

HIV-AIDS INFECTION IN DEVELOPING COUNTRIES: Clinical features, staging systems and basic concepts of management¹

Anke Bourgeois, E. Delaporte

Introduction

1. Natural History and Classification

The entire sequence of events for an average patient, without any specific treatment against HIV, is approximately ten years from seroconversion to death. Rates of progression appear similar by sex, race, and risk category if adjusted for quality of care. Patients with symptomatic primary HIV infection progress more rapidly than those with asymptomatic seroconversion. Age is an important variable: for patients aged from 16 to 24 years at seroconversion, the median time from seroconversion to AIDS is 15 years; for those aged more than 35 years at seroconversion, it is 6 years. It is longer for HIV-2 than for HIV-1. Anyway, the individual patient variation is extensive.

Inserire figura 1

The natural history of HIV infection is divided into the following stages (figure 1):

- Viral transmission: HIV infection is usually acquired through sexual intercourse, exposure to contaminated blood or perinatal transmission.
- Primary HIV infection (or "acute HIV infection" or "acute seroconversion syndrome"): symptomatic primary HIV infection has been reported in all major risk categories with a frequency of 50-90%. Most symptomatic patients seek medical consultation, but this diagnosis is infrequently recognised. The time from exposure to onset of symptoms is usually 2 to 4 weeks. Typical symptoms are fever, adenopathy, pharyngitis, rash, myalgias or arthralgias, diarrhoea, headache, nausea and vomiting, hepatosplenomegaly, and thrush. Laboratory findings include lymphopenia, followed by lymphocytosis with depletion of CD4 cells, CD8 lymphocytosis, and often atypical lymphocytes. The acute illness is generally accompanied by high level HIV viremia and so, the patients are highly contagious.
- Seroconversion: seroconversion with positive HIV serology generally takes place at 3 to 12 weeks following the viral transmission
- Clinical latent period ("stage A" according to the 1993 CDC classification): during this period, the patient is clinically asymptomatic and generally has no findings on physical exam, except for persistent generalised lymphadenopathy (PGL), defined as enlarged lymph nodes involving at least two non contiguous sites other than inguinal nodes.
- Early symptomatic HIV infection ("stage B" according to the 1993 CDC classification) (table 1). Infections occurring at this stage are generally due to "aggressive" pathogen agents.
- AIDS ("stage C" according to the 1993 CDC classification) or a CD4 cell count less than 200/mm³. More and more opportunistic infections, due to less pathogen agents, are occurring.
- Advanced HIV infection, characterised by a CD4 cell count <50/mm³.

¹ This document is incomplete as many tables and figures are missing.

Table 1: 1993 revised CDC classification

Clinical categories			
CD4 cell categories	A Asymptomatic or PGL or acute HIV infection	B* Symptomatic (not A or not C)	C** AIDS indicator condition
1/ >500/mm ³	A1	B1	C1
2/ 200-499/mm ³	A2	B2	C2
3/ <200/mm ³	A3	B3	C3

Note: all patients in categories A3, B3, C1-3 are reported as AIDS, based on the AIDS indicator conditions and/or a CD4 cell count less than 200/mm³.

*** Category B:** Symptomatic conditions not included in Category C that are
a) attributed to HIV infection or indicative of a defect in cell-mediated immunity, or
b) considered to have a clinical course or management complicated by HIV infection.

Examples of B conditions include but are not limited to:

- bacillary angiomatosis;
- thrush;
- _vulvovaginal candidiasis that is persistent, frequent or poorly responsive to therapy;
- cervical dysplasia (moderate or severe);
- cervical carcinoma in situ;
- _constitutional symptoms such as fever (38.5°C) or diarrhoea more than 1 month;
- oral hairy leukoplakia;
- _Herpes zoster involving two episodes or more than 1 dermatome;
- idiopathic thrombocytopenic purpura;
- listeriosis;
- _pelvic inflammatory disease (especially if complicated by tubo-ovarian abscess);
- peripheral neuropathy.

