Without biopsy and tissue cultures it is difficult to make the differential diagnosis between HSV and CMV ulcerative oesophagitis. Often there are bacterial and fungal secondary infections and an empiric antifungal treatment may slightly improve symptoms. The presence of small painful crops of vesicles in the mouth that evolve into destructive gingivostomatitis is suggestive of HSV infection. Treatment consists of acyclovir 400 mg 5 x daily for 1 week.

### **2.4 Epstein-Barr virus infection (EBV)**

Ulcers are located in the mid-oesophagus. Often the patient also has oral hairy leukoplakia. Both conditions may respond to acyclovir treatment.

### **2.5 Aphthous oesophagitis**

After CMV infection, most oesophageal ulcers are due to aphthous ulcers (40%). If very debilitating, a trial with steroids is justified: prednisolone 40 mg daily for 7-14 days. In the presence of fever, CMV is more likely than aphthous ulcers and treatment with steroids is contra-indicated. Palliative care to alleviate pain is the only available alternative.

### **2.6 Neurological disorders leading to dysphagia**

- HIV encephalopathy
- PML: progressive multifocal leuko-encephalopathy
- Neurological sequelae of Toxoplasma brain abscess, cryptococcal meningitis (see section on *Palliative Care*).

If available, a treatment with AZT may improve the symptoms of the first two conditions.

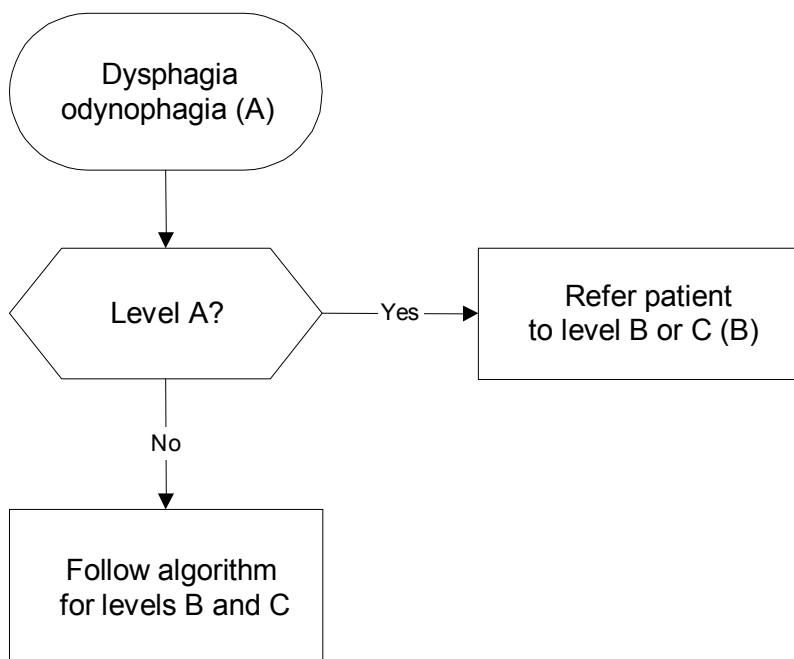
### **2.7 Malignancies**

- Kaposi's sarcoma
- Lymphoma.

For more details, go to *Lymphadenopathy*, chapter 9: section 2.6.

### 3 CLINICAL MANAGEMENT OF DYSPHAGIA/ODYNOPHAGIA

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#### Annotations dysphagia/odynophagia

(A) Odynophagia: pain when swallowing. Dysphagia: difficulty when swallowing. For its possible causes, see: *Introduction* section.

(B) *At level A*, no systemic antifungal or antiviral drugs are available. There are two possible situations:

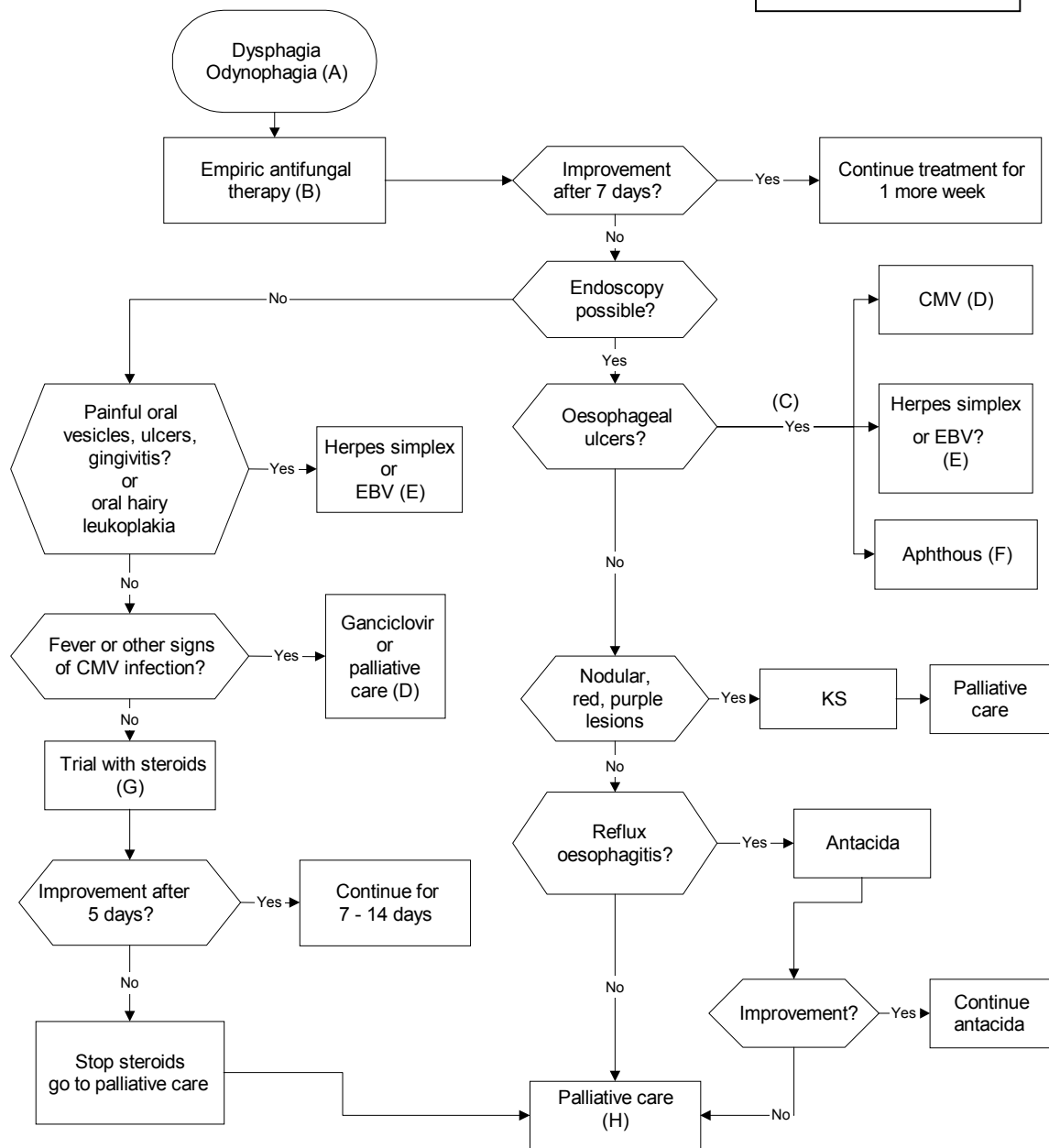
1. **The patient is in a generally good condition:** this problem needs to be treated as soon as possible to avoid weight loss and deterioration in the general condition. Refer the patient to levels B or C where treatable causes of odynophagia/dysphagia can be excluded or treated.

