Clinical Management of HIV/AIDS

The National Guidelines

Ministry of Health
Government of Pakistan

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National AIDS Control Programme
National Institute of Health
Islamabad

Joint UN Programme on HIV/AIDS
(UNAIDS) Pakistan

Preface

Ever since the beginning of AIDS epidemic in 1981, more and more people are becoming HIV infected every few seconds and dying of AIDS each minute. Ever expanding horizons of knowledge and awareness about Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) demand a dynamic approach to AIDS prevention and control.

Existence of standard guidelines for the people involved in HIV/AIDS prevention and control activities ensures that all efforts being made for the purpose are well coordinated and in right direction. Moreover, it is important to have guidelines written in the context of one's own culture, financial and resource constraints and standards of the medical practice.

In an effort to improve upon the existing practices, the National AIDS Control Programme (NACP), Ministry of Health, in collaboration with the Joint United Nations Programme on HIV/AIDS (UNAIDS), decided to lay down standard national guidelines for the Clinical Management of HIV/AIDS, applicable to all levels of healthcare facilities in the country. The guidelines have been developed and reviewed by renowned experts in their work field.

Purpose of the guidelines on Clinical Management, of HIV/AIDS is to provide an in-depth knowledge to the clinicians, both in the public as well as private sector that would help them to diagnose, manage and prevent further spread of the disease. Considering the constraints of lack of access to the latest developments in the medical field on part of the health professionals serving in the peripheral areas, an effort has been made to put detailed information on the subject. The guidelines contain brief information regarding laboratory diagnosis of HIV/AIDS as well, however the readers desirous of more information may consult the guidelines on HIV Testing. Similarly the importance of counselling in management of HIV/AIDS can also not be over emphasized. The readers are, therefore, also advised to consult the guidelines on counselling for HIV/AIDS developed by the National AIDS Control Programme and UNAIDS Pakistan.

Although a great effort has been put in to ensure a really useful and practicable manuscript yet there would be ample space for improvement, since the exercise has been carried out for the first time in Pakistan. Any suggestion, guidance and critique from the working specialists and medical professionals would be warmly welcome as it remains the main tool to enhance the quality of this manuscript in the years to come.

[Dr. Athar Saeed Dil]
Executive Director & National Coordinator

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Acknowledgements:

The National AIDS Control Programme and UNAIDS Pakistan gratefully acknowledge the work done by Dr. Naseem Salahuddin, the author of the guidelines on Clinical Management of HIV/AIDS who did the laborious work of guidelines development in context of the social environment prevalent in our society. Similarly, the inputs from the experts, listed at annexures I & II involved in review, consensus building and pre-testing work are also gratefully acknowledged!

The Provincial AIDS Control Programmes actively participated in the development process of these guidelines for which the NACP and UNAIDS are greatly indebted. Dr.Rana Muhammad Safdar, Dr. Najma Lalji, Dr. Hassan Orooj, Dr. Asma Bokhari and Dr. Aysha Asad of the NACP/UNAIDS managed all basic work, arranged workshops and rendered valuable services for the development and publishing of the guidelines. Their hard work and most useful inputs are acknowledged and endorsed with great pleasure.

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1. INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is the most severe manifestation of a clinical spectrum of illnesses caused by infection with human immunodeficiency virus (HIV), and characterized by the development of serious opportunistic infections, neoplasms, or other life-threatening conditions resulting from progressive HIV-induced immune suppression. AIDS is a relatively newly recognized disease, first reported in 1981 among young homosexual men in New York City, Los Angeles and San Francisco, who presented with unusual opportunistic infections. This discovery triggered off tremendous research that has culminated into fascinating insights into the functioning of the human immune system, as well as the virus, which destroys this system.

The pandemic affecting humans in every continent of the globe is a cause for great concern for loss of human lives. Its incidence rises by the day. Pakistan had remained sheltered from the virus for at least the first decade of the existence of AIDS. However, the graph of newly discovered HIV positive patients continues to rise by the year. If unreported cases are recognized, we may be taken by surprise. Hence the attempt on the part of this publication to assist clinicians to come to terms with the rising incidence of HIV/AIDS in Pakistan, and to help them diagnose, manage and prevent the further spread of the disease.

The rapid strides in our understanding of the disease have opened up possibilities for new modalities of diagnosis and management, making it exceedingly difficult for the average clinician to keep pace with newer developments. There have been many published paradigms for the management of AIDS by various health organizations, yet it is important to have guidelines written in the context of one's own culture, financial and resource constraints, and standards of medical practice.

AIDS is transmitted horizontally through sexual contact and blood or blood products, and vertically from mother to child. Given this fact the diagnosis of the disease should no longer evoke a reaction of curiosity or anxiety for the practicing clinician or the hospital administration or staff, as it did in the earlier history of AIDS. The AIDS patient should be given the same facilities, care and compassion as any patient with an ultimately fatal illness. Emphasis is laid time and again on a humane approach. The patient and the family should receive concern, attention and confidentiality from the physician in a non-judgmental manner that would encourage revisits and continuity of care. There is no substitute in the practice of medicine for a thorough history and physical examination. HIV and AIDS require meticulous inquiries, so that sound judgments can be made within the limits of the patient's resources. The goal should be to improve quality of life.

The clinician examining an AIDS patient is likely to recognize the same spectrum of infections, which he/she sees commonly in the non-AIDS population, such as oropharyngeal candidiasis, diarrhoea diseases, viral hepatitis, tuberculosis and skin and respiratory tract infections, to name a few. AIDS - specific opportunistic infections, e.g *pneumocystis carinii,* toxoplasmosis or atypical mycobacterial infections may not be easily diagnosable but clinical suspicion may be raised. Care has been taken to give detailed treatment regimens of diseases like TB, sexually transmitted diseases (STDs), and fungal infections.

This booklet is not intended to be a comprehensive discourse on AIDS, nor a substitute for textbook learning. It is meant to guide clinicians at various levels of health delivery system both in public and private sectors towards raising the index of suspicion, diagnosing and managing the HIV/AIDS patient within available resources, and to help refer the patient for appropriate care when these resources have been exhausted. It is also intended to be used as a training manual for physicians in clinical management of the disease.

Individual drug dosages have been given for adult as well as paediatric ages. As far as possible generic names of drugs have been used, except where a drug is known more commonly by its trade name. There is also a separate section for managing HIV/AIDS in the pregnant woman, in labour and in the newborn.

Antiretroviral (ARV) therapy is extremely expensive and generally not available in Pakistan at this time. However with mounting pressure globally for reduced prices of ARV therapy it may become available in future. The current recommendations for when and how to treat, and available drugs with dosages have also been included in tables at the end of the booklet. References are provided at the end for further reading.

2. HOW AN HIV/AIDS PATIENT PRESENTS TO THE DOCTOR

HIV spreads by only three means:

- Homo or heterosexual intercourse
- Through blood or blood products
- Mother to newborn child during pregnancy, childbirth or breast feeding

Most Pakistani males do not volunteer information about their extramarital heterosexual or homosexual experiences, and females will almost never talk about these. Obtaining risk factors is difficult, and hence misleading. A history of blood transfusion may not be significant since blood banks report a very low prevalence of HIV. In 1994-95, Baqi et al found a very low prevalence of HIV among commercial sex workers in a red light district in Karachi, and none among truck drivers. This situation, however, may change over time. In our experience most HIV or AIDS patients have presented under the following circumstances:

- Young or middle aged male deported from Gulf States or other countries where HIV testing is mandatory before renewal of work visas of overseas workers.
- History of visits or stay in countries with high prevalence of HIV, e.g. India, Thailand, sub-Saharan Africa, USA, etc.
- Homosexual male
- Transvestite
- Male, and infrequently, female indulging in extramarital sexual relations. ;
- Spouse of HIV/AIDS patient ("innocent bystander"). ″ .
- Newborn child of a known HIV positive mother.
- Child with failure to thrive
- Referral from blood bank screening or surveillance centers.
- Multiple transfusions of blood or blood products after 1982. Young males with hemophilia requiring replacement therapy with anti hemophiliac factors, have been infected.
- Jail inmates, usually from a foreign country
- Intravenous drug addicts, especially those sharing syringes and needles. Reuse of contaminated syringe and needle by unscrupulous medical practitioners is likely to add HIV to the already burgeoning incidence of Hepatitis B and C in our population.
- Sexual abuse
- History of sexually transmitted disease and especially of genital ulcer.
- Any patient with cardinal or characteristic findings of AIDS (see page 14)

Physicians are advised to ask relevant questions to assess risk factors, so as to increase the yield of early diagnosis, rather than wait for the disease to change to full blown AIDS. Patients visiting their doctors for any reason must be asked about their occupation, travel abroad, blood transfusion after 1982, and sexual habits. Women must be asked relevant histories about their husband's risks for HIV.

3. LABORATORY TESTS FOR HIV INFECTION

3.1 Anti-HIV antibody

Screening test for HIV is done by Enzyme-Linked Immunosorbent Assay (ELISA), which measures the antibody to the Human Immunodeficiency Virus (anti HIV), and not the virus itself. Laboratories report HIV-1, which is the common cause of most HIV infections, as well as HIV-2, another genetic variant with a distinctive clinical course and epidemiologic (though less frequent) distribution. Currently available tests are highly sensitive and specific. Since HIV is of low prevalence in Pakistan, the chances of false positivity are high. Rapid tests are available, but any positive test must be repeated by the same method or by Western Blot if affordable. WHO recommends three different tests using different techniques. For more detailed information about various available tests, the reader is referred to the guidelines on HIV antibody testing developed by the National AIDS Control Program.

In case of a suspected false positive or false negative test, the patient's risk factors must be reconsidered, and the tests repeated until a definite conclusion can be arrived at. There must be no doubt of the patient's HIV status, since a false positive or false negative result may have a devastating effect on the lives of the patient and the family.

3.2 Immune status

Once HIV is confirmed, a $CD4^+$ cell count would be extremely valuable in assessing the severity of the disease and for predicting the onset of opportunistic infections or other complications. The $CD4^+$ cell count in the normal healthy adult is 800 - 1000/ul. This test is available in only a few private laboratories in the country, and may not be affordable to all (Rs. 8,000). Moreover, it should be repeated every 3 - 6 months in the asymptomatic patient to assess progress and to decide about prophylaxis or treatment.

A rough, easier substitute is to obtain total leukocyte count and differential (TLC, DLC) and calculate the total lymphocyte count, which ranges from 7,000 cells/ul in the newborn, to 4,000 cells/ul in a child, to 2,000/ul in the adult. Of these lymphocytes half are T cells, while the remaining are B cells and natural killer cells. A total lymphocyte count of less than 1,000 cells/ul is strongly predictive of a $CD4^+$ count of less than 200/ul. Opportunistic infections may be anticipated at this level of lymphocyte count.

Examples: If TLC is 7,000 cells/ul and DLC shows 35% lymphocytes, the total lymphocyte count is calculated as:

$$\frac{(\text{TLCXLymphocyte \%})}{100} \qquad \frac{(7000)(35)}{100} = \qquad 2{,}45 \text{ cells/ul}$$

if TLC =7,000 cells/ul, DLC shows 5% lymphocytes,

$$\text{Total lymphocyte count} = \frac{(7000)(35)}{100} = 350/\text{ul}$$

Many other viral infections, malignancies, corticosteroids and immune suppressive can also cause lymphopenia.

3.3 Viral detection:

Quantitative viral load (VL) assays reflect more accurately the fluctuations in HIV viral load in response to antiretroviral therapy. Level of plasma viraemia is measured by detection of HIV RNA by PCR, and represents actively replicating virus. To date there is no facility available for viral load assay in Pakistan.

4. NATURAL COURSE OF HIV INFECTION

A person who becomes infected with HIV goes through several stages of the disease over several years.

- The **first stage** starts four to eight weeks after infection. The patient experiences Acute Retroviral Syndrome, which may last a week or two, and may be so nonspecific that HIV may not be suspected unless a definite history of exposure is elicited. It is during this phase that the viral load is maximum and the patient is most infectious to others. HIV-1 p24 antigen capture assay will be positive at this stage. Antibodies to HIV start to develop but the serologic test may be positive, negative or intermediate up to the first three months. If in doubt and clinical suspicion of infection remains high, the test should be repeated. :

- **Latent or asymptomatic phase** which may last five to ten years. The viral load falls to undetectable levels while the virus goes into latency. CD4+ counts are in reasonably good numbers

- **AIDS Related Complex (ARC):** Mild disease episodes may occur, which respond to appropriate therapy

- **AIDS:** Severe illness with opportunistic infections or malignancies. The average time from acute retroviral syndrome to full blown AIDS is eight years. Viral load is again high, while $CD4^+$ count falls. This progresses to the terminal stage.

- An individual patient may be a slow progressor or a rapid progressor, depending upon the viral load as well as the general state of health. It is estimated that 5% of HIV may never progress to AIDS.

TABLE 1 Relationship between Lymphocyte numbers, $CD4^+$ and clinical stage of disease

Clinical condition	Lymphocyte count cells/ul	CD4+ cell count/ul
No symptoms	> 2,500	500 - 600
Minor symptoms	1,000-2,500	350 - 500
Major symptoms and opportunistic infections	500 - 1, 000	200 - 550
AIDS	500 - 1, 000	<200

5. ACUTE RETROVIRAL SYNDROME

Signs and symptoms:

- Fever, lethargy, malaise, myalgias, headaches, nausea, vomiting
- Lymphadenopathy: focal or generalized
- Pharyngitis with pharyngeal oedema and tonsillar enlargement
- Rash: erythematous, maculopapular, urticaria, alopecia. Lesions may be on the face, trunk or extremities, followed by desquamation of skin of palms and soles
- Painful ulcers or exanthemas on the buccal mucosa, gingiva or palate. Oral or even ooesophageal candidiasis may be present.
- Syndrome of aseptic meningitis including retroorbital pain, headache, photophobia or cognitive dysfunction.
- Cranial, spinal nerve or spinal cord involvement causing isolated nerve palsies, myelopathy or Guillain Barre syndrome
- Lymphopenia may be marked at this stage with loss of both CD4 and CDS8 cells. Rebound of these numbers follows seroconversion.