****Category C:** Indicator conditions in case definition of AIDS (adults) 1995

- oesophageal, tracheal, bronchi or lungs candidiasis;
- invasive cervical cancer;
- extrapulmonary coccidioido-mycosis;
- extrapulmonary cryptococcosis;
- Cryptosporidiosis with diarrhea more than 1 month;
- _Cytomegalovirus of any organ other than liver, spleen or lymph nodes;
- CMV retinitis (with vision loss)
- _Herpes simplex with mucocutaneous ulcer more than 1 month or bronchitis, pneumonitis, oesophagitis;
- extrapulmonary histoplasmosis
- _HIV-associated dementia: disabling cognitive and/or other dysfunction interfering with occupation or activities of daily living;
- _HIV-associated wasting : involuntary weight loss more than 10% of baseline plus chronic diarrhea (>=2 loose stools/day >=30 days) or chronic weakness and documented enigmatic fever;
- Isosporis with diarrhea more than 1 month;
- Kaposi's sarcoma;
- _Lymphoma, non-Hodgkins of B-cell or unknown immunologic phenotype and histology showing small, noncleaved lymphoma or immunoblastic sarcoma;
- disseminated Mycobacterium avium infection;
- disseminated or pulmonary Mycobacterium tuberculosis infection;
- Nocardiosis;
- Pneumocystis carinii pneumonia;
- recurrent bacterial pneumonia (>=2 episodes in 12 months);
- progressive multifocale leukoencephalopathy;
- recurrent non typhi Salmonella septicaemia;
- extraintestinal strongyloidosis;
- toxoplasmosis of internal organ;
- Wasting syndrome due to HIV (as defined above)

2. AIDS definition

In the developing world, access to laboratory facilities being difficult, a clinical definition for AIDS was necessary. A first definition "the Bangui definition" was elaborated in 1986 (Table 2), and is still used on the field. The main goal for this definition was the epidemiological follow-up of AIDS cases. After several validation studies, specificity for this definition was 90%, with a sensitivity of only 60% for adults. Sensitivity and positive predictive value were poor for the paediatric definition.

Table 2: AIDS clinical definition in Africa (WHO/Bangui definition)	
<p>For adults</p> <p>Major criteria</p> <ul style="list-style-type: none"> - Weight loss >10% of baseline - Diarrhea > 1 month - Fever > 1 month (continuous or intermittent) <p>Minor criteria</p> <ul style="list-style-type: none"> - Cough > 1 month - Generalised pruritic dermatitis - Recurrent zona - Oropharyngeal candidiasis - Chronic Herpes - Generalised lymphadenopathy <p>Exclusion criteria</p> <ul style="list-style-type: none"> - Cancer - Severe malnutrition - Other aetiology <p>Aids diagnosis is done in presence of:</p> <ul style="list-style-type: none"> - at least 2 major criteria and at least 1 minor criteria or - aggressive Kaposi's sarcoma or proved cryptococcal meningitis 	<p>For children</p> <p>Major criteria</p> <ul style="list-style-type: none"> - Weight loss >10% of baseline - Diarrhea > 1 month <p>Minor criteria</p> <ul style="list-style-type: none"> - Persistent cough - Generalised pruritic dermatitis - Oropharyngeal candidiasis - Recurrent common infections (otitis, pharyngitis) - Mother's confirmed HIV infection - Generalised lymphadenopathy <p>Exclusion criteria</p> <ul style="list-style-type: none"> - Cancer - Severe malnutrition - Other aetiology <p>Aids diagnosis is done in presence of :</p> <ul style="list-style-type: none"> - at least 2 major criteria and - at least 1 minor criteria

3. Laboratory tests

HIV infection is established by detecting antibodies to the virus or by detecting the virus with p24 antigen, nucleic acid-based tests (PCR) or by culture. The standard test is the serology for antibody detection. There are two types: HIV-1 and HIV-2 which show 40-60% amino-acid homology. HIV-1 is divided into subtypes or clades designated group M (major) "A to J", group O (outlier) and group N. Subtype O shows 55-70% homology with other M-subtypes. Most common assay is an Elisa screening assay and a confirming Western Blot or Line Immuno Assay on EIA positive specimens. For laboratories where Western Blot or LIA are not available, the World Health Organisation (WHO) has recommended an alternative strategy based on a first Elisa test, as sensitive as possible, followed by a second Elisa test more specific for the reactive samples (Figure 2).