**Before starting palliative care, all treatable causes should be excluded at level B or C.**

2. **The patient is terminally ill and severely cachexic:** it may be mutually agreed between the patient, carer and health professional to withhold further treatment except for palliation (see section *Symptomatic and Palliative Care*).

## Dysphagia/odynophagia

Level B and C



### Annotations dysphagia/odynophagia (levels B and C)

(A) Odynophagia: pain when swallowing. Dysphagia: difficulty when swallowing.

(B) Candida oesophagitis is the most common cause of oesophagitis in patients complaining of dysphagia. Empirical treatment with systemic antifungal drugs is justified, especially when oral thrush is present.

Start with **fluconazole**, 200 mg as an initial loading dose followed by 100 mg daily until symptoms have resolved. Doses of up to 400 mg daily have been used in very resistant cases.

If fluconazole is not available, use **ketoconazole**: 200 mg-400 mg daily until remission is obtained, or **itraconazole**: doses start at 100 mg 2 x daily and can be increased to a maximum of 400 mg daily, for 10-14 days. Itraconazole capsules should be taken with food or an acid drink to increase their bioavailability. Drugs that increase the pH of the stomach (i.e. antacids, H2 blockers) can lead to decreased itraconazole absorption).

**Avoid concomitant use of fluconazole, itraconazole or ketoconazole with rifampicin and INH.**

(C) Two possibilities

- Biopsy and histopathology possible: treat according to the result.
- Biopsy and histopathology not possible: it is difficult to make a differential diagnosis only on the basis of clinical symptoms and endoscopic appearance of ulcers. *Solitary or a few large, deep ulcers in the lower third of the oesophagus are mostly due to CMV. Herpes simplex ulcers occur also in the lower third of the oesophagus, but are usually shallow and multiple. Mid-oesophageal multiple ulcers may be associated with EBV. Look for oral hairy leukoplakia. Herpes simplex and possibly EBV respond to acyclovir.*

(D) Most oesophageal ulcers are due to CMV infection (45%); the other main cause is aphthous ulcers (40%). In the presence of fever, CMV is more likely than aphthous ulcers and treatment with steroids is contra-indicated. Palliative care to alleviate pain is the only available treatment for this condition, as ganciclovir is usually not available.

(E) Definitive diagnosis of Herpes and EBV oesophageal ulcers requires endoscopic biopsy and histopathology. These conditions may respond to acyclovir 400 mg 5 x daily for 7 days.

(F) Aphthous lesions of the oesophagus. If very debilitating, a trial with steroids is justified: prednisolone 40 mg daily for 7-14 days.

(G) In the absence of fever, a trial of steroids for aphthous ulcers could be justified. In terminal AIDS care there should be no fear to use steroids.

(H) Palliative care consists of adapted feeding practices, painkillers and antacida (see: *Symptomatic and Palliative Care* section).



## 4 SYMPTOMATIC AND PALLIATIVE CARE <sup>3</sup>

### 4.1 Gastro-oesophageal reflux

- Raise head of bed so that patient lies in an upright position.
- To neutralise excess acid: aluminium or Mg hydroxide: 2-4 tabs 4 x daily, after meals and at bedtime.
- To reduce acid production: cimetidine 200 mg 2 x daily, or 800 mg at bedtime.

### 4.2 Difficulty when swallowing

- Test the patient's ability to swallow with a small quantity of water before each feeding to avoid aspiration of food.
- Minimise oral medication.
- Establish whether fluids or soft foods are easier to swallow.
- Cool, soft foods may be easiest to swallow.
- Let the family prepare small, but frequent meals.
- Feed slowly in the upright position.
- Nasogastric feeding tubes may be needed if long-term support is required, e.g. a patient who has a neurological deficit after a treated cryptococcal meningitis or Toxoplasma encephalitis, but who is otherwise in good physical condition.
- For odynophagia, the use of a nasogastric feeding tube should be discouraged as it often increases the likelihood of infection (Candida) and adds considerably to the discomfort.
- Give enough painkillers to allow food intake.

### 4.3 Pain

#### Analgesics

- Provide stepwise analgesia (see *Neurological Disorders*, chapter 7: section 5).
- Avoid NSAID when there is a history of reflux pathology or symptoms that improve with antacids or H2 blockers.

### 4.4 Last hours of life

- Loss of gag reflex and inability to swallow is one of the cardinal signs that death is occurring.
- No further administration of fluids and food.

- Fluids (saliva) may build up in the back of the throat and present as gurgling (death rattle). This is often perceived as choking and is distressing for the family and caregiver. Provide information and support.
- Keep mucous membranes moist, not wet.
- Scopolamine may reduce saliva production. An alternative is atropine (0,5 mg SC as often as needed), but this leads to cardiac, respiratory and CNS stimulation, which is not desired in this stage.
- In extreme situations oropharyngeal or nasopharyngeal suction may be needed (often very irritating).

## 5 Necessary Drugs and Equipment

Level A	Level B	Level C
<b>DRUGS</b>		
Aluminium hydroxide	Acyclovir	Acyclovir
Codeine	Aluminium hydroxide	Aluminium hydroxide
NSAID	Cimetidine	Cimetidine
Paracetamol	Codeine	Codeine
	Fluconazole/ itraconazole	Fluconazole/ itraconazole
	(Ketoconazole)	(Ganciclovir)
	Morphine	(Ketoconazole)
	NSAID	Morphine
	Paracetamol	NSAID
	Prednisolone	Paracetamol
		Prednisolone
	Scopolamine (atropine)	
		Scopolamine (atropine)
<b>LABORATORY AND MEDICAL EQUIPMENT</b>		
	Microscope	(Histopathology)
		Microscope
Naso-gastric feeding tube + syringes	Naso-gastric feeding tube + syringes	Endoscopy (+ Biopsy)
	Nasopharyngeal suction	Naso-gastric feeding tube + syringes
		Nasopharyngeal suction

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*This chapter is based partly on existing documents from MSF-Nairobi <sup>1</sup> and MSF-Thailand.*

*Recommended reading:*

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## **1 INTRODUCTION**

Many patients with HIV infection (80%-100%)<sup>2,3</sup> develop dermatological conditions at some point in the course of the disease. Skin conditions may be very disabling, disfiguring and even life-threatening.