The syndrome is by no means specific to HIV and may be seen in other acute viral infections such as infectious mononucleosis, EBV, etc. It may be easily missed if HIV is not suspected. Serology should be documented. If negative at this time, it should be repeated within 6-8 weeks. Antiretrovirai (ARV) therapy should be started immediately, since it is most effective at this stage. This is particularly important after a suspected exposure such as a contaminated sharp, or known sexual exposure. Although ARV is not known to eradicate HIV, it will reduce viral replication and hence viral load, resulting in delayed progression. This is a highly infectious phase and the patient should be counseled about its infectiousness to others.

6. MANAGING THE LATENT OR ASYMPTOMATIC HIV PATIENT

The approach to managing the asymptomatic HIV patient is to document a detailed history and physical examination, baseline laboratory investigations and X-rays.

6.1 History and review of systems

- Approximate date of exposure, or when HIV positivity was first detected.
- Sexual habits: one or more wives, extramarital partner/s, hetero- or homosexual preference.
- Route of infection e.g. transfusion of blood or blood products, homosexuality, intravenous drug usage, unprotected sex, or mother-to child transmission. This is helpful in counseling about discontinuing high-risk behaviour.
- Even if the patient has no presenting complaints, a complete review of each body system must be undertaken, e.g. fever, myalgia, fatigue, appetite, weight loss, oropharyngeal complaints, headaches, urinary symptoms, etc must be documented as baseline information.
- Menstrual history, parity, and if currently pregnant.
- Lead questions to determine STDs, such as genitourinary lesions, discharge, and pain.
- State of nutrition
- List of current medications.
- Immunization history
- Drug allergies
- Past history of tuberculosis, hepatitis, cardiovascular disease, pulmonary disease or diabetes.
- Occupation and exposure to chemicals, birds, animals
- Socioeconomic status and family support system
- For managing children with HIV/AIDS, it is important to record birth history, developmental progress and growth monitoring.

6.2 Physical examination

The HIV/AIDS patient should be examined in the same way as one would examine any non HIV patient. Gloves need not be worn for the ordinary examination except when in contact with body fluids.

- Record weight and vital signs
- Note any skin lesions or rash.
- Oral lesions such as thrush or leukoplakia

- Dental disease, gingivitis
- Lymphadenopathy in neck, axillae and groins
- Abdominal mass or organomegaly
- Neurological check
- Respiratory tract
- Eye examination including funduscopy by an experienced ophthalmologist, who should look especially for presence or absence of retinitis.
- Genital examination to look for genital warts, chancre, ulcers, vesicles or urethral discharge. Cervicovaginal examination to look for discharge or tenderness. A baseline Pap smear should be done.
- Anorectal examination for ulcers, herpes simplex, warts.
- All normal or abnormal findings should be documented in the patient's file for future reference.

6.3. Baseline laboratory investigations and X-rays

- HIV antibody by ELISA, confirmed by any other method available such, as Western Blot
- $CD4^+$ lymphocyte count and percentage (if affordable)
- HIV viral load (if available and affordable).
- Complete blood count: note hemoglobin, platelet count, TLC, DLC and total lymphocyte count
- Liver Function tests, serum creatinine.
- Tuberculin skin test. In early HIV infection this may be positive. As cell mediated immunity falls it may become negative. Even 5 mm induration should be taken as significant in immunocompromised patients.
- Serology: Hepatitis B surface antigen, Anti-HCV, VDRL. Toxoplasma and cytomegalovirus (IgG and IgM) may be done if easily affordable.
- Chest X-ray
- Urine analysis
- Pap smear

If still asymptomatic, the patient should be reviewed at least every six months, or more frequently as and when necessary, for review of symptoms. Lab. tests should be repeated selectively according to the patient's needs and financial resources. However, a hemoglobin and total lymphocyte count should be repeated at regular intervals in all cases. If the total lymphocyte count falls below 2000/ul, the physician must be on alert for the beginning of opportunistic infections.

7. PREVENTION OF INFECTIONS

7.1. Vaccinations

As the number of helper T cells ($CD4^+$) falls, the HIV patient is likely to acquire infections, some of which may be preventable with vaccines. These must be offered and given according to normal schedule in early HIV infection, before the CD4+ count starts to fall or symptoms of disease appear. Later in the course of HIV infection, the antibody response to vaccination may be inadequate. Some vaccines may actually contribute to a temporary increase in viral load, the clinical significance of which is not known. All vaccines are safe, except those prepared from live viruses: measles, mumps, rubella, yellow fever and varicella, or from live bacteria e.g. oral typhoid vaccine and BCG. There is no increase in the rate of adverse reactions from vaccines. The following vaccines may be given in descending order of priority:

1) Hepatitis B: Adult dose 20 ugm (1 ml), paediatric dose 10 ugm (0.5 ml) IM on day 0,1 month and 6 months.
2) 23-valent polysaccharide pneumococcal vaccine (Pneumovax) : 1 ml IM, once only for adults. A new 7-valent pneumococcal conjugate vaccine has recently become available in United States for use in young children, and is highly effective against invasive disease.
3) Meningococcal vaccine: 1 ml IM every 3-4 years. This is not recommended for children below 2 years age.
4) Haemophilus Influenza B (Hib): at 2, 4, 6 and 18 months
5) Influenza vaccine: 0.5 ml IM annually.

7.2. General health advice

HIV patients must be counseled to lead as normal a life as possible, including family and social life. HIV phobia must be discouraged and myths dispelled through proper explanations and counseling. Proximity to children need not be discouraged. They and their family and social contacts must be reassured that the infection does not spread by shaking hands, hugging, eating together, or any other casual contact. They may continue on their job, unless if their work poses danger to others through blood contact, or they feel they are unable to work because of symptoms.

- Sexual behaviour should be modified, and IV drug use discontinued.
- The AIDS patient should avoid contact with persons with respiratory tract infections
- Food eaten should be hygienically prepared and served.

- Undercooked meat should not be consumed because of the risk of helminths and toxoplasma :
- If reusing stored food, it should be thoroughly re-heated
- Food should be nutritious and well balanced in content
- Water used for drinking or for ice should be kept boiling for at least 1 minute, cooled and filtered before consuming.
- Moderate exercise and regular sleeping habits should be encouraged.
- Smoking, alcohol and illicit drugs should be avoided
- Physical and mental stress should be avoided
- Close contact with sick animals such as cats, dogs, cattle and birds should be avoided. Animal waste is particularly likely to cause infections such as toxoplasmosis, helminthiasis.
- Swallowing water from lakes, rivers and any source with possibly contaminated water should be avoided because of risk of cryptosporidiosis
- Latex condoms should be used during sexual intercourse.

No special precautions are needed for dishes, glasses, and eating utensils. However patients must be advised about normal hygienic practices, such as not drinking/eating out of the same bottle, fork, spoon, etc

The reader may refer to the book on HIV counseling published by UNAIDS.

7.3 Prophylaxis for opportunistic infections

The use of prophylaxis for opportunistic infections has been a major advance in HIV disease and has considerably reduced the onset of at least a few such infections. It may be mentioned, though, that wherever highly active antiretroviral therapy (HAART) has been used successfully, the incidence of opportunistic infections has declined, as has the need for prophylaxis.

Primary prophylaxis is that given prior to development of an infection. It is oral and life long.

Secondary prophylaxis is that given after acute treatment of an opportunistic infection to prevent or reduce the incidence of relapse. This is also called maintenance or chronic suppressive therapy. All drugs are oral and life long.

TABLE 2 Primary prophylaxis

Infection	Indication	Regiment: Drug/Dose
PCP	• $CD4^+$<200/ul • Thrush • Chemotherapy • Prior AIDS- defining illness	Trimethoprim-Sulfameth. Septran DS 1 daily or 3 times a week. For children: TMP8mg/kg/24hrs.+ SMX 25 mg/kg/24 hrs once a day, or 3 times a week
Tuberculosis	Positive M.T. History of Positive MT without prior prophylaxis Recent exposure to active TB	INH 300 mg daily for months, with pyridoxine 50 mg daily, or Rifampicin 600 mg + PZA 20 mg/kg daily for 2 months. For children: INH 10 mg/kg/day + Rif. 10 mg/kg once a day.
Disseminated Mycobacterium avium complex (MAC)	CD 4^+ < 50/ul	Azithromycin 1200mg once weekly. Children; 10 mg/kg once weekly, or Clarithromycin 500 mg twice a day. Children: 7.5 mg/kg twice a day
Toxoplasmosis	$CD4^+$<100/u land Toxoplasma IgG antibody positive	Cotrimox. (Septran DS) 1 daily. Children: TMP 8 mg/kg/O.D. or 3 times a week

Table 3 Secondary prophylaxis

Infection	Drug/Dose
PCP	Same as Primary
Disseminated MAC	Continue acute treatment indefinitely, e.g. Clarithromycin 500 mg B.D., plus Ethambutal 15-25 mg/kg/day Children: as above
Toxoplasma	Sulfadiazine 500 mg 6 hrly plus pyrimethamine 50 mg daily with leukovorin 10 mg daily. Children: as above
Herpes simplex (if severe or recurrent)	Acyclovir 400 mg twice daily. Children: 10mg/kgB.D.
Ooesophageal Candidiasis	Fluconazole 100 - 200 mg daily. Children: 3-6 mg/kg/day
Cryptococcus	Fluconazole 200 - 400 mg daily. Children: 3-6 mg/kg/day
CMV retinitis	Ganciclovir IV 5 mg/kg daily, or Oral 1 - 1.5 GTDS
Histoplasma	Itraconazole 200 mg twice daily
Aspergillus	Itraconazole 200 mg twice daily
Salmonella bacteremia	Ciprofloxacin 500 mg twice daily, or TMP-SMX DS twice daily for several months. Children: PMP 15-20 mg/kg/day +SMX 75-100 mg/kg/day (PO) B.D.

8. RECOGNITION OF SIGNS AND SYMPTOMS IN AIDS

As the viral load increases and $CD4^+$ count falls, the probabilities of various opportunistic infections and tumors rise. Much depends upon the geographical location and epidemiological factors, e.g. endemic T.B., fungi. The physician must be on the alert for the signs given below which may aid in the search for associated diseases; conversely, the indentification of findings may lead to interrogation for risk factors, and the diagnosis of AIDS in revers.

There are three sets of findings:

8.1. Cardinal

- Kaposi's Sarcoma. Lesions may be intraoral, generalized. Rapidly progressive or invasive.
- Pneumocystis carinii pneumonia (PCP)
- Tosoplasma encephalitis
- Oesophageal candidiasis
- Cytomegalovirus retinitis

8.2. Characterises:

(if no other obvious cause of immunosuppression is identified)

- Oral thrush (in patient not taking antibiotic)*
- Hairy leukopiakia
- Crypotococcal meningitis
- Miliary, extrapulmonray or noncavitary pulmonary tuberculosis
- Herpes zoster, past or present, multidermatomal, age< 50 years
- Severe prurigo
- High grade B cell lymphoma

8.3. Associated

- Weight loss (recent, unexplained) of > 10% baseline body weight
- A child with failure to thrive
- Loss of expected milestones in children

Fever, (continuous or intermitten) for > 1 month[xpr]
Ulcers (genital or perianal) for> 1 month[K]
Cough for > 1 month[1]*
Neurological complaints or findings including seizures, peripheral neuropathy, motor or sensory deficits, dementia and

progressively worsening headaches
- Generalized lymphadenopathy (extra - inguinal)[x]
- Drug reactions e.g. to thiacetazone, sulfonamides
- Recurrent or severe skin infections, e.g. warts, dermatophytes, folliculitis

Suspect symptomatic HIV infection if:
- Any one cardinal finding
- Two or more characteristic findings
- Any one characteristic finding plus two or more associated findings
- Three or more associated findings plus risk factor for HIV
- Two associated findings plus positive HIV laboratory test

Without the above equation, the symptoms may not be HIV related and other causes should be searched.

9. OPPORTUNISTIC INFECTIONS

Opportunistic infections are caused by microorganisms that are part of the normal flora of the mucosa or are hospital acquired, and generally colonize the area before causing infection. The frequency of infection begins to increase at neutrophil counts below 500/ul, but most serious infections occur when the count is, below 200/Ml. Absolute lymphopenia (<800/|jl), and CD4* count of below 200/^1 predispose to malignancy and opportunistic infections e.g. tuberculosis, toxoplasmosis, cryptococcosis, PML (progressive multifocal ieukoencephalopathy) or lymphoma, while higher $CD4^+$ counts make non-opportunistic infections such as herpes simplex, bacterial pneumonias and diarrhoeal diseases more likely.

9.1. Oral and oesophageal thrush Definition:

Fungal infection, which manifests itself as whitish plaques on the oral mucosa. They are usually located on the palatal or buccal mucosa, which bleeds easily on attempting to remove the plaque. Under the microscope, scrapings appear as pseudohyphae or blastospores of Candida albicans. Oral thrush is a superficial and non-invasive form of Candida infection, while oesoaphageal candidiasis is invasive.