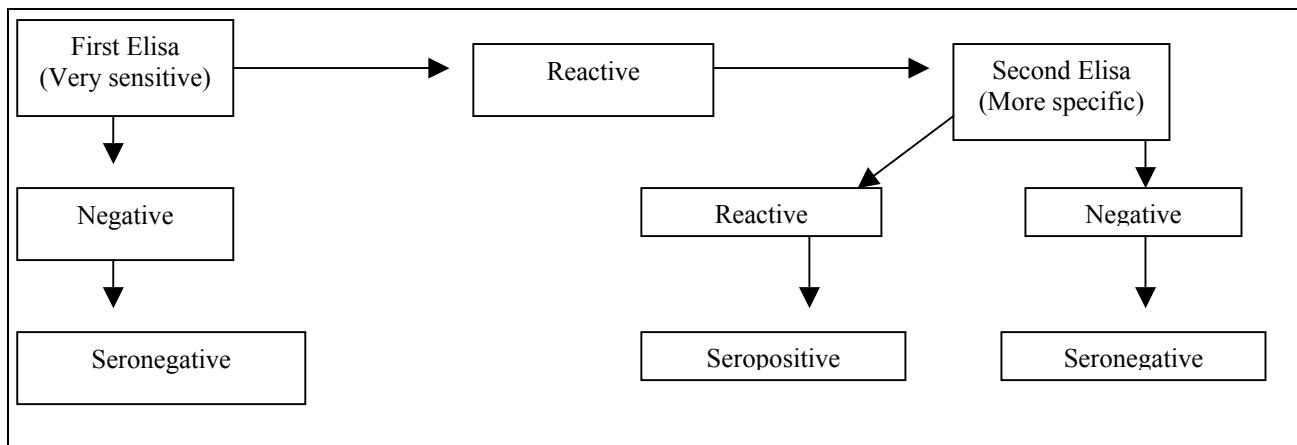


Fig. 2 – WHO alternative flow-chart for the diagnosis of HIV infection

African specificities

1. Specificities of opportunistic infections in adults living in Africa

General signs:

Most frequent signs in Africa are diarrhea, fever and wasting, generally associated with anorexia and asthenia. Chronic diarrhea, intermittent and recurrent, is observed in 40 to 90% of the cases, compared to around 6% in developed countries. Long or recurrent fever without any aetiology is a common symptom revealing HIV infection in more than 60% of the cases. In 70 to 100% of cases, the wasting syndrome, "slim disease", is strongly suggestive of AIDS. The weight loss is significant, with more than 10% of baseline weight.

Dermatological signs:

Isolated pruritus, localised or generalised, is persistent, and often resistant to usual drugs. Prurigo is the most common dermatitis, occurring in more than 20% of the patients. It is generally associated with a wasting, and is quite specific of HIV infection. Pruritus is often strong and recurrence is very frequent. The aetiology is not known, but there might be an allergic component. Hair modifications, as diffuse alopecia are also quite frequent. Hair is becoming fine, silky, with spontaneous straightening. Oral candidiasis is banal and can sometimes have severe consequences, preventing the patient to take food. Cutaneous cryptococcosis is more prevalent in Africa. It has to be distinguished from Molluscum contagiosum. Chronic herpetic infection, with superficial and painful ulceration is prevalent, as well as extensive and recurrent zona. Hair leukoplakia is probably due to the Epstein-Barr virus. Venereal warts and Molluscum contagiosum are often profuse and recurrent after treatment. Kaposi's sarcoma is less frequent in tropical areas than in the developed world, by contrast to the endemic Kaposi's sarcoma. Clinical aspect is generally typical.

Digestive signs:

Oesophageal signs, as dysphagia or retrosternal pains, are usually associated with candida oesophagitis. Herpes simplex virus and Cytomegalovirus can also be responsible of oesophageal ulcerations. Diarrhea, as written above, is one of the most frequent AIDS sign in tropical areas. Main causes are bacterial (Salmonella, Shigella...), and parasitological infections (Cryptosporidia,

Isospora, amoebiasis, giardiasis, helminthiasis). The HIV virus itself may be responsible of this diarrhea.