## **2 ACUTE HIV INFECTION**

The acute retroviral syndrome occurs approximately 1 month after primary infection. It may present as fever and rash. The rash is usually erythematous and maculo-papular. Other symptoms may be: arthralgia, lymphadenopathy, weight loss, meningo-encephalitis and pharyngitis. HIV antibody tests may still be negative. No specific treatment is indicated.

### 3 OPPORTUNISTIC INFECTIONS AND OTHER DISORDERS

The differential diagnosis includes the following pathogens:

**Bacterial infection:** *Staphylococcus aureus*, *Streptococcus* species, *Treponema pallidum*, *Bartonella* species  
**Mycobacterial disease:** *M. tuberculosis*, *M. Avium* complex  
**Viral infection:** Herpes simplex and zoster virus, molluscum contagiosum, condyloma accuminata  
**Infestations:** Scabies  
**Fungal infection:** seborrheic dermatitis, tinea corporis, pityriasis versicolor, *Penicillium Marneffeii*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Candida* species.

These conditions should be differentiated with:

**Non-infectious disorders:** Kaposi's sarcoma, drug eruptions, severe psoriasis, papular pruritic eruption (PPE), xerosis.

#### 3.1 Bacterial infections<sup>4</sup>

##### 3.1.1 *Staphylococcal and streptococcal infections*

Staphylococcal infections of the skin and staphylococcal bacteraemia are common among AIDS patients.

*Folliculitis and furunculosis*, which are usually caused by staphylococci, need careful management in HIV patients because life-threatening disseminated infections occur. Carbuncles (clusters of furuncles) with multiple openings form as a result of invasion and necrosis of the subcutis. Indwelling vascular catheters, neutropenia and lymphoedema due to Kaposi's sarcoma are risk factors for the development of staphylococcal bacteraemia.

*Pyomyositis*, caused most commonly by *Staphylococcus aureus*, has emerged as an unusual complication of HIV in Africa. In Tanzania, 62% of a series of patients with pyomyositis were HIV-infected. In the Northern hemisphere individual cases have been reported, but the condition is rare.

*Cellulitis and erysipelas* are streptococcal infections of the subcutaneous tissue resulting from contamination of minor wounds. In patients who remain untreated, life-threatening systemic infections may occur.

In general, HIV patients should have a local antiseptic at home to apply to minor wounds after washing. Mild localised infections are effectively treated with a topical antiseptic such as: gentian violet, polyvidone iodine or chlorhexidine.

However, when there is a deep-seated infection or high fever, systemic antibiotics should be prescribed<sup>1</sup>:

- (flu)cloxacillin 500 mg PO 4 x daily for 10 days, or
- (flu)cloxacillin 1-2 g IV 4 x daily for 10 days.

In the case of pyomyositis, surgical drainage is necessary together with antibiotics ((flu)cloxacillin).<sup>5</sup> Gram stain of pus can confirm the presence of Gram-positive cocci in clusters.

### **3.1.2 Syphilis**

Caused by *Treponema pallidum*.

*Primary syphilis*: a painless, indurated genital ulcer (chancre) at the site of inoculation, usually accompanied by inguinal lymphadenopathy. Even without treatment, chancres usually heal within a few weeks. VDRL or RPR is not positive until 7-10 days after appearance of the chancre.

*Secondary syphilis*: Weeks to months later, about 25% of untreated patients will develop a systemic illness with fever, rash, condyloma lata, lymphadenopathy and oral lesions (mucous patch). The rash typically involves the palms and the soles, and is maculo-papular.

Treatment of primary and secondary syphilis is benzathine penicillin 2,4 MIU IM. It is important to follow up VDRL after treatment, at 3, 6, 12 and 24 months. If the VDRL fails to decline, the patient must be retreated.

### **3.1.3 Bacillary angiomatosis**

Bacillary angiomatosis (BA) and bacillary peliosis are newly-recognised opportunistic infection in PLWH/A.<sup>6</sup> They are caused by tiny Gram-negative bacilli that are difficult to cultivate in the laboratory: *Bartonella henselae* and *Bartonella quintana*. These diseases are characterised in immunocompromised persons by angio-proliferative lesions (that look like Kaposi's sarcoma) in the skin and bone (bacillary angiomatosis) or in the liver and the spleen (peliosis hepatis).\*

BA is epidemiologically linked to exposure to cats, especially to young cats infested with fleas. Symptoms include fever, malaise, headache, hepatomegaly and skin lesions. Cutaneous lesions start with small red papules that gradually expand into large papular, nodular, pedunculated forms. They have a vascular appearance and the surface is friable and easy to bleed. Bacillary angiomatosis may be a life-threatening disease if it is not recognised early and treated promptly with antibiotics.

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\* In immuno-competent persons, *B.henselae* infection may cause granulomatous lymphadenitis, or cat scratch disease. The latter has been associated with cat scratches, rarely bites.

Differential diagnosis with Kaposi's sarcoma is not always easy. Treatment consists of erythromycin 500 mg 4 x daily for 2 months. An alternative is doxycycline 100 mg 2 x daily.

### **3.2 Mycobacterial disease**

Even in HIV patients, disseminated miliary tuberculosis of the skin is a rare form of tuberculosis.<sup>7</sup> The diagnosis should be suspected in a patient who has a papulo-pustular eruption on the trunk and the extremities and who is severely ill. It is caused by the haematogenous spread of tubercle bacilli to multiple organs including the skin.

Microscopic examination of the skin biopsy reveals numerous acid-fast bacilli.

However, the diagnosis of disseminated tuberculosis is often evident on clinical grounds, and aspiration and/or biopsy of lymph nodes has a higher diagnostic yield than a skin biopsy in extra pulmonary TB.<sup>8</sup>

### **3.3 Viral infections**

#### **3.3.1 Chronic muco-cutaneous herpes simplex**

This is one of the most annoying skin conditions in AIDS patients and tends to give rise to very painful and extensive lesions.

The usual localisation is ano-genital, although oro-labial lesions can be seen. Chronic (>3 weeks) ulcers are only seen with advanced immune suppression. If untreated, they can last for months and finally involve most of the genital and peri-anal skin and mucous membranes. The most effective treatment is, when available, acyclovir 200 mg 5 x daily for 7 days. In disseminated muco-cutaneous Herpes simplex infection treatment for 2 weeks is often necessary. Recurrences occur frequently (more than 6/year) in some patients. In that case, they may require lifelong suppressive therapy: acyclovir 200 mg 2 x daily or if not successful increase to 400 mg 2 x daily. If acyclovir is not available, the alternative is local antiseptics (gentian violet), paracetamol and amoxicillin in case of secondary infections.