Oral thrush:

Oral thrush is one of the earliest signs of HIV infection and appears when the $CD4^+$ Count is around 500/ul. The tongue appears beef red and curd-like plaques are seen on the tongue and buccal mucosa. Hairy leukoplakia may mimic oral thrush.

Treatment:

Nystatin (Nilstat): 1-2 teaspoonful oral suspension three times daily. Instruct the patient to swish around in the mouth before swallowing or spitting out. Alternatively, local application of 1 % gentian -violet solution twice daily for a few weeks.

Oesophageal candidiasis:

Oesophageal candidiasis may be considered more invasive form of candidiasis and appears with a further fall in $CD4^+$. Pneumocystis carinii pneumonia (PCP) appears about this time as well. There is pain on swallowing (odynophagia) or difficulty in swallowing (dysphagia). Oral thrush is usually seen extending into the pharynx,

however other causes of dysphagia or odynophagia are oesophageal infection from cytomegalovirus, aphthous ulcers or herpes simplex virus, and must be considered in the differentia! diagnosis. Painful swallowing is likely to reduce food intake and further aggravate malnutrition.

Treatment:

Oral ketoconazole (Nizoral) 200 mg twice daily with meals for 14 days (contraindicated in active liver disease). Alternatively, oral fluconazole (Diflucan) 200mg stat, followed by 100 mg daily for 14 days. Paediatric dose: 5-10 mg/kg/ day in 2 doses for 14 days.
There is a high likelihood of recurrence of oral or oesophageal candidiasis and a second course of antifungal agent may be needed, and maintained. In very severe cases, fluconazole 400 mgm/day, or amphoterecin B may be required.
If dysphagia persists despite appropriate therapy, other diagnoses must be considered. Oesophagoscopy and gastroscopy must be performed to rule out malignancy (carcinoma, lymphoma, Kaposi's sarcoma), acid reflux oesphagitis or ulceration

9.2. Chronic Diarrhoea

Definition: Passage of liquid stools three or more times a day for more than a month. Chronic diarrrhea is one of the most common manifestations of AIDS in developing countries

Etiology
Infections
- Salmonella sp.
- Shigella flexneri
- *Giardia lamblia*
- *Entamoeba histolytica*
- *Cryptosporidium*
- *Isospora belli*
- *Campylobacter sp.*
- Cytomegalovirus
- *Strongyloides stercoralis*
- Mycobacterium avium complex (MAC)
- *Enterotoxigenic E. coli (ETEC)*

• *Enteropathogenic E. coll (EPEC)*
• *Candida sp.*
• Rota virus

Malignancies:
- Kaposi's sarcoma involving gut
- Lymphoma

Drug reaction:
- Antibiotics

Idiopathic:
- HIV infection
- Otitis media, especially in children

Severe, continuous diarrhoea may lead to dehydration leading to renal failure. Hence a rapid clinical assessment is essential.

Clinical assessment of dehydration:

Moderate:
- Restless, irritable
- Rapid pulse
- Deep, rapid respiration
- Dry skin and mucosa, sunken eyes
- Urine flow dark and reduced in amount

Begin Oral Rehydration Salt (ORS) as fast as possible. If patient is able to retain, he may be given other fluids such as juice, broth, or semisolids such as *khichri, dalia,'dahi*$_t$ mashed banana or potato. In a child, breast-feeding should be continued. Animal milk should be reduced or replaced by yogurt. Supplementary vitamins and minerals should be given.

Severe:
• Conscious but apprehensive, cold, clammy extremities
• Pulse: rapid, feeble, thready
• Deep, rapid respiration
• Eyes sunken
• Skin and mucous membranes parched
• No urine output for six or more hours, bladder not palpable

At this stage oral rehydration may be slow, hence intravenous fluid must be started with dextrose in normal saline with potassium chloride. The rate of flow must be determined by the degree of severity and other

factors such as underlying heart disease. In children, Ringer's lactate 20-40 ml/kg in 2-4 hours should be given. Loperamide tablet 4 mg stat, followed by 2 mg after each unformed stool, maximum daily dose 16 mg may be given in non bloody diarrhoea. Haematocrit, blood urea nitrogen, serum creatinine and electrolytes must be measured, and hospitalization may be considered.

After the above first aid is in place, the cause of the diarrhoea should be assessed. Fever and bloody diarrhoea with mucous usually indicates salmonella, shigella or possibly *E. histolytica.*

Urgent, empirical treatment options are

- Oral quinolone. e.g ofloxacin 200 mg twice a day for 5 - 7 days. This may be used selectively in children 20 mg/kg/day in 2 divided doses
- Trimethoprim-sulfamethoxazole TMP-SMX (Septran DS one tablet twice a day for 5 days). For children: 5 mg/kg twice a day for 5 days. Ampicillin 50 mg/kg six hourly by mouth is preferable for Shigella dysentery in children.
- Oral Metronidazole (Flagyl) 200 - 400 mg three times a day for 5 days. For children 15 mg/kg in three divided doses for three days.
- Mebendazole 100 mg three times a day for 5 -7 days for intestinal helminths. This is not to be used in children < 2 years age.

Loperamide or other antimotility agents must not be used in bloody diarrhoea, because of the risk of toxic megacolon.

Acute non-bloody diarrhoea may be caused by any of the microbial agents listed below. Accurate diagnosis can be attempted by the following investigations:

• Microscopic examination of stool at least three times. Attention must be paid to presence of RBCs, leukocytes, cysts, ova and parasites.
• Stool culture for salmonella, shigella, campylobacter
• Barium enema and/or \
• Sigmoidoscopy and mucosal biopsy to look for ulcerations, malignancy, inflammatory bowel disease, mycobacterium avium complex If a specific diagnosis is made after investigations, the following therapy is recommended:

• **Salmonellosis and shigellosis:** Quinolones such as ofloxacin 200 mg, or ciprofloxacin 250 mg twice a day for 5 days. Alternatively, TMP-SMX (Septran DS) one tablet twice a day for 5 days. For children, TMP-SMX 5 mg/kg/day for 5 days, or ampicillin 50 mg/kg/day, six hourly, or nalidixic acid (Negram) 55mg/kg/day, six hourly, for five days.

- ***Campylobacter sp.:*** Erythromycin 2 Gm daily for 5 days. For children, 50 mg/kg in 4 divided doses for 5 days
- **Giardiasis:** Oral Metronidazole (Flagyl) 200 mg three times a day for 5 days. For children, 15mg/kg/day in 3 divided doses.
- ***Isospora belli:*** TMP-SMX (Septran DS one tablet four times a day for 10 days)
- **Strongyloidosis:** Thiabendazole 25 mg/kg three times a day for 3 days
- **Cryptosporidiosis:** There is no effective treatment. Supportive treatment with fluids and constipating agents may be used.
- **Mycobacterium avium complex (MAC):** Combination regimens including rifabutin, clofazimine, ethambutal, amikacin, clarithromycin, roxithromycin and others may assist individual patients, but are not established as efficacious.
- **Intestinal helminths:** Thiabendazole 50 mg/kg every 12 hours for two days

(Salmonellosis, shigellosis, campylobacteriosis and isosporiasis in HIV patients frequently relapse and may need re-treatment for 6-12 week course.)

Despite best attempts bacteriologic diagnosis may not be made, and empirical therapy may be an option after careful consideration:

a) Course of antimicrobial(s) best suited to the patient's condition. Paediatric dosages must be calculated according to weight.

b) Antimotility drugs such as lomotil, two tablets three or four times a day. Caution: may reduce motility, and should never be used in children.

c) *Ispaghul husk* 1 or 2 teaspoonful in a glassful of water taken 2 or 3 times per day may be given to give the stools some form or bulk

d) Adequate fluid replacement

9.3. Lymphadenopathy

Definition: Lymph node enlargement in a patient, which may be single or multiple, in one or more areas.

Etiology

HIV infection itself causes persistent generalized lymphadenopathy (PGL), defined as three or more separate lymph node groups, with at least two or more glands > 1.5 cm in diameter lasting more than one month and no other local pathology to explain it.

Other infections

Bacterial

•Tuberculosis

- Syphilis

Fungal

- Histoplasmosis

Viral

- Cytomegalovirus

Malignancies

- Kaposi's sarcoma
- Lymphoma

Dermatological conditions

- Seborrhoeic dermatitis
- Chronic pyoderma

Management of lymphadenopathy

A careful physical examination should identify any local or contiguous infection that might explain the lymphadenopathy:

- Papulosquamous skin rash and/or genital ulcer: suspect syphilis. Obtain VDRL and confirm with FTA-ABS if possible. Treat-with Benzathine penicillin (Penidure L.A.) 24 lakh units I.M. single dose.
- Unilateral lymph nodes, matted, fluctuant, slightly tender, with or without fever and weight loss: suspect tuberculous adenitis (very common in the general population even without HIV). Chest Xray is usually normal and not suggestive of tuberculosis. Fine needle aspiration cytology (FNAC) of the gland must be done for histopathology, AFB smear and T.B culture. Caseation is diagnostic of TB and treatment with appropriate anti TB drugs may be started. (For treatment of TB see page 41)
- If diagnosis is in doubt by FNAC, other diagnoses should be suspected, such as lymphoma, Kaposi and infiltrative fungal or mycobacterial disease. Excision biopsy should be done for histopathology, appropriate stain for fungus, and culture for fungi and TB.
- For management of lymphoma, Kaposi or unusual fungal infection the patient should be referred to the appropriate specialist.
- Benign follicular hyperplasia ("reactive") needs no treatment.

(FNAC is an easy and inexpensive procedure and can be done in any histopathology lab. where adequate cytopathology facilities are available.)

9.4. Headache

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

A careful history and examination should identify non-HIV related causes of headache, e.g. migraine, tension, sinusitis, refractive errors, dental diseases, anemia, hypertension, drugs. Headache may be part of systemic manifestation of acute fever such as typhoid, malaria, dengue, or other viral infections and should be treated according to the cause.

Etiology

Infections:

- Tuberculous meningitis
- Cryptococcal meningitis
- Toxoplasma meningoencephalitis
- Neurosyphilis
- Viral meningoencephalitis e.g. due to cytomegalovirus
- Chronic HIV meningitis
- Progressive multifocal leukoencephalopathy
- Cerebral malaria

Malignancy:

- Lymphoma

Drug side effect:

- Zidovudine

Headache with fever and/or neurological signs must be taken more seriously and the patient referred to a center with facilities for further examination. These include:

- Changes in mental state including loss of concentration, personality change (mild to psychotic), confusion, cognitive impairment and dementia.
- Focal neurological deficits including paresis, cranial nerve palsies, movement disorders, ataxia and aphasia. ;
- Seizures
- Evidence of meningeal irritation or raised intracranial pressure (neck stiff-ness, slow pulse). **AIDS patients may not present with typical features of meningitis.**

The following must be done immediately:

I. Examine with funduscope.
II. if there is no contraindication, perform lumbar puncture. CSF must be checked for protein, glucose, cells, acid fast bacilli, India ink smear and cryptococcus antigen, and VDRL
III. If focal signs are present, treat immediately for toxoplasmosis (see treatment on page 39)

Table 4 Cerebrospinal fluid in meningitis

Etiology	Biochemistry	Cell/ Differential	Microscopy	Culture	VDRL Serology
Pyogenic Bacteria	protein glucose	TLC > 500 Predominant neutrophils	Gram stain positive	Positive for bacteria	Negative
Cryptococcus neoformans	protein glucose	TLC < 500 Predominant monocytes	India ink positive	Positive for Cryptococcus	Negative
Mycobacterium tuberculosis	protein glucose	TLC < 500 Predominant Monocytes	AFB seen (although difficult)	Positive for M.TB.	Negative - ' v
Treponema patlidum	protein glucose	TLC < 500 Predominant Monocytes	Negative	Negative culture	Positive

If funduscopy shows gross papilloedema, and headache persists, CT scan should be done. MRI may have some advantages but is more expensive.

The following focal or ring enhancing lesions may be sought:

- Tuberculoma
- Toxoplasmosis (multiple enhancing lesions)
- Lymphoma
- Bacterial abscess
- Fungal abscess
- Kaposi's sarcoma (rare)

Treatment

Tuberculoma /TB meningitis: Anti TB therapy with 4 drugs as per recommendation. See page 41 for treatment.

Toxoplasmosis: usually responds well and promptly to treatment, and this response can be used to support the diagnosis. See page 39 for treatment

Lymphoma: no current treatment available. Prognosis guarded

Bacterial abscess/ meningitis: antibiotics. Abscess should be surgically drained as well. See page 43 for treatment.

Fungal abscess/ meningitis: Abscess should be drained and treated with antifungal agents. See page 44 for treatment

Neurosyphilis: See page 36 for treatment

9.5 HIV/AIDS-Associated skin diseases

Definition: The presence of a dermatpsis in a patient with symptomatic AIDS infection

Etiology ,;

Viral infections:

- Herpes zoster: multidermatomal or disseminated
- Disseminated varicella
- Herpes simplex
- Molluscum contagiosum
- Condyloma acuminata (genital wart)
- Bacterial infections:
- Furunculosis
- Impetigo and pyoderma (staphylococcal, streptococcal)

Fungal infections:

- Candidiasis
- Dermatophytosis

Malignancy:
- Kaposi's sarcoma

Other dermatoses:
- Drug eruptions, (especially to sulfa drugs), e.g. Erythema multiforme, Steven Johnson's syndrome
- Chronic prurigo or urticaria (blood parasites or other common etiologies excluded)
- Severe seborrhoeic dermatitis
- Generalized erythroderma
- Severe psoriasis
- Scabies, esp. Norwegian scabies

Skin diseases should be recognized clinically by the experienced clinician. Tests are not necessary in ordinary circumstances; hence treatment may be started immediately.

