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HIV Physician Training Course 2002,
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DISTANCE LEARNING COURSE

NERVOUS SYSTEM IN HIV INFECTION

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MODULE 1

OVERVIEW

HIV enters the brain immediately after infection, is present throughout the course of the disease, and, in the later stages, often manifests at every level of the neurological system. Central nervous system (CNS) and peripheral nervous system (PNS) disorders in HIV-infected individuals may result from: (1) **opportunistic infections (OI)**, (2) **neoplasms** and (3) **primary effects of HIV** itself. The nervous system may also be damaged (4) as a result of the **toxic effects of various treatments**.

The **primary HIV-associated neurologic diseases** include: **AIDS dementia, myelopathy, peripheral neuropathy, and myopathy. Secondary neurologic complications** include: **cryptococcal meningitis, tuberculous meningitis, neurosyphilis, *Toxoplasma* encephalitis (TE), progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) encephalitis and radiculomyelitis and primary CNS lymphoma.** Both primary and secondary complications should be considered when neurologic changes are observed in patients with HIV.

The **common presenting symptoms** of neurological disease are: **(a) headache; (b) seizures and weakness; (c) limb pain and (d) memory loss**. The **main neurological syndromes** occurring in HIV infection are: **(i) meningitis; (ii) focal neurological deficit; (iii) peripheral neuropathy and (iv) dementia.**

This module aims to improve your skills in approaching these symptoms and neurological syndromes.

OBJECTIVES

After completion of this module you should be able to:

1. List the common HIV related neurological diseases.
2. Recognize the different clinical syndromes and the main causative agents/disease conditions responsible for these syndromes.
3. Use clinical algorithms to diagnose and manage these conditions.

CONTENTS

Let us start with an activity for you to ***learn the approach of a patient presenting with headache. Study the table: "Table: Neurological Syndromes and Opportunistic Infections in AIDS" (page 34) in the reader.*** *Once you have finished reading this you should be able to undertake this activity.*

ACTIVITY 1.1

APPROACH TO HEADACHE (10 min)

Mr. S. is a 32-year old truck driver. He was diagnosed to have HIV infection 8 years ago. He had remained well till about one year ago, when he started losing weight. He was seen by a doctor in his hometown who, after tests revealed absolute lymphocyte count (ALC) 880 cells/µL, had prescribed co-trimoxazole (one double-strength tablet daily). He was on no other medicines. He now presents to your clinic with a 4-week history of headache, which had really worsened over the last one week. His wife reports that he has become progressively drowsy and disoriented over the last three days.

1. Which of the neurological syndromes do you think the patient is suffering from?

Focal cerebral lesions – ?

2. Now, list your differential diagnoses (most to least common) for Mr. S in the space provided below.

Meningitis	Focal cerebral lesion
1.	1. Tuberculosis
2.	2. Toxoplasmosis
3.	3. Lymphoma
4.	4. ~~Lep~~ PML

3. What additional history and clinical findings would you like to elicit in Mr. S to find out the type of neurological syndrome and its etiology?

HISTORY	EXAMINATION
1. Seizures	1. Focal signs + fundus
2. H/o TB.	2. chest for TB.
Drugs.	3. neck rigidity
	3.
	4.

FEEDBACK 1.1

1. Which neurological syndrome do you think the patient is suffering from?

This patient may be having meningitis or a focal cerebral lesion.

The history of worsening headache and worsening sensorium in HIV infection should make you consider a diagnosis of meningitis. Usually meningitis is associated with fever but this may not always be true in HIV infection.

The worsening sensorium and headache should also make you consider a focal cerebral lesion. This would present with a history of seizures or focal neurological symptoms (such as hemiplegia). This may therefore be considered less likely in him.

2. Differential Diagnoses

Meningitis	Focal cerebral lesion
1. Cryptococcal meningitis	1. Cerebral toxoplasmosis
2. TB meningitis	2. Tuberculoma
3. Syphilitic meningitis	3. Lymphoma
	4.Progressive multi-focal leucoencephalopathy (PML)

3. History and physical examination

HISTORY	EXAMINATION
1. Seizures	1. Neck stiffness
2. Focal neurological symptoms	2. Level of consciousness
	3. Papilloedema
	4. Weakness of limbs (focal deficit)

	5. Skin involvement (cryptococcal infection) 6. Lung signs, lymphadenopathy (TB or cryptococcal infection)

Before you undertake the next activity study the figure: ***"Approach to patient with meningitis in HIV infection"*** *(page 35). Then start the activity.*

ACTIVITY 1.2

MENINGITIS IN HIV INFECTION (10 min)

On physical examination, Mr. S appears emaciated. His pulse rate is 72/min, blood pressure 140/95 mmHg, temperature 38° C (100.4° F). He is very drowsy, localizes pain and opens eyes to pain. He appears pale, but has no lymphadenopathy. Oral thrush is present and there are few umbilicated, papular skin lesions on the face (see photo 1A page 44) and anterior chest wall.