#### **3.3.2 Shingles (Herpes zoster)**

Herpes zoster in a young person is highly predictive for HIV infection. Almost 25% of PWLH/A experience recurrences of Herpes zoster.<sup>9</sup> Lesions can become necrotic and extensive, taking a long time to heal. If they involve the ophthalmic branch of the trigeminus nerve (V), they can involve the cornea and cause corneal scarring with loss of vision in that eye. This is an indication to treat with acyclovir, 800 mg 5 x daily for 7 days. Oral acyclovir should also be given to patients who have extensive and necrotic lesions. Additional treatment consists of topical antiseptics to accelerate drying of the lesions and to prevent secondary bacterial infection. Pain relief may also be necessary: NSAID and/or



carbamazepine 200-600 mg daily or clomipramine 25-75 mg. clomipramine and carbamazepine are also effective in controlling post-zoster neuralgias. Non-controlled studies suggest that a milky extract from the frangipani tree would accelerate healing and decrease pain (communication from MSF-Nairobi).

### **3.3.3 *Molluscum contagiosum***

A viral skin infection, characterised by centrally umbilicated, non-pruritic papules on the face, neck, and ano-genital areas, that is more commonly seen in PLWH/A. Lesions in the face tend to proliferate, especially if injured during shaving. Differential diagnosis has to be made with disseminated cryptococcosis, histoplasmosis and penicilliosis. Those systemic mycoses are usually associated with fever, pulmonary or meningeal involvement.

Molluscum contagiosum usually does not require treatment. It is possible to prick the centre of the lesion with a needle dipped in Phenol, followed by expression of the central core. Alternatively cryotherapy (liquid nitrogen), electro-coagulation or curettage can be proposed.

### **3.3.4 *Genital warts (Condyloma accuminata)***

Genital warts can be seen as STI in any patient, but they are much more frequent in HIV-infected patients. The lesions can be very extensive and cauliflower-like, involving both the genital and the peri-anal region. The lesions are caused by a virus (human papillomavirus) which can also give rise to cervix and anal cancer. Patients with small numbers of warts are often asymptomatic. Other patients may have pruritus, bleeding, or pain. Genital warts should only be treated in the case of large lesions. If the number of lesions is small, treatment is best done by the patient with daily podophyllotoxin 0.5% solution strictly on the lesions<sup>†</sup>. Let it dry. Protect the unaffected skin with vaseline or zinc ointment. Wash with water and soap after 1-4 hours. Allow drying before removing speculum in vaginal warts. Apply twice a day and repeat every day for 3 consecutive days per week for 4 weeks maximum.

Improper treatment can cause painful ulcerations. More extensive lesions (condyloma < 3 cm) should be treated by cryotherapy or cauterisation. Total volume of podophyllotoxin should not exceed 0.5ml per day. Podophyllotoxin should not be used during pregnancy. It is also contra-indicated for cervical, urethral, anorectal and buccal condylomata.

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<sup>†</sup> Podophyllotoxin is preferred above Podophyllum resin 10 or 25%, which is much more caustic and has to be applied by the health staff.

### 3.4 Scabies

Scabies can lead to extensive disease in AIDS patients, with hypertrophic, hyperkeratotic lesions that become secondarily infected with bacteria. This condition is called Norwegian scabies. The mites can be seen by microscope on a KOH preparation of skin scales. It can be life-threatening when secondary infection is severe. Treatment is with benzyl benzoate 20% (3 consecutive days on whole body except the face.) Itching can be relieved by chlorpheniramine 4 mg, 3-4 tabs daily. After treatment, all clothes and bed linen should be washed and dried. Do not forget to treat family members who have scabies as well. Persistent itching after treatment is frequent and can be treated with a steroid cream (hydrocortisone 1%). Any long-lasting itchy dermatitis in HIV-infected patients who do not respond to topical antifungal drugs justifies a trial with benzyl benzoate.

Ivermectin is an effective alternative when available (dose: 12 mg (2 tablets) in a single dose). In case of Norwegian scabies, it is best to combine ivermectin with the topical treatment of benzyl benzoate lotion. In case of scabies with surinfection, the surinfection should first be treated with local chlorhexidine/cetrimide and antibiotics (TMP/SMX, or cloxacillin or doxycycline). After 3 days, start benzyl benzoate lotion.

### 3.5 Fungal skin disease<sup>10</sup>

Fungal skin disease is extremely common in HIV-infected patients. It usually responds to topical antifungal drugs (Whitfield's, gentian violet, imidazole cream, ketoconazole cream).

#### 3.5.1 Seborrheic dermatitis

Seborrheic dermatitis is a very common complaint and is one of the earliest clinical markers of HIV infection. The most common locations are in the hairline, eyebrows, nasolabial folds and chest. Involvement of the groin is also frequently noted. The role of *Malassezia furfur* in causing seborrheic dermatitis is controversial. This condition responds well to topical antifungals. In general, treatment needs to be continued for 14 days after symptoms have disappeared:

- Whitfield's ointment 2 x daily, or
- gentian violet 2 x daily, or
- ketoconazole ointment 2 x daily, or
- miconazole 2% cream 2 x daily.

For severe inflammation, a topical steroid cream can be added to the miconazole cream. For refractory cases, oral ketoconazole can be used: 200 mg daily for 7-14 days.

### **3.5.2 Pityriasis versicolor and Malassezia folliculitis**

These conditions rarely require treatment except for aesthetic reasons. Pityriasis versicolor (caused by overgrowth of *Malassezia furfur*) is neither more common nor does it present clinically differently in HIV-positive patients compared to HIV-negatives. Treatment consists of a single oral dose of ketoconazole 400 mg or 200 mg daily for 3 days, or topical application of selenium sulphide or ketoconazole cream 2% or ketoconazole shampoo.

*M. furfur* can cause folliculitis in HIV-positive patients. *Malassezia* folliculitis responds well to treatment with ketoconazole (200 mg daily for 10-14 days).

### **3.5.3 Dermatophytosis**

Tinea corporis, tinea pedis, tinea cruris and onychomycosis all occur more frequently in patients with HIV infection. The most frequent is *tinea pedis*. In uncomplicated cases, treatment with local imidazole cream (1% clotrimazole, 2% miconazole) or Whitfield's ointment is sufficient. Treatment is necessary for 4 weeks. In severe cases, oral griseofulvin (10 mg/kg daily for 4 weeks) may be necessary.

*Onychomycosis* is also frequent in HIV-positive patients. Because onychomycosis requires long-term therapy and not all patients with dystrophic nails have a fungal infection, it is necessary to make a correct diagnosis. Direct microscopy of KOH preparations is sufficient. Griseofulvin 10 mg/kg daily should be given for 12-18 months. If available, pulsed therapy with itraconazole (200 mg 2 x daily for the first 7 days of each month for 4 months) is effective.

*Tinea cruris* follows tinea pedis and onychomycosis in frequency. Potassium hydroxide (KOH) preparation of skin scraping can distinguish it from seborrheic dermatitis, which also frequently involves the groin.

*Tinea corporis* is an extension from tinea cruris. Start treatment with local imidazole cream. If ineffective, switch to an oral drug.