Treatment

Herpes zoster: Apply local soothing lotions. If severe, may use oral or intravenous acyclovir 10 mg/kg three times daily. (400 - 800 mg daily for 5 days). Steroids are indicated in herpes zoster ophthalmicus.

Herpes simplex: If lesions are persistent and painful one may use oral acyclovir 200 mg 5 times a day for 5 - 7 days. If recurrent problem, use acyclovir 200 mg twice daily for suppression.

Moiluscum contagiosum: Crush lesion with tooth forceps and apply antiseptic ointment. Alternatively, cryotherapy with liquid nitrogen is recommended. Electrical cauterization may be done.

Condyloma acuminata (genital wart): Treat with podophyllin 20% solution 1-2 times per week, until cleared. Alternatively, cryotherapy with liquid nitrogen is recommended.

Furunculosis, impetigo and pyoderma: Treat with oral penicillin 250-mgm qid, cloxacillin 250 mg qid, amoxicillin/clavulanate 375 mg tds, or .a cephalosporin for ten days.

Candidiasis: Local application of 1% gentian violet, or miconazole ointment twice daily until cleared. In severe cases oral ketoconazole 200 mg daily or oral fluconazole 50 mg daily may be given for 5 - 7 days.

Dermatophytosis: Topical broad-spectrum antifungal agents may be given. In severe cases oral griseofulvin 500 mg twice daily may be given or terbenafine

Kaposl sarcoma (KS): Single lesions may be treated with intralesional therapy with vinblastine or alpha interferon, cryotherapy with liquid nitrogen, or surgical excision. Radiotherapy is used for intraoral or pharyngeal KS, painful cutaneous KS and lymphoedema of the face and extremities. Rapidly progressing or disseminated KS is difficult to treat and is associated with poor prognosis

Drug eruptions: Withdraw drugs, use antihistamines. Corticosteroids may be used only in life threatening conditions.

Prurigo: Topical calamine lotion. Antihistamine may be useful. Topical steroid may be applied.

Seborrheic dermatitis or generalized erythroderma: Treat according to underlying condition. In severe cases topical antifungal agents may be used, such as Clotrimazole.or miconazole. Topical corticosteroids (1% hydrocortisone). Topical coal tar may be helpful. If candidiasis co-exists, topical ketoconazole may be used.

Psoriasis: Coal tar in salicylate ointment applied twice daily. If severe, topical and/ or systemic steroids may be used. Topical Ditheranole 0.5 - 1 % may be applied.
Scabies: Gamma benzene hexachlorine (Lindane) topical lotion should be applied to the whole body below the neck. Leave overnight and then bathe. In severe cases this may be repeated after a week.

9.6 Respiratory Conditions

Definition: Persistence or worsening of cough and/or chest pain and /or dyspnoea in a patient with symptomatic AIDS infection. Chest X-ray may be normal or atypical.

Etiology

Infections:

- Pyogenic bacteria: most commonly *S. pneumoniae*
- Atypical pneumonia e.g. Legionella, Mycoplasma
- *Mycobacterium tuberculosis* ~
- *Pneumocyctis carinii pneumonia* (PC'P)
- Fungal infection (cryptococcus, aspergillus, histoplasma, coccidioiodomycosis)
- Atypical mycobacteria
- Others: cytomegalovirus, nocardia

Malignancies:

- Kaposi sarcoma
- Lymphoma

Others:

- Lymphoid interstitial pneumonitis

Other associated conditions:

- Pleural effusion/empyema (associated with tuberculosis, bacterial infection or cancer i
- Cavitary lesion •
- Pneumothorax (associated with tuberculosis, PCP or cancer)
- Pericardial effusion (often associated with tuberculosis)

If physical examination reveals respiratory distress, defined as cyanosis, tachypnoea, tachycardia, intercostal indrawing, or. use of accessory muscles, then referral to an appropriate centre should be made immediately. Arterial blood gases should be measured and inspired oxygen therapy must be started. Use of assisted mechanical ventilation should be considered.

Investigating Respiratory Conditions

- Chest X-ray: to look for pulmonary infiltrates, consolidation, pneumothorax, pleural effusion, and empyema. Findings may be atypical in the severely immunecompromised patient, e.g. pulmonary TB may not necessarily present with infiltrates or cavitation. Radiologic diagnosis of PCP infection may be highly variable, ranging from normal to classic bilateral diffuse ground glass infiltrates.

- Sputum smears for Gram stain, acid-fast stain, fungus, as well as cultures for bacteria, M.Tb and fungus.
- If pleural effusion is present it must be aspirated and studied for protein, cholesterol, cell count, pH, cytology, gram stain and culture.
- Serum LDH may be markedly elevated in PCP infection.
- Fiberoptic bronchoscopy with bronchoalveolar lavage may be needed if no microbial diagnosis is made
- PO_2 is low in PCP

Treatment
Selection of antimicrobial agent depends upon identification of the organism:

Bacterial infection is the most common and treatable condition; hence broad spectrum antibiotics must be started. Amoxicillin/clavulanate, macrolides, cephalosporins, quinolones or Co-trimoxazole may be used.

If mycobacterium tuberculosis is suspected and identified a combination of four anti TB drugs should be started. Drugs may be changed or modified when sensitivities become available, (for treatment see page 41)

Pneumocystis carinii: Oral or intravenous trimethoprim-sulfamethoxazole (TMP 20 mg/kg plus SMX 75 mg/kg in 4 daily divided doses. For a 65 kg person the dose of Septran is 3 tablets four times a day. For children: TMP 5 mg/kg/dose + SMX 25 mg/kg/dose every six hours. PCP may initially worsen; hence therapy should be given for at least a week before assessment is made. If there is improvement, continue for 14 - 21 days. Corticosteroids e.g. prednisolone 40 mg daily in 2 doses must be used in severely ill patients. Paediatric dose: 1-2 mg/kg in 2 doses.

Deep fungal infection: Fluconazole 100 -200 mg four times daily by mouth or intravenously may be used. Paediatric dose: 100 mg twice a day. Alternatively, amphoterecin may be given (see page 44)

Pulmonary Kaposi sarcoma is rapidly fatal. Combined chemotherapy and radiotherapy may be justified.

Cytomegalovirus pneumonitis is diagnosed incidentally at bronchoscopy. In invasive CMV infection, a trial of gancyclovir 5 mg/kg twice daily IV for 10 days may be given.

Lymphoid interstitial pneumonitis is seen mainly in children and may be treated with corticosteroids.

9.7. Fever Of Unknown Origin

Definition: Petersdorf and Beeson's definition of Fever of Unknown Origin in 1961 has long been accepted with the modification that the patient need not be in a hospital setting. "Fever higher than 38°C (101°F) on several occasions, persisting without diagnosis for at least three weeks, in spite of at least one week's investigations" is now the acceptable definition.

The primary phase of HIV infection itself is a cause of fever, and precedes seroconversion. In later phases of HIV infection fever usually signifies some other opportunistic infection, which can have devastating effects if not diagnosed and treated as early as possible. In the immunodeficient patient signs of inflammation other than fever are notoriously absent or modified, leading to atypical presentation.

Etiology Infection

Mycobacterial

- Mycobacterium tuberculosis
- Mycobacterium avium complex (MAC)

Fungal

- Cryptococcosis

Bacterial

- Salmonella sp.
- S. pneumoniae
- H. influenzae

Viral
- Cytomegalovirus
- Epstein-Barr virus
- HIV itself
- Acute viral hepatitis

Protzoal
- *Malaria (both P. vivax and P. falciparum) "*
- *Pneumocystis carinii*
- *Toxoplasma gondii*

Malignancy
- Lymphoma

Drug induced fever

A detailed history, examination and routine lab. tests must be done to rule out other systemic infections enumerated in previous sections of this book.

Investigations for Fever of Unknown Origin

Investigations for diagnosis of fever must be carried out in light of the patient's clinical condition. Test results, especially serology, may not always be as expected, depending upon the degree of immune deficiency. The lower the CD4 count, the less the body is able to mount a reaction of inflammation.

Immediate and routine tests are:
- Complete blood count
- Liver function tests
- Malaria parasite smear
- Routine biochemistry
- Blood culture
- Urine analysis
- Chest X-ray

If tests are not available or affordable it may be reasonable to treat the patient for some of the common infections in the community, such as malaria, typhoid, gastrointestinal infections with appropriate anti infective agents.

If no clue is found to diagnosis, and fever persists, the patient should be referred to a centre for further tests. Depending upon the clinical situation these may include:

- Ultrasonogram of the abdomen
- CT scan of chest, abdomen
- CT scan of the head
- Lumbar puncture
- Bone marrow aspiration and culture
- Sputum examination for Mycobacterium tuberculosis, fungus
- Bronchoscopy and bronchoalveolar lavage
- Gastric aspirate for M.Tb in children
- Upper and lower GI endoscopy

Treatment will depend upon provisional or proven diagnosis, and is indicated in each section. If, however, tests are unavailable or unaffordable, it may be reasonable to treat empirically after careful consideration, with antiTB drugs while keeping options open for other diagnoses.

10. SPECIAL PROBLEMS OF CHILDREN WITH AIDS

Children usually acquire HIV infection from their mothers during pregnancy, childbirth or breast-feeding. Several children and young adult male haemophiliacs have been diagnosed with HIV after anti haemophilic factor transfusions.

A new born with a positive anti HIV may have one of two implications:

i) The baby is carrying maternal IgG HIV antibodies (i.e. persistence of maternal anti-bodies following placental transfer), ii) The baby is HIV infected and will continue to test positive.

If HIV related symptoms appear, or $CD4^+$ count is < 400 or hypergammaglobulinemia is present, the likelihood of HIV infection is greater. The test should be repeated every 6 months until the child is 15 months old, by which time circulating antibodies should have disappeared and HIV test should become negative. If HIV test remains positive the child is infected with HIV.

10.1. FAILURE TO THRIVE (FTT) OR MALNUTRITION

FTT implies an infant whose physical growth is significantly less than that of his /her peers (below the 3rd on 5th percentile). If prior record of weights or growth velocity is not available, a child may be classified as:

Severe FTT

- If weight is less than 60% of normal
- Presence of oedema

Moderate FTT:

- If weight is 60-80% of normal for height

Causes of FTT:

- Failure of mother to provide adequate calories (young mother with inadequate knowledge, unusual dietary beliefs, low socioeconomic conditions, large families, improper weaning, depression in mother.
- Failure of child to take or retain adequate calories, vomiting, diarrhoea, mal-absorption. Difficulty in swallowing, oral motor dysfunction and anatomical abnormalities must be ruled out.

• Failure to thrive despite adequate calories. Rule out organic causes such as chronic diseases of the GI tract, kidneys, cardiovascular system, endocrine system, central nervous system, inborn errors of metabolism, chromosomal abnormalities or malignancies.

If none of these is responsible, HIV may be considered in the etiology. In HIV infection a combination of factors such as stress, diminished production of growth factors, or end-organ resistance to the growth - promoting effects of such factors may all play a part.

10.2. NEUROLOGIC ABNORMALITIES IN A CHILD

Definition: Neurological abnormalities in a child with symptomatic AIDS infection may include the following presentations:

Progressive encephalopathy: progressive decline in motor, cognitive or language function evident as loss or increasing delay in developmental milestone achievement; onset can be as early as the first year of life but can occur at any time.

Static encephalopathy: motor dysfunction and other developmental deficits of varying severity that are non-progressive as documented on serial neurological and developmental examinations. It can be due to the effects of HIV on the developing CMS, or related to non-HIV factors such as prematurity, neonatal asphyxia or the effects of in utero drug and alcohol exposures. Static HIV encephalopathy is diagnosed in the absence of alternative explanations for developmental delays and/or neurological dysfunction.

Acute episodes: acute onset of seizures, focal neurological abnormalities (e.g. toxoplasmosis) or meningism (e.g.cryptococcal, bacterial, tuberculous meningitis or CMV encephalitis.)
Acute deterioration can also be due to side effects of drugs, such as peripheral neuropathy from zaicitabine.

***Management of neurological disorders in a child depends upon the cause. Infection must be treated as in the adult Static or progressive motor or cognitive dysfunction requires supportive* care.**

11. SEXUALLY TRANSMITTED DISEASES

Definition: Group of infectious diseases principally transmitted through sexual intercourse.

Etiology

Bacterial

- *N.gonorrhoea*
- Chlamydia, causing non gonococcal urethritis
- *Treponema pallidum* causing syphilis
- *Haemophilus ducreyi,* causing chancroid
- *Ureaplasma urealyticum*
- *Gardnerella vaginalis*

Viral

- HIV 1 and 2
- Herpes simplex
- *Condyloma acuminate,* causing anogenital warts
- Molluscum contagiosum

Other

- *Trichomonas vaginalis*
- *Sarcoptes scabei (itch mite)*

TABLE 5 *Symptoms of STDs*

STD Syndroms	**Common causes**
Urethral discharge	Neisseria gonorrhoea, Chlamydia trachomatis
Genital ulcer syndrome (GUS)	Treponema pallidum, H. ducreyi, C.trachomatis, C.granulomatis, Herpes simplex virus
Vaginal discharge	N. gonorrhoea, C.trachomatis, T.vaginalis, C.albicans,Gardenerella vaginalis
Pelvic inflammatory/disease	Neisseria gonorrhoea, Chlamydia trachomatis, anaerobic bacteria, TB, other pyogenic organisms
Bubo	H. ducreyi, C. trachomatis, other pyogenic organisms

Scrotal swelling	N. gonorrhoea, C. trachomatis, other pyogenic organisms, viruses and surgical conditions

Diagnosis

Urethral or vaginal discharge:

If urethral discharge in the male is not obvious, ask the patient to milk the urethra and collect the discharge for gram staining. More than 5 polymorphs per field indicate urethritis, and presence of gram-negative diplococci indicates presence of gonococcal infection.