Examination of cardiovascular, respiratory system are normal. CNS examination shows no papilledema, no focal neurological deficits, bilaterally extensor plantar reflexes and terminal neck stiffness.

1. What is your diagnosis? What is the reason you are considering this diagnosis?

1.Diagnosis: Meningitis Suppurative / Cryptococcal 2. Reason for diagnosis: · No sign of TB · Skin lesion – · ? BP

2. What tests will you order to confirm your diagnosis and rule out other differential diagnoses?

1. India Ink 2. Cryptococcal Antigen 3. ? culture 4. VDRL – Serum & CSF 5. ~~TB culture~~ Acid Fast Stain

FEEDBACK 1.2

1. What is your diagnosis? What is the reason you are considering this diagnosis?

Diagnosis: Cryptococcal meningitis

Reason for diagnosis: Molluscum-like skin lesions should make think of cryptococcal infection.

2. What tests will you order to confirm your diagnosis and rule out other differential diagnoses?

1. CSF - opening pressure
2. CSF -total and differential WBC count
3. CSF - Gram stain, India ink test, Cryptococcal antigen (if available), AFB smear
4. Blood and CSF VDRL
5. Routine bacterial, fungal and mycobacterial cultures (if available)

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ACTIVITY 1.3

CSF ANALYSIS (10 min)

A lumbar puncture was done for Mr. S. The opening pressure was 290 mm water. His CSF analysis showed 8 WBC (all lymphocytes), glucose 30 mg/dl and protein 95 mg/dl.

1. What is the differential diagnosis of the CSF picture?

2. The India ink preparation is shown in the photo 1B (page 44). Describe what you see and identify the organism.

Description -
Identification -

FEEDBACK 1.3

1. What is the differential diagnosis of the CSF picture?

The CSF shows: mildly increased WBC count and protein and low glucose (<40 mg/dl). The differential diagnosis includes:

Cryptococcal meningitis

TB meningitis

Syphilitic meningitis

2. Describe what you see and identify the organism

Description - Budding yeast like organism with capsule surrounding it.

Identification -This is the typical appearance of *Cryptococcus neoformans*

A positive India Ink test is confirms the diagnosis of cryptococcal meningitis. A negative test does not rule out the diagnosis.

Before you undertake the next activity ***read "Cryptococcal Meningitis" (page 36)*** *in the reader.*

ACTIVITY 1.4

CRYPTOCOCCAL MENINGITIS (10 min)

1. The relatives of the patient ask you what the prognosis of the patient is like. Would you describe the prognosis to be good or poor?

Poor prognosis
- Raised CSF, ↓ Sugar.
- India Ink +ve

2. Which therapy would you choose for Mr. S.

Drug: ? Amphotericin Fluconazole 100 mg/kg x2wks

Dose:

Duration: 200 mg o D .. life

Total cost:

3. Mr. S 's sensorium worsens on treatment and headache and vomiting increase. What additional therapeutic intervention would you perform?

Reduce CSF pressure - drain alt days 5ml

4. What side effects of treatment will you monitor for and how will you manage these?

FEEDBACK 1.4

1. Would you describe the prognosis to be good or poor?

Poor prognosis: low CSF cell response, India Ink positive, extra-neural disease, altered consciousness, low CSF glucose

2. Which therapy would you choose for Mr. S?

Amphotericin 0.7 mg/kg/day (IV) with Flucytosine 100 mg/Kg in 4 divided doses (orally) for 2 weeks followed by fluconazole 400 mg OD (orally) for 10 weeks.

Maintenance therapy 200 mg OD life long

In view of the poor prognostic features Amphotericin therapy is preferred. If flucytosine is not available, then Amphotericin alone can be given for 2 week alone followed by fluconzole.

To start Amphotericin give first dose 1 mg in 100 ml 5% dextrose over 1 hour, monitoring vital signs every 15 minutes. If no serious adverse events occur, this is followed 4 hours later with 0.7 mg/Kg in 500 ml 5% dextrose infusion over 4-6 hours.

Total cost of Amphotericin (2weeks) followed by fluconazole (10 weeks) : Rs. 7900.

If he cannot afford Amphotericin treatment then oral fluconazole may be an alternative option. In a patient without poor prognostic features oral fluconazole may be considered one of the first options. It has fewer side effects is less costly and can be administered in the outpatient setting.

3.Mr. S 's sensorium worsens on treatment and headache and vomiting increase. What additional therapeutic intervention would you perform?