Respiratory signs:

The most common pulmonary infections are banal pneumopathy (Streptococcus pneumonia, Haemophilus influenzae...) and tuberculosis. Extrapulmonary tuberculosis seems more frequent in HIV patients. Pneumocystosis is less prevalent than in industrialised countries.

Neurological signs:

In case of localised neurological sign, cerebral toxoplasmosis must be suspected, and specific treatment has to be started. Same symptomatology and scanographic aspect is sometimes caused by cerebral lymphoma, cryptococome or tuberculome. Cryptococcal neuromeningitis, quite prevalent in Africa, is responsible of severe headache and fever. Superior functions troubles evocates papovavirus progressive multifocal encephalitis or HIV encephalitis. HIV or CMV myelitis are not exceptional. Peripheral neuropathies as multinevritis or polyradiculonevritis are due to HIV.

Ocular signs:

Keeness of vision reduction corresponds usually to CMV retinitis. Vascular lesions appear also frequent in Africa.

Adenopathies:

Except common adenopathies due to chronic lymphadenopathic syndrome, malignant lymphoma or disseminated diseases (tuberculosis, atypical mycobacteria, Kaposi's sarcoma, deep mycosis or leishmania) are responsible of painful adenopathies.

Systemic diseases:

Some infections present only with fever and general alteration. It is the case for minor salmonellas, but also tuberculosis (often associated with hepatosplenomegaly), or visceral leishmaniosis, histoplasmosis and coccidioidomycosis.

2. Specificities of opportunistic infections in children living in Africa

The asymptomatic period is shorter than in adults, and the first symptoms occur generally before the third year of life. The prognosis is worse when disease starts earlier.

First symptoms are failure to thrive, oral thrush and chronic diarrhea. After 1 year, polyadenopathy, hepatomegaly with or without splenomegaly, often associated with parotiditis and interstitial lymphoid pneumopathy were described.

The incidence rate of neurological lesions is high, with psychomotor delay, pyramidal syndrome, ataxia, extrapyramidal rigidity, convulsions.

3. African specificities concerning antiretroviral treatment

In Africa, clinical particularities have some therapeutic implications. Tuberculosis is quite frequent, and specific therapy against it complicates ARV prescription and contra-indicates some protease inhibitors. Viral hepatitis B and C are also very prevalent in all sub-Saharan areas and pose some problems first for protease inhibitors, especially ritonavir, second for hepatotoxic nucleosides such as didanosine, zalcitabine and stavudine. The frequency of glomerular lesions, more or less severe, makes the use of indinavir, which may increase the creatinine rate, difficult. Anaemia, often well tolerated, is a limiting factor for the prescription of zidovudine, and also cotrimoxazole.

Regimen's choice is limited by the presence of HIV-2 in West-Africa and of HIV-1 group O, especially in Cameroon. In fact, non nucleoside reverse transcriptase inhibitors are ineffective on these viruses. It is necessary to evaluate other drugs against HIV-2. The first results with protease inhibitors are promising for HIV-2 and HIV-1 A and E subtypes. However, G subtype appears less sensitive in vitro to the protease inhibitors. Nucleoside analogues seem fully effective on the whole subtypes.

Psychosocial and medical care of persons living with HIV

1. Psychosocial care

Psychosocial care is as important as medical care. If possible, it is better to have a counsellor specifically trained for the HIV counselling. The first effort to do with people living with HIV/AIDS is to make them accept their serologic status and to make them understand how to live positively with HIV/AIDS. Then, it is essential to convince them of the importance of a regular follow-up. The counsellor has to explain how to prevent reinfection and sexual or blood transmission. Informations about hygiene, nutrition, sport... have to be given.