Urethral discharge due to gonorrhoea is usually thick and yellow- green, while discharge due to chlamydia is usually white or mucoid.

Vaginal discharge in the female may be physiological or due to vaginitis and cervicitis. Vaginal discharge is pathological when it becomes abnormal in colour, quantity or odour.

- If mucopurulent, treat for gonorrhoea plus chlamydia
- If profuse discharge, treat for Trichomoniasis and bacterial vaginosis
- White, curd-like discharge, treat for candidiasis

Genital ulcer syndrome (GUS)

The most common causes are primary syphilis, chancroid and genital herpes. Examine the patient and note the number, size, shape and location of ulcer, and palpate for inguinal lymphnodes.

Ulcer due to primary syphilis is usually single, painless and firm in consistency, while ulcers due to chancroid are usually multiple, painful and soft in consistency.

If recurrent vesicular lesions are present the cause is probably herpes simplex

Pelvic inflammatory disease (PID)

Lower abdominal pain, vaginal discharge, dyspareunia, menorrhagia, dysmenorrhoea and fever may be indicative of PID. An experienced gynecologist should do an adequate pelvic examination, and therapy should be instituted empirically.

Neonatal conjunctivitis

This is a potentially blinding condition and must be treated immediately. Various organisms may be responsible and a swab must be taken from the eye discharge for gram stain.

Treatment of STDs

Gonorrhoea: Single injection of Ceftriaxone 250 mg IM, or a single dose 400 mg Ofloxacin PO

Chlamydia: Cap. Doxycycline 100 mg twice daily orally for 7 days

Candidiasis: Clotrimazole vaginal tablet single dose for insertion, or Fluconazole single dose 150 mg

Trichomoniasis and bacterial vaginosis: Tablet metronidazole (flagyl) 2 Grams, single dose

Syphilis:
Primary or < 1 year:
Single injection Benzathine Penicillin (Penidure LA) 2.4 million units (24 lakh units) IM. In case of penicillin allergy (history of anaphylaxis or drug rash) use Doxycycline 100 mg twice daily for 15 days. For pregnant women with penicillin allergy use Erythromycin 500 mg four times a day for 15 days.

Latent, > 1 year, indeterminate duration cardiovascular or late benign
Benzathine Penicillin (Penidure LA) 2.4 million units IM weekly for three weeks . Total dose 7.2 million units
Neurosyphilis: Benzyl penicillin 3-4 million units 4 hourly IV for 10 -14 days. This condition is not easy to treat. Sequential serum and CSF serology should be followed.

Chancroid: Ciprofloxacin 500 mg as single dose orally

Herpes genitalis:
- For primary attack: Acyclovir 200 mg five times a day for 7 days
- For subsequent attacks: Acyclovir 200 mg three times a day for 6 weeks or longer

Pelvic inflammatory disease: Injection Ceftriaxone 500 mg daily, plus Doxycycline 100 mg twice daily, plus metronidazole 400 mg twice daily by mouth or injection for two days after clinical improvement has occurred. If intrauterine device is present it may be removed.

Gonococcal ophthalmia: Single injection of Ceftriaxone 50 mg/kg IM Local eye treatment with normal saline and application of 1% silver nitrate solution or 1% tetracycline eye ointment.

For more detailed Information please consult National Guidelines on "Syndromic Management of STDs

12. CYTOMEGALOVIRUS (CMV) INFECTION

CMV infection, as assessed by serology, is almost universal among HIV patients who have acquired disease by homosexual route. It occurs in the late stages of the disease when the CD4+ count falls below 50 cells/ul. Retinitis is the most commonly recognized disorder caused by CMV. It may involve the macula and optic disk rapidly to cause retinal detachment and ultimately blindness. An experenced ophthalmologist should be consulted.

CMV can also cause oesphagitis, colitis, rectal ulcers and pneumonitis, which may be clinically indistinguishable from syndromes caused by other pathogens, hence diagnosis should be made by histology. CMV is often responsible for chronic fatigue syndrome and HIV wasting syndrome.

Therapy should be given urgently with IV ganciclovir at a dose of 5 mg/kg every 12 hours, or foscarnet 60 mg/kg every 8 hours for 3 weeks

13. TOXOPLASMOSIS

Toxoplasma gondii is a parasitic infection spread through cat faeces and also through consumption of undercooked meat. Most adults have been infected at some stage of their lives, as evidenced by presence of IgG antibodies. In the patient with HIV infection, toxoplasma infection occurs by reactivation rather than by primary infection. IgG rather than IgM antibody is more closely related to active toxoplasma infection in HIV/AIDS patients, as IgM levels may be falsely negative because of impaired antibody production. Thus patients having IgG antibodies against toxoplasma usually have fairly advanced disease, whereas lack of IgG militates against the diagnosis of toxoplasmosis. Toxoplasmosis manifests commonly as cerebral disease with focal signs such as hemi-paresis or seizures; Retinochoroiditis (less commonly), pneumonitis, disseminated disease, and a sepsis-like syndrome have been reported. With $CD4^+$ counts below 100/ul and a space -occupying,lesion, the differential diagnoses are tuberculoma, toxoplasmosis and lymphoma.

When cerebral toxoplasmosis is suspected or confirmed, it is reasonable to start empirical therapy for toxoplasma with pyrimethamine and sulfadiazine. If the diagnosis is correct, CT scan or MRI of the brain will show a dramatic reduction in size of the lesion within 10 to 15 days after therapy.

- The loading dose for pyrimethamine is 75-100 mg, then 25 - 50. mg daily, plus sulfadiazine 6-8 Gm daily. Since both drugs are not available separately in Pakistan, Fansidar may be used. Each tablet of Fansidar contains pyrimethamine 25 mg, plus sulfadoxine 500 mg. This combination, though, is not accurate for treatment of toxoplasmosis. Fansidar may be given as 4 tablets after meals in loading dose, followed by 2 tablets daily, plus folinic acid (leukovorin) 10-75 mg daily.

- Altenatively: pyrimethamine alone 100 mg, plus clindamycin 300 - 600 mg IV 6 hourly.

If the response is good, lifelong chronic suppressive therapy is advisable with pyrimethamine 25 mg daily plus sulfadiazine 500 mg weekly (Fansidar 1 tab weekly). If there is no response to primary therapy, a diagnosis of toxoplasmosis is unlikely, and alternative diagnoses must be considered.

14. HEPATITIS B AND C

Both hepatitis B (HBV) and C (HCV) have assumed very high proportions of prevalence in our communities throughout Pakistan. The routes of transmission are through blood and blood products and also through sexual and maternal transmission. Both are much more communicable than HIV. To a large extent health care providers bear the responsibility of spreading HBV and HCV through use of unsterile needles for injections.

However, other modes of spread are through sharing, toothbrushes and razors, ear or nose piercing, tatooing, dental and other surgical equipment. Both illnesses may follow subclinical infections. Sequelae of chronic hepatitis, namely cirrhosis and hepatocellular carcinoma are largely the causes of end stage liver disease.

Since HBV is vaccine preventable, immunization must be done earlier in the course of HIV. There is no vaccine for HCV. Prevention of both is through avoidance of unsterile needles. Avoidance of reuse of unsterile needles and sharp equipments by doctors, dentists, midwives and other practitioners will definitely reduce the spread of HBV, HCV and HIV.

Co-infection of HCV with HIV does not worsen liver disease, and does not warrant separate treatment of HCV

15. THERAPY OF SPECIFIC INFECTIONS

15.1 ANTI TUBERCULOSIS THERAPY

Treatment of tuberculosis in the AIDS patient is no different than in the non-AIDS patient, however the chances of MDR are much higher in the AIDS patient. Also, the diagnosis of TB in AIDS patient is more difficult to make, since typical X-ray pattern may be lacking. Every attempt should be made to obtain a smear, culture and sensitivity.

Drugs available are: INH (H), Rifampicin (R), Ethambutal (E), Pyrazinamide (Z), Thiacetazone (THI), Streptomycin (STM)

WHO offers guidelines for management of TB according to three clinical categories:

Category I:
1) Newly diagnosed smear positive pulmonary TB
2) Newly diagnosed seriously ill patients with TB e.g. meningitis, pericarditis, peritonitis, pleurisy
3) Spinal TB
4) Smear negative pulmonary TB with extensive parenchymal involvement
5) Intestinal and genitourinary TB

Intensive phase: H,R,E,Z for 2 months. Check sputum if possible

Continuation phase: If smear negative, H,E or H,R for 6 months
If smear positive, H,R,E,Z for another one month, then H,E or H,R for 5 months

If extrapulmonary TB, may be continued for 8-10 months

Category II:
Smear positive relapse and failure cases

Intensive phase: H,R,E,Z,S for 2 months, then H,R,E,Z for one month. Check sputum smear.

Continuation phase: If smear negative, H,R,E for 5 months
- If smear positive, H,R,E,Z for 1 month. Check sputum smear again.
- If still smear positive, culture sputum and continue H,R,E for 5 months
- If still smear and culture positive refer to chest or ID specialist. Such patients may need life-long treatment.

Category III:

Sputum smear negative pulmonary and TB adenitis, skin

Intensive phase: H,R,Z for 2 months

Continuation phase: H,E or H,Th for 6 months

The above are simply guidelines. Actual therapy should take into consideration factors such as disease severity, drug availability, toxicity, etc., and treatment may be individualized.

In general:

- Initial Intensive phase is given for 2 months
- Continuation phase is given with 2 drugs for 4 - 10 months
- New cases of smear positive pulmonary tuberculosis are treated for 6 - 8 months
- Serious extrapulmonary tuberculosis is treated for 8-12 months.
- Sputum smear should be examined at 2 months, 5 months and at end of treatment.
- Where facilities exist sputum should be sent for culture and drug sensitivity, and treatment adjusted according to sensitivity.
- Thiacetazone should not be used in HIV cases because of severe hypersensitivity reactions
- Priority should be given to supervised treatment in the initial phase of treatment.
- In children sputum is difficult to obtain, hence gastric aspirate may be used.
- E should be avoided in small children who cannot report visual toxicity
- Anti TB drugs should not be withheld from pregnant women with HIV and TB
- Breast feeding should not be discontinued during treatment for tuberculosis without HIV

TABLE 6 Anti tuberculosis Therapy**

Drug (Abbrev.)	**Dose (mg/kg)**		**Dose (mg)**	
		<33 kg	33-50 kg	>51 kg
INH (H)	05	200	300	300
Rifampicin (R)	10	300	450	600
Ethambutal (E)	15-25	800	1200	1600
Pyrazinamide (Z)	15-30	1000	1500	2000
Streptomycin (S)	15	500	750	19
Thiacetazone (THI) (Not to be used in the AIDS patient)	2.5	100	150	150

**** Endorsed by WHO and IUATLD**

TABLE 7 Paediatric age

INH (H)	10-20 mg/kg
Rifampicin	1 0 -20 mg/kg
Ethambuta! (E)	15-25 mg/kg
Pyrazinamide (Z)	15-30 mg/kg
Streptomycin (S)	20- 40 mg/kg
Thiacetazone (THI)(not to be used in AIDS patient)	2.5 mg/kg

15.2. THERAPY OF BACTERIAL MENINGITIS

Definitive therapy depends upon identification of the causative organism; however the likely organisms in the adult are S. pneumoniae or N. meningitidis. Among immunocompromised patients, fungus or M. tuberculosis must also be considered.

- *N.meningitidis:* aqeous penicillin is the drug of choice. Dose: 4.0 million units every 4 hours intravenously for 7 -10 days
- S. *pneumoniae:* because of the possibility of penicillin resistance, the antibiotic of choice now is Ceftriaxone 2 Gm 12 hourly IV for 7 - 10 days.

Children: 50 mg/kg 12 hourly IV. Alternatively, Vancomycin 1 Gm 12 hourly

IV. Paediatric dose: 40 -60 mg/kg 8 hrly

- *H. influenza:* usually in children, infrequently in the adult: Adult dose: Ampicillin 2 gm 6 hourly IV plus Cefotaxime 2 gm six hourly. Paediatric dose for both ampicillin and cefotaxime: 50 mg/kg 12 hourly IV

15.3. THERAPY OF DEEP FUNGAL INFECTIONS

Fluconazole (Diflucan™) is available both for oral and intravenous use. It is effective only against a limited species of fungi.

Amphotericin B (Fungizone™) is a broad spectrum antifunga! agent. The drug is toxic and help should be taken from an experienced physician. Test dose of 1mg diluted in 10 ml dextrose should be given over 5-10 minutes. If no reaction occurs such as rash, fever or hypotension, proceed with 10-20 mg diluted in dextrose as a slow infusion. Increase the dose daily up to a maximum of 0.7 -1 rng/kg as a slow infusion. Total dose given over several days to weeks is 1 - 2 Gm of amphotericin.

Side/toxic effects are fever, chills, phlebitis at the site of the infusion, hypotension, hypokalemia, hypomagnesemia, anemia or renal insufficiency. Infusion may be suspended for a few days if needed.