In the case of *scalp ringworm*, treat with griseofulvin 10 mg/kg daily for at least 6 weeks. Topical application of Whitfield's ointment or an imidazole cream may accelerate clearing of scaly lesions on the scalp.

### **3.5.4 Muco-cutaneous candidiasis**

The most frequent presentation is oral thrush (see: *Oral Lesions*, chapter 10). *Candida* intertrigo is uncommon in PLWHA, but severely immunocompromised patients may have balanitis, distal urethritis, or paronychia (nail infection). KOH preparation of affected areas may show pseudohyphae and budding yeasts. Topical anti-fungal cream twice a day is usually effective (clotrimazole cream 1%, miconazole cream 2%). This treatment can be combined with local application of gentian violet to keep the lesions and the

surrounding skin dry. In generalised skin infections, oral ketoconazole 200 mg daily or oral fluconazole 50 mg 2 x daily for 2 weeks is effective.

### **3.5.5 Deep mycosis**

70% of patients with disseminated *Penicillium marneffe*i infection (Southeast Asia and China) will have skin lesions. Histoplasmosis and cryptococcosis can also present with pustules, nodules, ulcers and papules. Patients with cryptococcosis and penicilliosis may have molluscum contagiosum-like, centrally umbilicated lesions. These are typically located on the trunk and face. The organism may be seen by microscopic examination of skin scrapings, touch preparations of skin biopsy or lymph node aspirate stained with Wright's stain, or Cotton-blue stain. Bone marrow aspirate is diagnostic in 100% of cases of disseminated infections. The diagnosis is confirmed by culturing the fungus from clinical specimens. Those techniques are not readily available in developing countries. Diagnosis is suggested by the clinical picture. Patients usually have high fever and other symptoms such as severe anaemia, cough, lymphadenopathy, hepatomegaly and meningeal signs, which suggest the diagnosis (see: *Respiratory Problems* and *Neurological Disorders*, chapter 6 & 7).

Initial treatment of penicilliosis should be with amphotericin B 0,6 mg/kg daily IV for 2 weeks, followed by itraconazole 200 mg 2 x daily for 10 weeks. Mortality from disseminated *P.marneffe*i infection in patients with AIDS is about 20%, despite effective antifungal therapy.<sup>11</sup> Long-term suppressive therapy with itraconazole 200 mg daily should be given to prevent relapse. The treatment of choice for cryptococcosis is amphotericin B 0,7 mg/kg daily followed by fluconazole 400 mg daily for 8 weeks. Secondary prophylaxis with fluconazole 200 mg daily is necessary to prevent relapse. In non-severely ill patients, oral itraconazole (400 mg daily) or oral fluconazole (400 mg daily) may be sufficient.

### **3.6 Papular pruritic eruption (PPE)**

This affects up to 30% of HIV patients. PPE is a chronic symmetric papular eruption, predominant at the extensor surface of upper and lower extremities. It is very itchy and frequently secondarily infected. Underlying causes are scabies, folliculitis (bacterial or fungal), seborrheic dermatitis, dry skin and drug reactions. Treatment for an underlying cause should be given first.

*Bacterial folliculitis* appears more on the axilla and the thighs and responds to topical antiseptics.

*Eosinophilic folliculitis* is characterised by urticarial follicular papules above the nipple line for which potent topical steroids and antihistamines are the first choice.

*Malassezia folliculitis* responds to ketoconazole 200 mg daily.

Every pruritic rash that is not resolved with antifungal drugs justifies a trial with benzyl benzoate. After this, symptomatic treatment with calamine lotion, bath oil, antihistamines (chlorpheniramine 4 mg 3 x daily), topical triamcinolone 0,02% cream can be tried. In Thailand, antidepressants have been recommended in case of refractory, invalidating prurigo.

### 3.7 Xerosis

This skin condition is frequently encountered in PLWH/A.<sup>3</sup> The aetiology is not known. Lesions consist of a diffuse, pruritic, scaly rash, involving mainly the limbs and the back. Treatment is topical with dry skin lotion, or, when important scaling is present, with Whitfield's ointment, twice a day for 2-4 weeks. For pruritus: chlorpheniramine 4 mg 3 x daily for 1 month. If no improvement a trial with benzyl benzoate to treat scabies may be worthwhile.

### 3.8 Kaposi's sarcoma (KS)

This cancer of the skin and the blood vessels is rarely seen in HIV-negative patients and is thus an indicator disease of symptomatic HIV infection. It is caused by a sexually transmitted Herpes virus (HHV8). Lesions are usually multiple and can involve the skin as well as mucous membranes. Cutaneous lesions occur most commonly on the trunk, the extremities and the face. Initially lesions are papular. Later the papules become nodules and plaques, and the colour changes from dark brown to violet. Since the use of HAART in the US, the incidence of Kaposi's sarcoma has dramatically decreased. In Asian patients, Kaposi's sarcoma is very rare.<sup>3</sup>

No curative treatment exists for KS. The goal of treatment is palliation. KS responds to some chemotherapeutic agents (vincristine), but these drugs are not easily available in developing countries. Intralesional injection of vinblastine has a response rate of 90% (the lesion becomes smaller but does not disappear). The duration of palliation is 4-5 months. Pain relief can be obtained by following stepwise analgesia (see: *Neurological Disorders*, chapter 7, section 5).

### 3.9 Psoriasis

Psoriasis is not more frequent in HIV-positive than in HIV-negative persons. However, extensive, severe psoriasis is often observed in AIDS patients.<sup>12</sup> All patients should expose their skin lesions to UVB (walk in the sun in the early morning and late afternoon in the tropics).

#### For limited disease

- Betamethasone 0,1% cream applied on the lesions 2 x daily for 2 weeks.
- 5% LCD (liquor carbonis detergens) in triamcinolone 0,02% applied on skin lesions 2 x daily until recovery.

- Coal tar in salicylate ointment 2 x daily.

Scalp: Polytar shampoo once a day.

Skin folds: 1% hydrocortisone cream on the lesions 2 x daily.

### Generalised disease

Topical treatment as in limited diseases combined with (if available) etretinate 0,75 - 1 mg/kg daily in 2-3 divided doses (max 75 mg daily) for 2-4 weeks, followed by 0,5 mg/kg daily for another 6-8 weeks. Etretinate is contra-indicated in pregnancy. Methotrexate, a frequently used alternative treatment for severe psoriasis, should be avoided in HIV patients, because of severe additional immune suppression.

Good results have been described with AZT and other antiretroviral drugs.

### **3.10 Bedsores**

This is a frequent problem in bedridden patients. Clean the wound every day with normal saline and keep it as dry as possible. Apply zinc oxide ointment around the wound and iodine in the wound. In case of secondary infection, use antibiotics. Prevention: frequent massages on pressure points by family members (instructed by physiotherapist). Turn the patient over in bed every 3-4 hours. Avoid moist or wet bed sheets.

Pain treatment is provided with stepwise analgesia.