2. Medical care

Regular follow-up allows for screening and early diagnosis and treatment of many opportunistic or non opportunistic diseases. Tuberculosis is one of the commonest infection occurring in Africa, which is essential to treat as early as possible. Even without antiretroviral treatment, a regular follow-up will improve the survival and quality of life of HIV/AIDS people. Furthermore, it will also help to prevent the spread of the epidemic.

a - Prophylaxis by antimicrobial agents

Cotrimoxazole: In Europe and North America, pulmonary pneumocystosis and cerebral toxoplasmosis incidence were reduced by the use of cotrimoxazole, when the CD4 cell count are below 200/mm³, and if the haemoglobin rate is more than 7g/dl and the creatinine rate below 130 mM/l. However, 15% to 30% of the patients do not tolerate this prophylaxis (cutaneous rashes, neutropenia, hepatic or renal toxicity). This toxicity is partially dependant on the dose. Even if the bacterial environment is quite different in Africa, prophylaxis with cotrimoxazole should be prescribed to prevent *Pneumocystis carinii* (even if it is less frequent), *Isosporis belli* (one of the most common aetiology for diarrhea), recurrent bacterial pneumopathies and *Salmonella* bacteriemia. It seems that it is necessary to give this prophylaxis for patients with a CD4 cell count below 300/mm³.

Recommended regimen are:

Cotrimoxazole 800/60 mg or 400/80mg po daily or Cotrimoxazole 400/80 mg po 3 x/week

Mycobacterium tuberculosis prophylaxis: tuberculosis is one of the commonest and earliest opportunistic infection in Africa. It is therefore important to prevent it. Some studies in Haïti, Uganda and Zambia showed that tuberculosis incidence decrease using isoniazid. However, these results are not confirmed at long term because of reactivation or reinfection. Moreover, it appears very difficult, from the point of view of costs and adherence, to propose life-long prophylaxis. Furthermore, it could lead to the emergence of drugs resistant strains. By contrast, active screening for tuberculosis among seropositive patients is strongly recommended and cost effective. In case of personal or familiar tuberculosis history, a prophylaxis could be initiated:

Preferred regimen are:

- INH 300 mg + pyridoxine 50 mg po qd x 12 months
- INH 900 mg + pyridoxine 50 mg 2 x/week x 12 months

Alternative regimen are:

- Rifampicin 600 mg po qd x 12 months
- Rifampicin 600 mg/day plus pyrazinamide 20 mg/kg/day x 2 months
- Rifampicin 600 mg 2x/week plus pyrazinamide 50 mg/kg 2x/week x 2 months.

b - Prophylaxis by immunisation

Principles: HIV-infected persons should not receive live virus or live bacteria vaccines. Killed or inactivated vaccines pose no danger to immunosuppressed patients. Symptomatic HIV-infected persons have suboptimal responses to vaccines, hence all single-dose vaccines should be given as early as possible in the course of HIV infection to obtain an optimal immune response.

Recommendations: Pneumococcal vaccine is recommended as high priority, with revaccination at 5 years. Tetanus-diphtheria vaccine should be administered as usual by recommended for adults, every ten years. Hepatitis B vaccine could be used if necessary, i-e in presence of susceptible injection drug users, sexually active gay men, prostitutes, sexually active heterosexual men and women with STDs or more than 1 partner in the last 6 months, and household or sex contacts of HBsAg carriers. The following vaccines are contraindicated: measles, mumps, rubella, BCG, oral polio, varicella-zoster, yellow fever.

c - Management of opportunistic diseases in HIV/AIDS adults

The WHO has recommended some algorithms for the management of HIV infected patients. The main are described below in a schematic format (for chronic diarrhea, respiratory manifestations, headache and fever). Table 3 summarizes treatment regimens recommended for opportunistic infections, table 4 for non-infectious diseases.

Insert 4 management schemes and tables 3 & 4

d - Management of children living with HIV/AIDS in Africa

Primary prevention: Materno-foetal and breast-feeding transmission can be prevented as previously described. Security for blood products and sterilisation of all materials must be enhanced, improving the staff training and the furniture purchase.

It is also very important to improve the care of pregnant women because the severity of maternal infections is directly associated to the materno-foetal transmission rate and the severe clinical forms of children.