16. GUIDELINES FOR THE USE OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

The availability of an increasing number of antiretroviral (ARV) agents and the rapid evolution of new information has introduced extraordinary complexity into the treatment of HIV infected persons. In 1996 guidelines were developed for the management of HIV-infected adults and adolescents. The report recommends laboratory monitoring of plasma levels of HIV -RNA. ARV regimens are complex, have major side effects, pose difficulty with compliance, and carry serious potential consequences with the risk of resistance from non-adherence to the drug regimen or sub-optimal levels of ARV agents.

The results with HAART when used appropriately continue to show promising results as judged by reduction of opportunistic infections and improved quality of life. Treatment should be offered to all patients with:

- Acute Retroviral syndrome.
- Within six months of seroconversion.
- Symptoms ascribed to HIV infection, e.g. wasting, thrush, unexplained fever.
- CD 4+< 500/cmm, or plasma HIV RNA > 10,000 copies /mi (DNA assay).

Mono or bi-therapy with ARV agents produces a serious risk of development of drug resistance. Triple therapy must be used, along with other drugs used for primary or secondary prophylaxis or treatment of opportunistic infections.

The goal is maximum viral suppression for as long as possible. Combination of ARV agents must be used. They have many side effects ranging from mild to severe requiring change or discontinuation of therapy. The difficulties are compounded by drug interactions with other anti infectives such as ketoconazole and rifampicin, among others. Only an infectious disease specialist with experience in the field of HIV management must monitor the patient.

In recent months there has been an increased demand by developing countries with high prevalence of HIV/AIDS for international help in obtaining drugs at low cost. Since there is a possibility of ARV availability in Pakistan in the near future, more detail is being included through tables and charts.

TABLE 8
Risks and benefits of early initiation of Antiretroviral Therapy in the symptomatic HIV-infected Patient

Potential Benefits

- Control of viral replication and mutation; reduction of viral burden
- Prevention of progressive immunodeficiency; potential maintenance or reconstruction of a normal immune system
- Delayed progression to AIDS and prolongation of life
- Decreased risk of selection of resistant virus
- Decreased risk of drug toxicity
- Possible decreased risk of viral transmission

Potential Risks

- Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens
- Earlier development of drug resistance
- Transmission of drug resistant virus
- Limitation in future choices of antiretroviral agents due to development of resistance
- Unknown long term toxicity of antiretroviral drugs
- Unknown duration of effectiveness of current antiretroviral therapies

TABLE 9 ANTIRETROVIRAL DRUGS

Generic name	Brand name	Usual dose	Major toxlclty	Particular indications	{Relative) Contraindications
NUCLEOSIDES (NRTIs) Ziagen (abacavir sulphate) 300 mg BID Comblvir (lamuvidine/Zidovudine) 150/300 mg 1 table BID				> I NRTI should be included in any regimen (unless suspected drug resistant or intolerance)	
AZT (zidovudine) (ZDV)	Retrovir®	300 mg bid or 200 mg tid	• HematotogJcmacTocytasis -anemia, neuropenia » Gl- nausea, vomiting • Occasional myopathy	HIV thrombocytopenia:HIV encephalopathy: Px of maternal-infant transmission; Px for occupational exposure	Anemia Neutropenia Baseline nausea _
DD1 (Didanosiane)	Videx®	200 mg bid or 300-400 mg qd	* Pancreatitis Occasional Peripheral neuropathy		Hx of pancreatitis, Active ethanolism Difficulty timing med with meals Use of indinavir (complex dosing)
DDC (stavudine)	Hivid®	0.75 mg tid	• Peripheral, neuropathy • Occasional pancreatitis	Need for simple well - tolerated med	Peripheral neuropathy Need for BID regimen
D4T {Stavudine)	Zerit®	40 mg bid, if wt <fiO kg: 30 mg bid	• Peripheral, neuropathy • Occas. Pancreatitis	Need for BID well-tolerated med	Peripheral neuropathy
3TC (lamivudine)	Epivir®	150 trig bid	• Occas, nausea, hepatitis, periph neuropathy	Need for BID well-tolerated med	Only combine with AZT or D4T -never use alone
[PROTEASE INHIBITORS (Pis) Agenerase Amprenavir 1200 mg BID (gel capsule) (oral solution also available) Skin rashes. Steven-Johnson syndrome, Gi-N, V, D. Depression				Very high viral load	Difficulty timing med with meals or taking large no. or size pilis Suboptimal compliance
Indinavir	Crixivan®	800 mg Q 8h ac Or 1200mgq 12hac	• Gl (N&V, D) • Renal calculi • Elav. Unconj. Bilirubin • Occas. hepatitis		Hx of renal calculi Inability to drink 1g, vol. of fluid Renal insufficiency Use of DDl (complex dosing)
Nelfinavjr	Viraept®	750 mg tid pc or 1250 rnfl BID pc	• Diarrhoea • Occas, hepatitis	Baseline nausea (vs other Pis)	
Ritonavir	Norvir®	600 mg bid PC	• GlfN&V.D) • Paresthesis • Occas. Hepatitis		Baseline nausea Lack of refrigerator
Saquinavir	Fortovase ®	1200mgtid pc (combo with ritonavir 400 mg BID pc)	• GI(N&V, D) • Occas. Hepatitis		Need for BID regimen
NON-NUCLEOSIDE REVERSE TRANSCRIPT ASE INHIBITORS (NNRTIs)				Need for simple well-tolerated med	Very high viral load or lack of strong mods to combine wtthNNRTI

Nevlraplne	Viramine ®	200mgqdx14 d, then 200 mq bid	* Rash • Occas. Hepatitis	Possibly HIV encephalopathy Possibly peripartum prophylaxis	
Delavirdine	Rescriptor ®	400 mg tid	• Rash • Occas. Hepatitis		Need for BID regimen. However, probably can give as 600 mg BID
Efavlrenz	Sustive ®	200 mg x 3 capsule od	• CNS - Dizziness, insomnia, abnormal dreaming • Rash		

TABLE 10 Drugs that should not be used with Antiretroviral

Drug Category	Indianavir	Ritonavir*	Saquina-Vir	Nelfinavir	Nevi rapine	Delavirdine	Efavirenz
Analgesics	(None)	Meperidine Piroxicam Propoxyph-ene	(None)	(None)	(None)	(None)	(None)
Ca++chann el blocker	(None)	Bepridil	(None)	(None)	(None)	(None)	(None)
Cardiac	(None)	Amlodipine Enacainide Propafenone Quinidine	(None)	(None)	(None)	(None)	(None)
Lipid lowering Agnets	Simvast-ain Lovasta-Tin	Simvastain Lovastatin	Simvastain Lovasta-Tin	Simvastain Lovastatin	(None)	Simvastain Lovastatin	(None)
Anti-Mycobacter ial	Rifampin	(None)	Rifampin, Rifabutin	Rifampin	(None)	Rifampin, Rifabutin	(None)
Antihistam-ine	Astemiz-ole Terfenad-Ine	Astemizole Terfenadine	Astemizole Terfena-Dine	Astemizole Terfenadine	(None)	Astemizole Terfena-Dine	Astemizole Terfenadine
Gstrointest-inal Drugs	Cisapride	Cisapride	Cisapride	(None)	Cisapride	Cisapride H-2 blockers Proton pump inhibitors	(none)
Antidepress ant	(none)	Bupropion	(none)	(none)	(none)	(none)	(none)
Neuroleptic	(none)	Clozpaine Primozide	(none)	(none)	(none)	(none)	(none)
Psychotro-pic	Mdazlam Triazoiam	Clorazepate Diazepam Estazolam Flurazepam Midazolam Trizolam.Zol pidem	Midazolam Triazoiam	Midazolam Triazoiam	(none)	Midazolam Triazoiam	Midazolam Triazoiam

Ergot Alkaloids (vasocon-strictor ergota-mine**)	Dihydroergot amine (D.H.E.45)	Dihydroergotamine (D.H.E.45)	Dihydroergot amine (D.H.E.45)	Dihydroergo t amine (D.H.E.45)	(none)	Dihydroergot amine (D.H.E.45)	Dihydroergot amine (D.H.E.45)

*The contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP206, or unknown pathways are included in this table. Actual interactions may or may not occur in patients. ** This is likely a class effect.

Suggested Alternatives: Simvastatin, lovastatin; atorvastatin, pravastatin, fluvastatln, cerivastatin (alternatives should be used with caution) Rifabutin; clarithromycin, azithromycin (MAI prophylaxia); clarithromycin, ethambu-toi (MAI treatnent)Astemizole, terfenadine; loratidine, Midazolam, triazolam; temazepam, lorazepam

TABLE 11 HIV-Re!ated Drugs with Overlapping Toxicities

Bone Marrow suppression	Peripheral Neuropathy	Pancreatitis	Nephrotoxicity	Hepatotoxi-city	Rash	Diarrhoea	Ocular Effects
Cidofovir Cotrimoxazole Cytotoxic Chemother-apy Dapsone Flucytosine Ganciclovir Hydroxyurea Interferon Primaquine Pyrimetha mine Ribavirin Trimetrexate Zidovudine	Didanosine Lsoniazid Stavudine Zalcitabine	Cotrimox-azole Didanosine Lamivudine Children Pentami dine Ritonavir	Adefovir Aminoglyco sides Amphotericin Cidofovir Foscamet Indinavir Pentamidine Ritonavir	Delavirdine Efavlrenz Fluconazole Isoniazid Itraconazole Ketoconaz ole Nevirapine NRTls Protease Inhibitors Rifabutin Rifampin	Abacavir Cotrimoxa zole Dapsone NNRTIs Protease Inhibitors	Didanosine Clindamycin Nelfinavir Ritonavir	Didanosine Ethambutor Rifabutin Cidofovir

TABLE 12 Indications for Plasma HIV RNA Testing'

CLINICAL INDICATION	INFORMATION	USE
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV anti-body test is negative or indeterminate	Diagnosis*
Initial evaluation of newly diagnosed HIV infection	Baseline viral load "set point"	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Decision to start therapy
2-8 weeks after initiation of antiretro-viral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 months after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4*T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

*Acute illness (e.g., bacterial pneumonia, tuberculosis, HSV, PCP, etc.) and immunizations can cause increase in plasma HIV RNA for 2-4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

** Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods such as Western blot serology performed 2-4 months after the initial indeterminate or negative test.

TABLE 13 Indications for the initiation of antiretroviral therapy in the chronically HIV-infected patient

Clinical Category	CD4*T Cell Count and HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4+T Cells <500/mm[J] or HIV RNA > 10,000 (bDNA) or >20,000 (RT-PCR)	Treatment should be offered. Strength or recommendation is based on prognosis for disease-free survival as shown in Table IV and willingness of the patient to accept therapy.[1]
Asymptomatic	CD4-HT Cells >500/mm[d] and HIV RNA <10,000 (bDNA) or <20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

[1] Some experts would observe patients with CD4T cell counts between 350 - 500/mm^3 and HIV RNA levels < 10,000 (bDNA) or<20,000 (RT-PCR)

TABLE 14 Recommended Antiretroviral Agents for Treatment of Established HIV Infection

Preferred	Strong evidence of clinical benefit and/or sustained suppression of plasma viral load. One choice each from column A and column B. Drugs are listed in random, not priority, order. **Column A** / **Column B** Indinavir / ZDV -i- ddl Nelfinavir / d4T + ddl Ritonavir / ZDV + ddC Saquinavir-SGC* / ZDV + 3TC** Ritonavir + Saquinavir SGC or HGC / d4T + 3TC** Efavirenz / ddl+-3TC"
Alternative	Less likely to provide sustained virus suppression Nevirapine or delavirdine + 2 NRTIs (Column B, above)*' Abacavir + ZDV + 3TC*
Not generally Recommended	Strong evidence of clinical benefit but initial virus suppression is not sustained in most patients. 2NRTIs (Column B, above) ____Saquinavir-HGC + 2NRTIs (Column B. above)**
Not Recommended	**Evidence against use, virologically undesirable, or overlapping toxicities.** All monotherapies ###) d4T + ZDV ddC + ddl t ddC + d4T fddC + 3TC

* Use of ritonavir 400 mg b.i.d. with saquinavair-SGC (Fortovase) 400 mg b.i.d. results in similar drug exposure and antiretroviral activity as when using 400 mg b.i.d. of saquinavir-HGC (Invirase) in combination with ritonavir. However, this combination with Fortovase has not been extensively studied, and gastrointestinal toxicity may be greater when using Fortovase.

** High-level resistance to 3TC develops within 2-4 weeks in partially suppressive regimens; optional use in 3-drug antiretroviral combinations that reduce viral load to undetectable levels.

*** The combination of any of the 3 available NNRTs + 2 NRTIs can suppress viremia to undetectable levels in the majority of patients remaining on treatment for > 28 weeks. An efavirenz-containing regimen has been shown to compare favorably to a Pi-containing regimen with regard to suppression of viremia through 48 weeks; such head-to-head comparative trials have not been performed with nevirapine or delavirdine. Of note, use of efavirenz, nevirapine or deiavirdine may result in resistance that precludes efficacy of any other member of this drug class.

Virologic and immunologic responses obtained with abacavir + ZDC + 3TC are similar to those obtained with Indinavir + ZDV + 3TC at 48 weeks. The durability of virai load suppression with this regimen that includes drugs from a single drug class (i.e. NRTIs) is uncertain; in addition, abacavir is associated with a potential life-threatening hypersensitivity reaction. For these reasons, a Pi-containing or efavirenz containing regiment is preferred until longer-term data are available for an abacavir-containing 3 NRTI regimen.