### **3.11 Drug reactions**

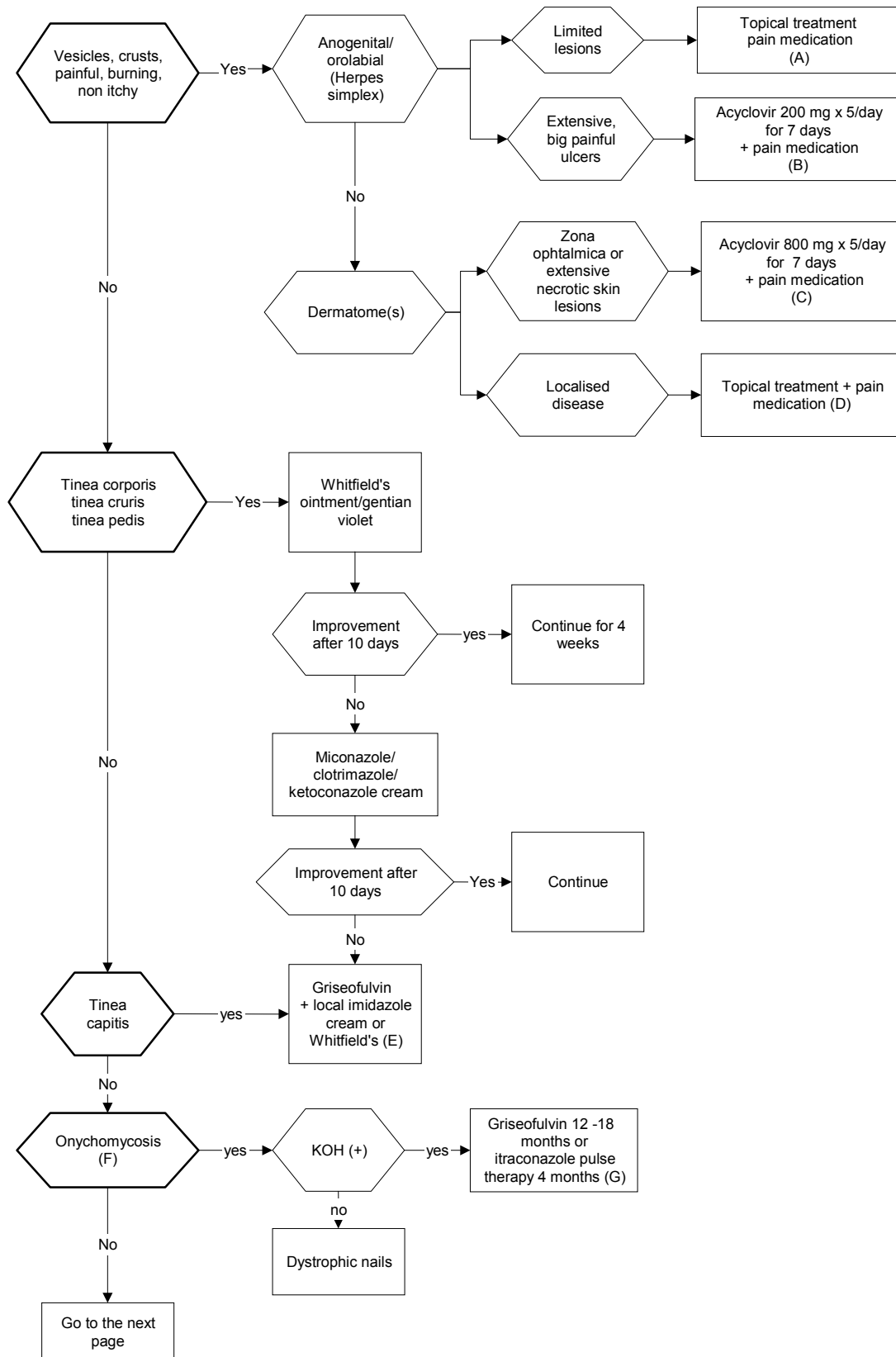
Drug reactions are common in PLWH/A and are directly related to the degree of immunosuppression. The drugs that are most frequently involved are TMP/SMX, dapsone and amoxicillin. A morbilliform rash is most frequently observed. Treat with chlorpheniramine 4 mg 3-4 x daily. In case of severe reactions, stop the drug.

If Stevens-Johnson syndrome occurs, the patient needs to be admitted to a hospital for aggressive treatment (rehydration, nasogastric tube feeding, antiseptic treatment of areas of epidermolysis. Early in the course, before extensive skin breakdown, it is useful to give steroids: prednisolone 1 mg/kg daily for 1 week.

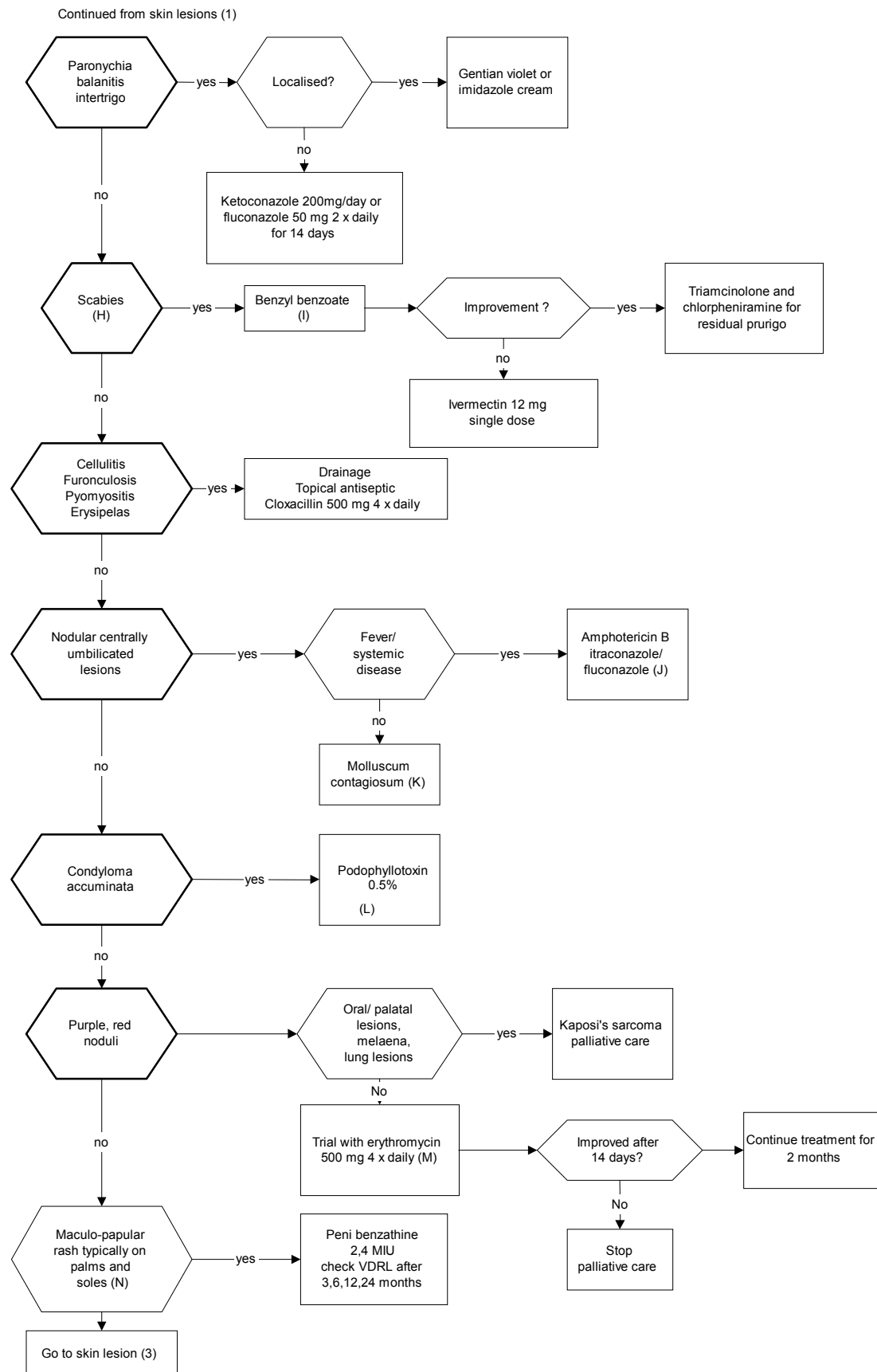
In case of extensive epidermolysis, do not use steroids because of the risk of infection and bacteraemia. In case of high fever, treat with broad-spectrum antibiotics that cover both Gram-positives and Gram-negatives (ceftriaxone + amikacin or ciprofloxacin). However, do not use the culprit drug!!