Secondary prevention: It is necessary to treat systematically every infection, even if it appears mild, particularly for cutaneous, nose-and-throat and bronchopulmonary infections, as well as digestive candidiasis. Early diagnosis and adequate treatment may reduce mortality due to HIV.

Cotrimoxazole prophylaxis has to be strengthened, because of the increasing risk for pneumocystis carinii infection, but also to protect against other bacterial infections. This prophylaxis can be given daily in the first months. The recommended dose is 25 mg/kg/day.

Tuberculosis prophylaxis for children living with infected adults is recommended with the following regimen: Rifabutine (Ansatipine* 150mg caps) 10 to 20 mg/kg/day once.

Supplementation with vitamin A shows a benefit, especially because of a reduction of diarrhea episodes. Recommended doses are: 50 000 UI at 1 and 3 months, 100 000 UI at 6 and 9 months, 200 000 UI at 12 and 15 months. The common vaccination program has to be followed, especially for the BCG at birth: General measures, as nutritional surveillance and food hygiene, have to be reinforced.

Birth	BCG + oral polio
6 weeks	Diphtheria, tetanus, whooping cough + oral polio
10 weeks	Diphtheria, tetanus, whooping cough + oral polio
14 weeks	Diphtheria, tetanus, whooping cough + oral polio
9 months	Measles
1 year	Diphtheria, tetanus, whooping cough and polio booster

Antiretroviral therapy

1. Antiretroviral therapy in adults

a - Introduction

The introduction of new antiretroviral drugs (ARV) in industrialised countries has significantly improved the survival of HIV-infected persons. The effects of ARV consist of a reduction of the plasmatic viral load, and, more moderately, of the biological fluids or lymph nodes viral load. This viral load decrease is associated with a partial restoration of the circulating CD4 lymphocytes. Moreover, the use of AZT during pregnancy allows a very important reduction of perinatal transmission, in the absence of breast-feeding.

Factors related to the ARV cost and the need of a relative advanced technical equipment have limited the diffusion of these drugs in the developing world. Nevertheless, ARV should be available for every HIV-infected person, who is entitled to receive it according to the scientific knowledge.

b - Recommendations

The first step before introducing ARV is to prevent, diagnose and cure opportunistic infections, particularly tuberculosis. ARV should only be prescribed if adherence and correct patient follow-up, including communities and persons living with HIV/AIDS associations, are assured. The serological diagnosis must be reliable and laboratory facilities available. Monotherapy has to be proscribed because of rapid resistance emergence. Whenever possible, triple therapy should be used, both for children and adults. ARV treatment for women should be a priority. Treatment must be established for an indefinite duration. Indications proposed for developing countries according to clinical situations, CD4 cell count and viral load are summarized in table 6.

Clinical situation	CD4 cell count	Viral load	ARV treatment
Asymptomatic	< 350/mm ³	Any value	Yes
	350-500/mm ³	Undetermined	To be discussed*
		<10 000 <10 000	Yes No
	>500	Undetermined <10 000 >10 000	To be discussed* Yes No
	Undetermined	Undetermined	No
Symptomatic	Any value	Any value	Yes
Terminal stage	Any value	Any value	To be discussed (cost-benefit ratio)

*To be discussed, taking account financial means

c - Therapeutic strategies

Treatment strategies should be regularly adapted to the results of ongoing trials.

Nucleoside analogs bitherapy:

Among associations with zidovudine (AZT), the most current are zidovudine/didanosine (ddI) and zidovudine/zalcitabine (ddC). Zalcitabine is recommended for early stages.

The association of zidovudine with lamivudine (3TC) is interesting because of a longer delay for AZT resistance emergence.

Among associations without zidovudine (AZT), Stavudine (D4T) with ddI, and D4T/3TC are proposed because of their tolerance and efficacy.

Encouraging but discordant results were obtained with ddI/hydroxyurea. The gain is modest for severe haematology toxicity.

Nucleoside analogs and protease inhibitors bitherapy: The efficacy is high but lower than that of the correspondent tritherapy :

- zidovudine (AZT) and saquinavir (SQV) < AZT-ddC-SQV
- zidovudine (AZT) and indinavir (IDV) < AZT-3TC-IDV

Other bitherapies, such as stavudine/saquinavir or stavudine/nelfinavir are under evaluation.