Use of saquinavir-HGC (Invirase) is generally not recommended, except in combination with ritonavir.

Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4+Tcell counts to prevent perinatal transmission This combination of NRTIs is not recommended based on lack of clinical data using the combination and/or overlapping toxicites.

TABLE 15 Possible Regimens for Patients Who Have Failed Antiretroviral Therapy: A Work in Progress *#

Prior Regimen	New Regimen (Not listed in priority order)
2NRTIS + Neifinavir Ritonavir Indinavir Saquinavir 2 NRTIs +NNRTI	2 new NRTIs + RTV;or IDV; or SQV + RTV; or NNRTI ## + RTV; or NNRT! + IDV[1] SQV + RTV **; NFV + NNRTi; or NFV + SQV SQV + RTV; NFV + NNRTI; or NFV + SQV RTV + SQV; or NNRTI + IDV
2 NRTIs	2 new NRTIs + a protease inhibitor 2 new NRTIs + a protease inhibitor 2 new NRTIs + RTV + SQV 1 new NRTI + 1 NNRTI + a protease inhibitor 2 protease inhibitors + NNRTI
1 NRTI	2 new NRTIs + a protease inhibitor 2 new NRTis + NNRTI 1 new NRT! + 1 NNRTI + a protease inhibitor

* These alternative regimens have not been proven to be clinically effective and were arrived at through discussion by the Panel of theoretically possible alternative treatments and the elimination of those alternatives with evidence of being ineffective.

RTV = ritonavir, IDV = indinavir, SQV= saquinavir, NVP = nevirapine, NFV = nel-finavir, DLV = delavirdine

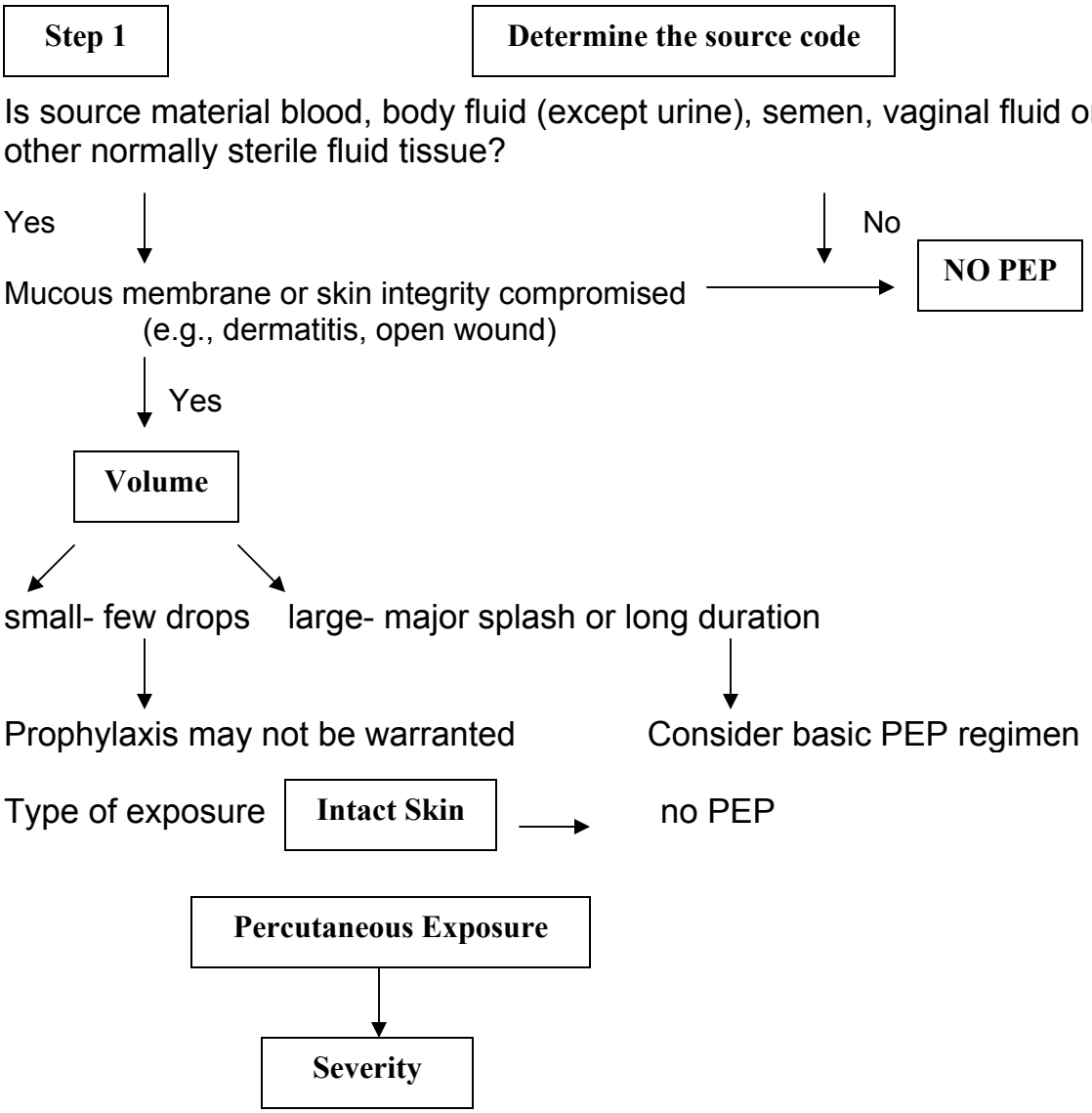
** There are some clinical trials with viral burden data to support this recommendation.

Nevirapine induces and delavirdine inhibits CYP450 enzymes, and this must be considered in combining these drugs with other agents. Efavirenz is a mixed inducer/inhibitor of CYP450 enzymes; concentration of cohcomitantly administered

drugs can be increased or decreased depending upon the specific enzyme pathway involved.

17. PRE & POST EXPOSURE PROPHYLAXIS

Table 16 HIV Post-exposure Prophylaxis (PEP) after occupational or accidental exposure



Less severe: Solid needle/scratch
Rx with basic PEP regimen

Severe: Large bore hollow needle deep puncture, visible blood needle used in vein of source
Rx —> Recommend expanded regimen

Step 2 **Determine HIV Status code**

What is the HIV Status of the exposure source? A.

A. HIV-ve => no PEP

B. HIV +ve low titer exposure, asymptomatic / high CD4; => no PEP

C. HIV+ve high titer exposure, advanced ADIS (low CD4/high VL)

Rx Expanded Regimen

D. Status Unknown =>depends upon exposure settings as in step 1

PRE-EXPOSURE PROPHYLAXIS (PEP)

i. Basic Regimen

Combivir (lamuvidine/AZT) Dose 150/300 mg tablet b.i.d.

II Expanded Regimen

Combivir + either Indinavir 800 mg q 8°
Or Nelfinavir 750 mg PO q 8°

Monitor for drug side effects for four weeks. Recheck status of exposed person.

PEP following sexual exposure

HIV +ve source——> *assessment* same as for needle stick

Trasmission risk for single episode of

- penile-anal sexual exposure: 0.1 - 0.3 %
- receptive vaginal exposure: 0.1-0.2%
- unknown for receptive oral intercourse

18. SPECIAL PROBLEMS OF WOMEN WITH HIV

As a number of deported Pakistani men return to their hometowns, it is highly likely that their wives will acquire infection as "innocent bystanders", who will in turn pass it on to their newborn. The primary physician must be acutely aware of the husband's history of travel or stay abroad or his state of health.

Women are more easily infected with HIV for several reasons related to their anatomy and their socioeconomic status. The vagina acts as a receptacle where semen is likely to collect and remain for some time; associated infections such as STDs, cervical erosions and cervical cancers give opportunity to the virus to penetrate more efficiently. Socially, women in poorer societies are more likely to be exploited. They have no or very little control over their sexual lives; husbands with multiple wives or sex partners outside of marriage are likely to pass on STDs including HIV.

Women with HIV have to make difficult choices regarding contraception, pregnancy, childbirth and breast-feeding. The "Guidelines for Clinical management" will provide suggestions but it is expected that the subject will be discussed in detail in the booklet on Counseling.

It is extremely important to detect and treat all gynaecological infections in the female as early as possible, since their persistence can become an entry point for HIV. Non-STD infections like candidiasis and trichomoniasis should be treated adequately, as should gonorrhoea, herpes genitalis and syphilis. (See section on STDs). Since the incidence of cervical cancer rises in the sexually active female, and more so in those with multiple sex partners, all such women should have a base line PAP smear which should be repeated every one to two years.

Women should be properly informed about contraception. Women with HIV infection can use most contraceptives, i.e. condoms, oral contraceptive pills, injectable progesterones, spermicidals and sterilization. Intrauterine device is not recommended as they may promote pelvic inflammatory disease.

Pregnancy does not seem to have any significant effect on the progress of HIV disease in the early asymptomatic phase. However, in the advanced HIV disease it may progress rapidly to full blown AIDS. There may be either no ill effect on the pregnancy, or it may cause retardation of intrauterine growth, prematurity, still-births or congenital infections.

An HIV positive woman has approximately 30% chance of transmitting HIV to the newborn during pregnancy, childbirth or breastfeeding. The chances are obviously higher in advanced stage of the disease, high viral load and low CD4 count in the mother.

Pregnant women with HIV must receive extra emotional support and antenatal care. Minor opportunistic infections such as oral or vaginal candidiasis must be treated appropriately. Artificial rupture of membranes and episiotomy should be avoided as far as possible.

19 SUGGESTED HYGIENIC PRACTICES FOR MANAGEMENT OF THE NEONATE

Care must be taken not to cause trauma to the newborn during birth. The mother's body fluids must be removed from the baby with a soft towel or tissue.

Avoid unnecessary suctioning, unless there is thick, heavy meconium or fluids in the mouth or nose

Anti retroviral therapy is recommended for reducing mother -to-child transmission during childbirth (see Table 17)

19.1 BREAST FEEDING

Breast feeding itself can contribute a significant risk of mother to child transmission, depending upon the mother's state of HIV viral load, her CD4 level, her general state of health, presence of other opportunistic infections and Vitamin A deficiency. Presence of thrush or gastroenteritis in the baby further increases the risk.

On the other hand babies who are not breast-fed are deprived of the benefits of breast milk and are at risk of malnutrition, gastroenteritis and other infective conditions.

On the balance, then, these factors should be carefully weighed before advising on the most appropriate method for feeding the baby. If the mother can afford human milk substitute (powdered formula preparations), these may be more advisable. Mixed feeding (breast and bottle) should be discouraged as the risk of HIV transmission is higher with mixed feeding compared to exclusive breast feeding.

19.2 CONSIDERATIONS FOR ARV THERAPY IN THE HIV-INFECTED PREGNANT WOMAN

Optimal ARV therapy in the pregnant HIV- infected woman should be the same as for non- pregnant infected adults. Most experts recommend continuation of a maximally suppressive regimen even during the first trimester. To date, the only drugs that have been shown to reduce the risk of perinatal HIV transmission are zidovudine (ZDV) and nevirapine (see table 17)

TABLE 17 Zidovudine (ZDV) Perinatal Transmisson Prophylaxis Regimen

ANTEPRATUM	Initiation at 14-34 weeks gestation and continued throughout Pregnancy ZDV 100 mg 5 times daily, or ZDV 200 mg 3 times daily, or ZDV 300 mg twice daily
INTRAPARTUM	During labor, ZDV 2 mg/kg IV over one hour, followed by continuous infusion of 1 mg/kg until delivery.
PROSTPARTUM	Oral administration of ZDV to the newborn (ZDV syrup 2 mg/kg *every* 6 hours) for the first 6 weeks of life, beginning at 8-12 hours after birth.

There are now different recommendations for developing countries if cost is a consideration. An alternative to short course to ZDV is nevirapine 200 mg po once to the woman in labour, and once orally to the newborn (2 mg/kg) within 72 hours after birth.

20. SUGGESTED HYGIENIC PRACTICES FOR PREVENTION OF BLOOD BORNE INFECTIONS FOR SURGEONS, GYNECOLOGISTS AND THOSE HANDLING HUMAN BLOOD OR TISSUES

All patients receiving care in hospitals or doctors offices, irrespective of their diagnoses must be treated in a manner which should minimize the risk of transmission of any kind of microorganism from patient to health care worker (and vice versa) and among other patients. These are standard precautions and should be practiced at all normal times.

HIV cannot enter through normal intact skin. However there is always a small risk of it entering through very small cracks, cuts or abrasions in the skin. All patients should be anticipated to have HIV or HBV or HCV, and extra precautions should be taken to avoid blood spilling or splashing on the skin, eyes or mucosa.

All protective items such as gloves, masks, plastic aprons must be readily available in areas where these may be needed. Endoscopists, surgeons, nurses, phlebotomists, pathologists and morticians should take special care in all cases at all times.

- Hands should be washed after all patient contact, irrespective of whether gloves are worn, and immediately after blood, body fluids, secretions, excretions or possibly contaminated items or equipment are handled.
- Gloves should be worn if touching blood, body fluids, secretions, excretions or contaminated objects. Gloves should be changed between patients, after wound dressing or contact with contaminated items.
- Mask, plastic gowns and eye protection should be worn to protect skin and mucous membranes during procedures that may result in splashing of body fluids.
- Reusable equipment should be cleaned and sterilized before reuse.
- Soiled linen should be transported in a bag
- Sharp needles and instruments should be handled with care. Never remove, bend, break, or manipulate needles by hand. Used needles, scalpel blades and other sharp items should be placed in appropriate puncture-proof containers.