## 4 CLINICAL MANAGEMENT OF SKIN LESIONS

### SKIN LESIONS (1)



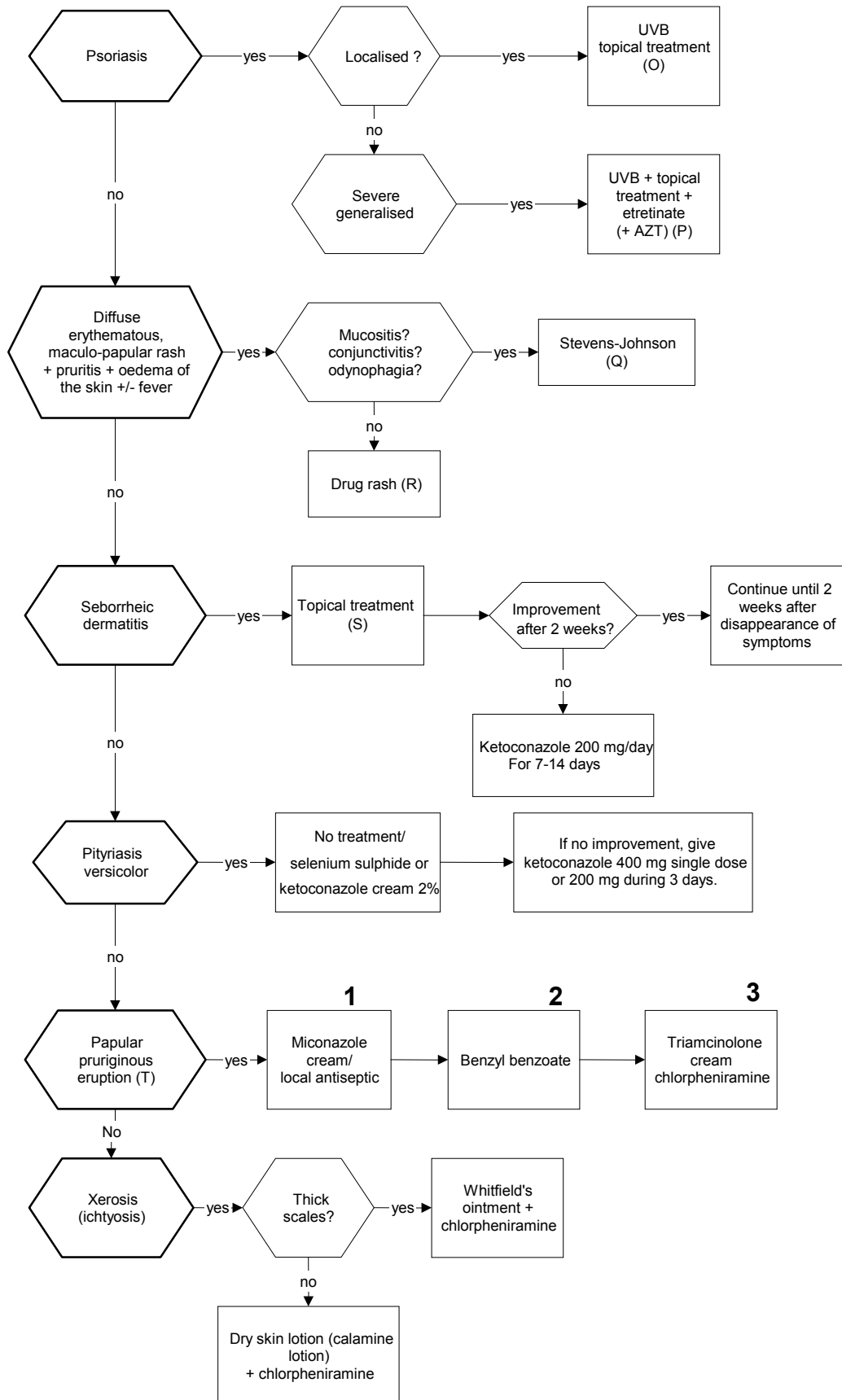
## SKIN LESIONS (2)





## SKIN LESIONS (3)

continued from skin lesion (2)



## **Annotations skin lesions**

There is no distinction between levels of care here.