Tritherapies including 2 nucleoside analogs and 1 protease inhibitor: It is the best association in terms of extended virological and immunological efficacy. After 6 to 12 months of treatment, the mean viral load decrease is from 1.5 to 2 log. In 10 to 15% of the cases, early intolerance is noted. Furthermore, after 10 to 12 months, there are 10 to 20% of immunovirological failure.

Tritherapies including 3 nucleoside analogs: Some associations (AZT-ddI-3TC and D4T-ddI-3TC) are under evaluation, notably for the treatment at seroconversion. The advantage is that of significant viral load reduction without the side effects and drug interactions (rifampicine) of protease inhibitors.

Associations with protease inhibitors: Some are under study, especially ritonavir and saquinavir. The goal is to block (for example with ritonavir) the p450 cytochrome with lower doses and so to increase the action of the second protease inhibitor. The 2 protease inhibitors have to be associated with 1 or 2 nucleosides analogs. These regimens are limited to patients at late stages who have already received several drugs.

	2 nucleosidic inhibitors	protease inhibitors		
1-Triple therapy with protease inhibitor	AZT-ddI AZT-ddC AZT-3TC D4T-ddI D4T-3TC	One of the 5 possibilities	Indinavir Nelfinavir Ritonavir	One of the 3 possibilities
2-Multitherapies less strong and less studied – Triple therapies with saquinavir – Triple therapies with a non nucleoside reverse transcriptase inhibitor	- Waiting for the EOF capsules -Only one association (AZT-ddI-nevirapine) is validated			
3 - Triple therapies with 3 nucleoside analogs	Some trials in course: – AZT-ddI-3TC – D4T-ddI-3TC			
4. Bitherapy with 2 nucleoside analogs, especially during anti-tuberculosis treatment (Clinical interest validated)	AZT-ddI and AZT-ddC			

d - Associations which are contraindicated

- Stavudine/zalcitabine (D4T/ddC): toxicity risk
- Zidovudine/stavudine (AZT/D4T): antagonism, toxicity
- Didanosine/zalcitabine (ddI/ddC): non coherent
- Didanosine/lamivudine (ddI/3TC): non validated
- Zalcitabine/lamivudine (ddC/3TC): non validated
- Indinavir/saquinavir (IDV/SQV): antagonism

e - Tuberculosis treatment associated with antiretroviral treatment

Patient never treated with Protease Inhibitor (PI):

Quadritherapy during 2 months followed by bitherapy (isoniazid + rifampicin) for 4 months.

At the end of this treatment, it is possible to start with PI.

Patients already receiving PI:

- Stop PI during the whole anti-tuberculosis treatment. The tuberculosis is then optimally treated, but emergence of resistant virus can appear, and the viral load can increase.
- Stop PI during the period of "induction" treatment (isoniazid, rifampicin, ethambutol, pirazinamid, 2 to 3 months), followed by isoniazid and ethambutol 16 months long, restarting PI. The short interruption of PI will prevent resistance emergence, but the anti-tuberculosis treatment will be long and sub optimal.
- Continue the PI, using indinavir (800 mg x 3/day). Quadritherapy using rifabutin (150 mg/day) instead of rifampicin for 4 months, followed by 6 months of isoniazid + rifabutin. Such regimen must be further evaluated.

f - Change of ARV

It is based on any clinical, immunological or virological progression.

Patient with prior monotherapy: a bitherapy or better a triple therapy must be prescribed, using preferentially drugs other than those used before.

Patient with prior bitherapy: if clinical or immunological progression is observed, the best is to change the 2 nucleoside analogs and, if possible, to associate a protease inhibitor.

2. Antiretroviral therapy by pregnant women

a - Mother to child transmission

In countries where breast-feeding is rare, the estimated risk of perinatal transmission for HIV-1 is 15 to 20%. Studies conducted in african countries where breast-feeding is very common show an increased risk, from 25 to 30%. For HIV-2, the perinatal transmission rate is only 1 to 2%.