In case of accidental needle stick:

- The area should be squeezed to get blood out, and then washed in flowing water followed by cleansing with disinfectant.

- Rinse out the eye or mouth if these are exposed.

- Spilled blood or body fluids should be immediately disinfected with chemicals and wiped thoroughly dry. In an emergent situation household bleach may be used. Gloves should be worn while cleaning.

- For HBV prophylaxis in an unimmunized person Hepatitis B immuneglobulin (HBIG) plus vaccine series should be initiated.

- For HIV postexposure prophylaxis, triple therapy with a combination of a protease inhibitor and two reverse transcriptase inhibitors is recommended.

HIV is, luckily, easily destroyed by Intermediate Level Disinfection (ILD), which should be used for non-critical or semi critical items, i.e. those items which do not come in contact with the bloodstream or normally sterile body areas. Examples are respiratory therapy equipment, bronchoscopes, endoscopes, stethoscopes, bedpans, etc. Intermediate Level Disinfectants are 70 - 90% alcohol, chlorine compounds, phenolic and iodophoric preparations. For critical items glutaraldehyde, chlorine dioxide or 6% hydrogen peroxide may be used. Manufacturer's recommendations should be followed for safety of individual equipment.

21. WHEN AND WHERE TO REFER THE PATIENT WITH HIV/AIDS

It is expected that the practicing clinician should be able to suspect and diagnose the HIV/AIDS patient with reasonable efficiency, and be able to manage the asymptomatic patient in the clinic. He/she should be able to interpret changes in the patient's condition and diagnose common opportunistic infections such as oropharyngeal candidiasis, diarrhoea, pulmonary infections and skin infections.

Help may be sought at any time when the primary physician deems it beyond his/her scope or ability to manage the case. Early referral may be sought under the following specific conditions:

- Prolonged fever without localizing signs
- Persistent fever and headache suggestive of intracranial infection
- Persistent fever and cough not responding to antibiotics
- Sepsis
- Dehydration
- The patient requires hospitalization for invasive diagnostic or therapeutic procedures.
- Hospitalization for parenteral therapy.
- For consideration of ARV therapy

The proposed referral system for HIV/AIDS has been annexed at the end of the Protocol at annex IV. A list of AIDS surveillance centres is also available at annex III. For further information on the subject, the clinicians may contact the author of the guidelines on the following address;

Dr. Naseem Salahuddin: 493-9612/276 Liaquat National Hospital, Karachi 493-0051/1024 Aga Khan University Hospital, Karachi 566-2266, 542-0828 Clinic Fax: 493-8386 **Email: naseemsal@hotmail.com**

Other relevant information can also be obtained from the National and Provincial AIDS Control Programmes.

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23. Appendix

23.1. SELF ASSESSMENT TEST

Answer either True or False:

1- HIV/AIDS is transmitted by:

a) Blood and blood products	True	False
b) Shaking hands	True	False
c) Hugging	True	False
d) Sexual contact	True	False
e) From pregnant woman to newborn	True	False
f) Insect bite	True	False
g) Very easily by needle stick injury	True	False

2. The following questions should be asked to all patients for HIV risk assessment:

a) Husband's history of illness or cause of death	True	False
b) Have you ever donated blood	True	False
c) Have you ever received blood	True	False
d) Have you ever had:		
i) Genital ulcer	True	False
ii) Abnormal vaginal discharge	True	False
iii) Urethral discharge	True	False
e) Do you get premature ejaculation	True	False
f) Do you or have you ever had erectile dysfunction	True	False
g) Have you ever traveled abroad	True	False
h) Have you had sex outside marriage	True	False

3. Patients suspected of having HIV should have the following lab. tests:

a) HIV viral culture	True	False
b) Antibody to HIV	True	False
c) HIV antigen test	True	False

4. The following should be done for patients with known HIV:

a) They should be isolated at home	True	False
b) Never be admitted in a general ward in hospital	True	False
c) Contacts should wear gowns and gloves	True	False
d) Universal, not special, precautions should be observed	True	False
e) The patient's chart should be marked "HIV Positive" in prominent letters	True	False

5. Asymptomatic HIV patients should be advised/ managed with:

a) Reassurance only	True	False
b) Reassurance plus documentation of baseline clinical findings, lab tests and counseling	True	False
c) He/she should be advised to quit his/her job	True	False
d) Does not need protected sex	True	False
e) Pt. does not need followup unless symptoms develop	True	.False
f) Pts. should be followed regularly and any changes documented	True	False

6. HIV patients may be given the following vaccines without caution:

a) Influenza	True	False
b) BCG	True	False
c) Hepatitis B	True	False
d) Meningococca! meningitis	True	False
e) Measles, Mumps, Rubella	True	False

7. Cardinal (Diagnostic) findings of HIV/AIDS include:

a) Kaposi's Sarcoma	True	False
b) Pneumocystis carinii	True	False
c) Qral thrush	True	False
d) Herpes zoster	True	False
e) Oesophageal candidiasis	True	False
f) TB	True	False

8. Characteristic signs of HIV/AIDS include:

a) Hairy leukoplakia	True	False
b) Severe weight loss	True	False
c) Continuous fever	True	False
d) Recurrent Herpes simplex	True	False

9. The differential diagnoses of ring enhancing lesion on CAT scan are:

a) Tuberculoma	True	False
b) Cryptococcal meningitis	True	False
c) Toxoplasmosis	True	False
d) Cytomegalovirus	True	False
e) Brain abscess	True	False

10. Treatment of TB in a patient with AIDS:

a) Is different from that of.non AIDS patient	True	False
b) Thiacetazone must be included in the treatment	True	False
c) Doses of antiTB drugs must be prescribed according to the patient's weight	True	False

Key:

1 a) True b) False c) False d) True e) True f) False g) False
2 a) True b) False c) True d) i) True ii) True iii) True e) False f) False g) True h) True
3 a) False b) True c) False
4 a) False b) False c) False d) True e) False
5 a) False b) True c) False d) False e) False f) True
6 a) True b) False c) False d) False e) False
7 a) True b) True c) False d) False e) True f) False
8 a) True b) False c) False d) False
9 a) True b) False c) True d) False e) True
10 a) False b) False c) True

Annex:- 1

Participants of the Consensus Building workshop for the "Guidelines on Clinical Management of HIV/AIDS"

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Annex: -II

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5. Dr. Khalida	General Practitioner, Lahore
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7. Dr. Sara	WMO Civil Hospital Karachi
8. Dr. Nadeem M. Khan	Dermatologist, Institute of Skin Diseases Karachi

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2. Dr. Huma Quddusi	Sr. Registrar, Gynae/Obs. Sandeman Prov. Hosp., Quetta
3. Dr. Rubina Shah	Prof, of Gynae/Obs. Sandeman Prov. Hospital, Quetta
4. Dr. Abdul Malik Tareen	Dermatologist, Sandeman Provincial Hospital, Quetta
5. Dr. Abdul Khaliq	Registrar Medicine, Civil Hospital Quetta
6. Dr. Khalid A. Gichki	General Practitioner, Quetta
7. Dr. Muneer Ahmed	General Practitioner, Quetta
8. Dr. Abida Shabqadar	Dermatologist, Bolan Medical College, Quetta

Participant from NWFP:

1. Dr. Anwar Sultana	Astt. Prof. Gynae/Obs. Hayatabad Medical Complex, Peshawar

Annex:-III

List of the HIV/AIDS Surveillance Centre

FEDERAL AREAS

1. National AIDS Referral Centre, National Institute of Health, Islamabad.
2. Federal Government Services Hospital, Islamabad.
3. Pakistan Institute of Medical Sciences, Islamabad.
4. DHQ Hospital, Skurdu.
5. DHQ Hospital, Gilgit.

PUNJAB

6. Armed Forces Institute of Pathology, Rawalpindi.
7. T.B. Centre, Rawalpindi.
8. The department of microbiology, Shaikh Zayed Hospital, Lahore.
9. The department of Pathology, Holy Family Hospital, Rawalpindi.
10. The department of Pathology, Rawalpindi Medical College, Rawalpindi.
11. Institute of Punjab Blood Transfusion Services, Lahore.
12. The department of Pathology, College of Community Medicine, Lahore.
13. The department of Pathology, Services Hospital, Lahore.
14. The Medical Superintendent, DHQ Hospital, Dera Ghazi Khan.
15. The Medical Superintendent, DHQ Hospital, Chakwat.
16. The Medical Superintendent, B.V. Hospital, Bahawalpure.
17. The Department of Pathology, Nishter Medical College, Multan.
18 Sanitarium Hospital, Murree.

SINDH

19. Jinnah Postgraduate Medical Centre, Karachi. I
20. Government Seamen's Dispensary Port Health Department, Karachi.
21. AIDS Control Programme Services Hospital Indoor Block, M.A. Jinnah Road, Karachi.
22. Institute of Skin Diseases, Preedy Street Regal Chowk Sadar, Karachi.
23. Liyari General Hospital, Liyari, Karachi.
24. The department of Pathology, Peoples Medical College, Nawabshah.
25. The department of pathology , Chandka Medical College, Larkana.
26. Civil Hospital, Mirpur Khas.
27. The department of pathology, Liaquat Medical College, Jamshoro.
28. Civil Hospital, Sukkur.

NWFP

29. The department of Pathology, Lady reading Hospital, Peshawar.
30. The department of Pathology, Khyber Medical College, Peshawar.
31. The department of Pathology, Ayub Medical College, Abbottabad,
32. DHQ Hospital, Saidu Sharif.
33. DHQ Hospital, D.I. Khan.
34. DHQ Hospital, Kohat.
35. DHQ Hospital, Mardan.

BALOCHISTAN.

36. The department of pathology, Civil Hospital, Quetta.
37. Fatima Jinnah General & Chest Hospital, Quetta.
38. DHQ Hospital, Turbat.
39. DHQ Hospital, D.M. Jamali.
40. DHQ Hospital, Sibi.
41. DHQ Hospital, Lorali.
42. DHQ Hospital, Khuzdar.
43. DHQ Hospital, Gawadar.

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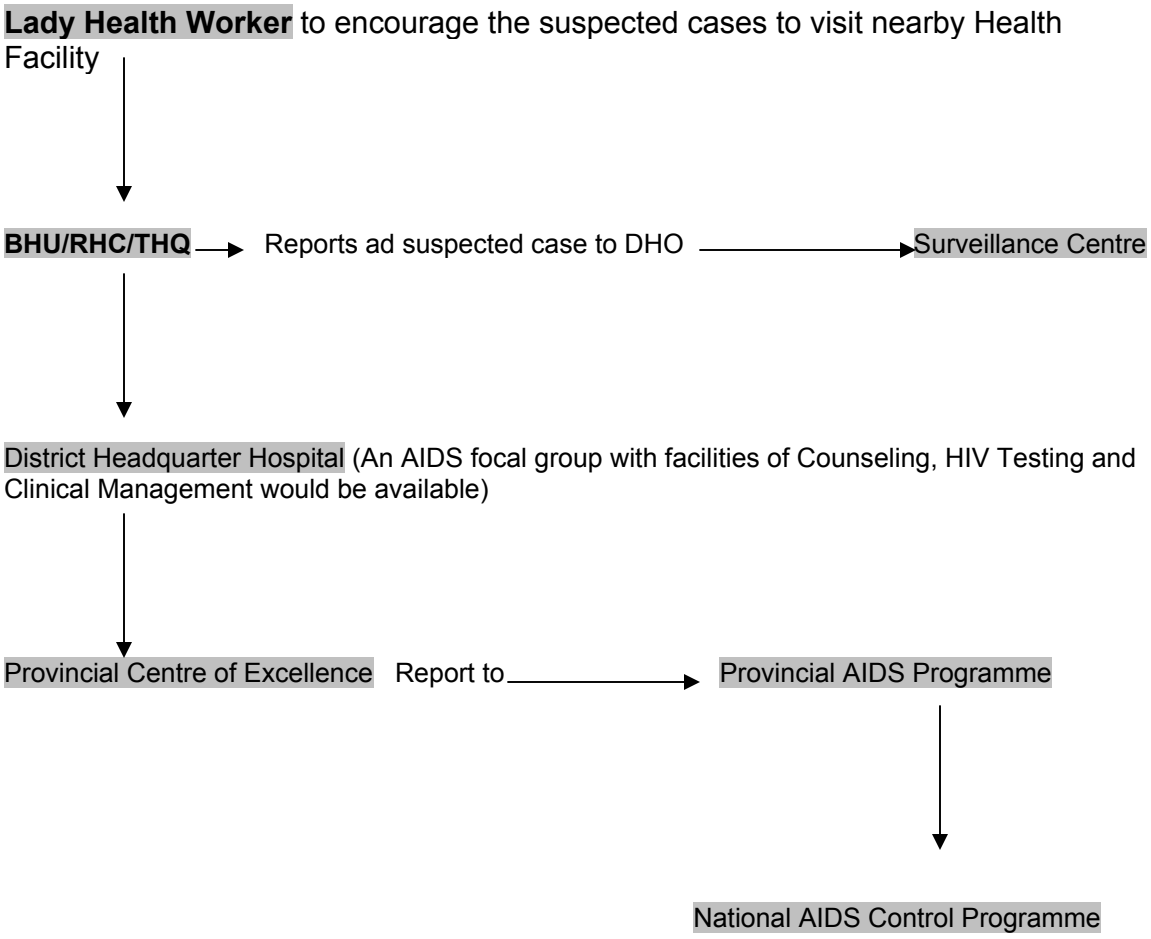
Annex:-IV

Proposed Referral System for HIV/AIDS



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