- (A) NSAID, paracetamol and gentian violet, or polyvidone iodine.
- (B) Pain medication: stepwise analgesia. If recurrences are frequent, give suppressive therapy: acyclovir 200 mg 2 x daily or 400 mg 2 x daily.
- (C) In addition to acyclovir, topical antiseptics, NSAID and carbamazepine 200-600 mg daily or clomipramine 25-75 mg daily in the evening (see: *Neurological disorders*, chapter 7: section 5.2).
- (D) Gentian violet + NSAID + carbamazepine or clomipramine.
- (E) Tinea capitis requires treatment with griseofulvin 10 mg/kg daily for at least 6 weeks. Addition of imidazole ointment or Whitfield's will clear scalp scales more rapidly. Severe dermatophytosis or ringworm infection resistant to local therapy may also be treated with griseofulvin 10 mg/kg daily for 4 weeks.
- (F) Dermatophytosis of the nail (onychomycosis) has to be distinguished from infection of the nail wall or nail bed, which is usually due to candida (paronychia).
- (G) Not all patients with dystrophic nails have a fungal infection. Because the treatment is long, it is good to confirm the diagnosis. Direct microscopic examination of a KOH preparation of subungual scrapings will show the presence of hyphae in the case of onychomycosis. In that case, treat with griseofulvin 10 mg/kg daily for 12-18 months. If available, pulsed therapy with itraconazole (200 mg 2 x daily for the first 7 days of each month for 4 months) is also effective.
- (H) In case of scabies with secondary infection, it is better to treat this secondary infection first. Start some days later with benzyl benzoate.
- (I) Apply benzyl benzoate 25% on the whole body, except the face, on 3 consecutive days. Clean clothes and bed linen. Treat family members with symptoms.
- (J) In a patient with nodular skin lesions, ulcers, papules and lymphadenopathy and who is severely ill, the differential diagnosis between disseminated deep fungal infections and disseminated mycobacterial disease has to be made. In the absence of a skin biopsy and appropriate staining, this may be challenging. Try to find other arguments for mycobacterial disease (miliary TB, AFB on lymph node aspirate, etc). In the case of meningeal involvement, do Indian ink stain on CSF. In case of productive cough, do AFB and Gram stain, or Cotton-blue stain.

- (K) Molluscum contagiosum usually is asymptomatic. It might be decided to treat it for aesthetic reasons.
- (L) Genital warts should only be treated if they are large and causing symptoms. Apply podophyllotoxin 0.5% twice daily strictly on the wart. Protect the surrounding healthy skin. Ask the patient to wash off the podophyllotoxin 1-4 hours later. Repeat daily for 3 consecutive days per week for 4 weeks maximum. Do not use with pregnant women.
- (M) Because it is sometimes difficult to distinguish clinically between bacillary angiomatosis and Kaposi's sarcoma, a trial with erythromycin is justified. If no response after 14 days, doxycycline can be tried. If there is still no response, stop treatment and give palliative care.
- (N) Very suggestive for secondary syphilis. Check VDRL (rarely negative in secondary syphilis) Patients sometimes do not remember that they had a primary chancre. Follow up VDRL at 3, 6, 12, 24 months. If no decline in VDRL, treat the patient again.
- (O) See: *Introduction* section.
- (P) See: *Introduction* section.
- (Q) Diffuse erythematous or maculo-papular rash, fever and mucositis (oral and vaginal lesions, conjunctivitis, inability to swallow), are suggestive of Stevens-Johnson syndrome. This is a life-threatening disease and requires hospitalisation in an ICU if available. It is most often associated with the intake of sulphonamides (TMP/SMX and dapsone) or thiacetazone. Stop the offending drug. If epidermolysis is not yet present, corticosteroids may reverse the inflammatory process (prednisolone 40-60 mg daily for one week). In case of extensive skin breakdown, steroids enhance the risk of secondary infections. The patient should be treated as a burn patient. Use aseptic techniques to clean and cover the wounds, give aggressive IV rehydration, provide feeding via NG tube. In case of high fever and/or chills, start broad-spectrum antibiotics (ceftriaxone / amikacin). Stevens-Johnson syndrome has a mortality rate of 50%.
- (R) Drug rash: Stop the drug and give symptomatic treatment: chlorpheniramine 4 mg 3-4 x daily and triamcinolone cream. In case of a non-life-threatening rash due to TMP/SMX, consideration might be given to re-trying the therapy after two weeks.<sup>13</sup> The reason for doing this is that TMP/SMX is such a valuable drug for prophylaxis of PCP, toxoplasmosis and bacterial infections in PLWH/A.  
 Example of a regimen of **gradual dose escalation**:
- TMP/SMX suspension (40 mg TMP + 200 mg SMX/5 ml):
  - 1 ml 3 x daily
  - 2 ml 3 x daily
  - then 5 ml daily for 3 days
  - then 10 ml daily for 3 days

- then 20 ml daily for 3 days
- then 1 DS tab daily or 1 SS tab daily (if DS is not supported).

After desensitisation, under surveillance, up to 70% of patients may again tolerate TMP/SMX.<sup>14</sup>

(S) Topical treatment that is effective for seborrheic dermatitis:

- gentian violet
- Whitfield's ointment
- miconazole or clotrimazole cream
- ketoconazole cream.

Apply treatment 2 x daily and, if effective, continue treatment for 2 weeks after all symptoms have disappeared. In case of severe inflammation, the miconazole cream or the ketoconazole cream can be mixed with a topical steroid.

(T) Chronic symmetric papular eruption, often with secondary infection. Underlying causes can be scabies, fungal and bacterial disease. These need to be treated first.

1. Malassezia folliculitis will respond to miconazole and bacterial folliculitis to antiseptic topical treatment.
2. All pruriginous lesions that do not respond to antifungal therapy justify a trial with benzyl benzoate.
3. When there is no response to antifungals and anti-scabies treatment, give symptomatic treatment.

## 5 NECESSARY DRUGS AND EQUIPMENT

level A	level B	level C
<b>TOPICAL DRUGS</b>		
Benzyl benzoate	Benzyl benzoate	Benzyl benzoate
Calamine lotion	Betamethasone 0,1%	Betamethasone 0,1%
Chlorhexidine	Calamine lotion	Calamine lotion
Dry skin lotion	Chlorhexidine	Chlorhexidine
Gentian violet	Dry skin lotion	Dry skin lotion
Hydrocortisone 1% cream	Gentian violet	Gentian violet
Polyvidone iodine	Hydrocortisone 1% cream	Hydrocortisone 1% cream
Whitfield's	Imidazole cream	Imidazole cream
Zinc oxide ointment	Ketoconazole cream	Ketoconazole cream
	Polytar shampoo	Podophyllotoxin 0.5%
	Polyvidone iodine	Polytar shampoo
	Triamcinolone + 5% LCD	Polyvidone iodine
	Whitfield's	Triamcinolone + 5% LCD
	Zinc oxide ointment	Whitfield's
		Zinc oxide ointment
<b>SYSTEMIC TREATMENT</b>		
Chlorpheniramine tablet	Acyclovir 200 mg	Acyclovir 200 mg
NSAID	Acyclovir 800 mg	Acyclovir 800 mg
Paracetamol	Clomipramine	Clomipramine
	Carbamazepine	Carbamazepine
	Chlorpheniramine	Chlorpheniramine
	Doxycycline	Doxycycline
	Erythromycin	Erythromycin
	(Flu)cloxacillin	Etretinate
	Griseofulvin	(Flu)cloxacillin
	(Ketoconazole)	Fluconazole
	NSAID	Griseofulvin
	Paracetamol	Itraconazole
	Prednisolone	(Ivermectin)
		(Ketoconazole)
	Benzathine penicillin	NSAID
		Paracetamol
		Prednisolone
		Amphotericin B
		Benzathine penicillin
		(Vincristine)

LABORATORY AND MEDICAL EQUIPMENT		
	KOH	Cotton-blue or Wright's stain
	Microscope	KOH
		Microscope
		Cryotherapy or electro-coagulation

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