When there is no breast-feeding, HIV is principally transmitted during the latest phase of the pregnancy and during the labour. In Africa it has not been demonstrated that caesarean section could reduce the transmission rate. In case of breast-feeding, the most common situation in the developing world, the transmission is distributed as following: for a global rate of 25 to 30%, 25 to 30% of the transmission happens before 28 gestation weeks, 50 to 60% between the late pregnancy, the labour and the early breast-feeding period (the first week). Post natal transmission can continue for long time, and represents 15 to 20% of the global risk for HIV-1 transmission. Studies have also shown that the risk of transmission is increased by a CD4 count below 200/mm³, maternal vitamin A deficiency, malaria and breast abscess.

b - Prevention of mother to child HIV transmission

Before 1996, WHO and UNICEF recommended the breast-feeding in the developing world, taking into account its benefits for the children. In 1996, UNAIDS recommended individual strategies, based on the specific family conditions, in countries where breast-feeding promotion is the rule.

Monotherapy with AZT was evaluated in a double blind therapeutic trial against placebo, which was interrupted in 1994 when the first intermediary analysis showed a reduction of the transmission rate from 25.5% to 8.3%. Several studies with AZT simplified regimen are under evaluation. Other trials evaluating preventive measures are undergoing: genital disinfection during the labour, vitamin A supplementation, passive immunisation.

c - Antiretroviral recommendations

In case a pregnant woman who can afford to buy ARV drugs, medical staff has to propose a screening test for HIV, to advise against breast-feeding and to treat as follows:

- Before delivery: AZT (300 mg 2x/d, 200 mg 3x/d or 100 mg 5x/d) initiated at 14-34 weeks of gestation and continued to onset of labour
- During labour: IV AZT (loading infusion of 2 mg/kg IV for one hour followed by continuous infusion 1 mg/kg per hour until delivery)
- Infant: AZT for the new-born (AZT syrup at 2 mg/kg every 6 hours) for the first 6 weeks of life beginning 8-12 hours after birth.

More recent advances in antiretroviral therapy have raised the new issue of antiretroviral therapy of the pregnant women as well as antiretroviral prophylaxis to reduce the risk of perinatal transmission. With regard to dosing requirements, only three drugs have undergone pharmacokinetic analysis in pregnancy: AZT, 3TC and nevirapine. All three are well tolerated and show pharmacokinetic data similar to those for non-pregnant subjects. There are few studies that address the safety of many of these drugs in the neonate except for anecdotal clinical experiences, limited clinical trials, and animal toxicity studies.

3. Antiretroviral treatment after exposure of health care workers

In case of blood, bloody body fluids, semen or vaginal secretions exposure, skin should be first washed with soap and water, mucous membranes should be flushed with water.

In case of high risk exposure, the association AZT/3TC should be offered. A protease inhibitor (indinavir or ritonavir) has to be added in case of major danger (deep injection, contaminating patient at a late stage). These regimens have to be continued for 4 weeks.

4. Antiretroviral treatment by children

a - Introduction

Materno-foetal transmission, breast-feeding, blood transfusion and sexual abuses are the main routes for the HIV transmission in the developing world. As for adults, prevention and prophylaxis are the most important means to fight against AIDS, but antiretroviral therapy, when it is accessible, can also be proposed in certain situations.

b - Antiretroviral drugs

c - Indications

Children under 2 years:

Children infected during pregnancy or at labour, considered as in the primo-infection stage, could be treated by ARV, particularly if they present signs of disease. Furthermore, in Africa, mortality is very high during the first 2 years of life. Breast feeding is also the most common situation, extending the contamination period after the birth. Early diagnosis is difficult because of the lack of appropriate laboratory equipment (for viral cultures or PCR).

Diagnosis could be based on p24 antigenemia or serological conversion after 10 months, when breast-feeding was interrupted at least 3 months before.

Older children

Symptomatic children must be treated, particularly those presenting clinical manifestations showing an important immunodeficiency (as a zona). Treatment regimens follow the same principles as for adults. Bitherapy (2 NRTI) can be proposed, and triple therapy must be initiated in case of clinical or biological progression under bitherapy.

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