In view of the elevated CSF pressure >280 mm a therapeutic lumbar puncture is recommended at 2-3 day intervals removing 10-20 ml CSF at a time. Following therapeutic LP the closing pressure should be checked.

4. What side effects of treatment will you monitor for and how will you manage these?

Amphotericin

Febrile reaction- Aspirin or paracetamol. Can be reduced by administering hydrocortisone 10-50 mg prior to the infusion.

Hypotension, nausea and vomiting 1-3 hours post-infusion (initial test dose may predict patients who develop hypotension)

Nephrotoxicity- Monitor creatinine twice a week. Reduce dose or stop if creatinine > 3 mg/dl, Prevent by ensuring hydration, normal saline infusion 1 L/day, avoid concurrent nephrotoxic drugs.

Hypokalemia- check K+ 2 times/week; correct with oral KCl

Anaemia-does not require dose alteration.

Phlebitis or pain at the infusion site- may be prevented by using central line.

ACTIVITY 1.5

APPROACH TO LIMB WEAKNESS (10 min)

Mr. G, works as a butcher. He was detected to be HIV seropositive 5 years ago, when he attended an STD clinic for recurrent genital ulcers which were diagnosed as herpes progenitalis. Two years ago, he was diagnosed to have tuberculous lymphadenitis (cervical), for which he was on regular anti-tuberculous therapy (ATT) for one year (3HREZ/9HR). He was also prescribed co-trimoxazole prophylaxis, which he discontinued after the course of ATT was over. One week ago, he had an episode of seizures involving the right side of face and right upper limb while working in his shop. Over the next few days he had recurrent seizures and could not attend work. He also noticed progressive weakness of right upper and lower limbs over the last two days. When seen in the clinic, he was confused, restless and examination revealed motor aphasia and right-sided hemiparesis.

1. Which type of neurological syndrome does this patient have? Write down the differential diagnosis in order of probability.

Neurological syndrome:

Focal Cerebral lesion

Differential diagnosis:

Tuberculoma

Toxoplasmosis

FEEDBACK 1.5

1. Which type of neurological syndrome does this patient have? Write down the differential diagnosis in order of probability.

Focal cerebral lesion- in view of the focal neurological deficit. The right side hemiplegia and motor aphasia localize the lesion to the left frontal lobe.

Differential diagnosis:

T.E.

Tuberculoma

CNS lymphoma

Progressive multi-focal leukoencephalopthy

Toxoplasma encephalitis would be the most likely diagnosis because it is the commonest cause of focal cerebral lesions in PLWHA. Also, he had discontinued prophylaxis (co-trimoxazole) which may have resulted in reactivation of latent infection.

Before doing the next exercise ***study the figure, "Approach to focal cerebral syndrome in HIV infection" (page 38).*** *Once you have finished reading you are ready to start the exercise.*

ACTIVITY 1.6

CT SCAN (10 min)

Study the Photo 1C (see page 44) which is a brain CAT scan (contrast plus) image of Mr. G.

1. Describe the appearance of these lesions.

Site -

Shape -

Isodense/hypodense/hyperdense -

Pressure effect and oedema -

2. What are all the differential diagnoses of lesions with similar appearance on CAT scan?

3. Which blood test will help you identify which of these diagnoses Mr. G is likely to have?

FEEDBACK 1.6

1. Given below is the brain CAT scan (contrast plus) images of Mr. G. Describe the appearance of these lesions.

Multiple 'ring-enhancing' (a hypodense lesion which enhances on contrast administration only along the periphery) lesions with surrounding edema and mass effect.

2. What are all the differential diagnoses of lesions with similar appearance on CAT scan?

- Toxoplasma encephalitis
- Primary CNS lymphoma
- CNS tuberculoma
- Neurocysticercosis
- Brain abscess
- Glioblastoma and other brain tumours

3. Which blood test will help you identify which of these diagnoses Mr. G is likely to have?

IgG toxoplasma antibody titre. The absence of these antibodies excludes the diagnosis of toxoplasma encephalitis. The presence of antibodies with a ring enhancing lesion on the CT scan should lead to a presumptive diagnosis of toxoplasma encephalitis.

Prior to doing the next exercise ***read, "Toxoplasma encephalitis" (page 39)*** *in the reader. Following this you can proceed to the next exercise.*

ACTIVITY 1.7

TOXOPLASMA ENCEPHALITIS (10 min)

1. Mr. G's anti-toxoplasma antibody test could not be done, as it was not available in the hospital laboratory. What treatment will you start for Mr. G?

Drugs - Septran DS/TM/ + IBS OD Inj
+ Sulphadiazine 0.5 gm QBH x 2wks + 0.5 gm QBH x ?
+ Pyrimethamine -
+ Folinic Acid 10mg OD

Dose:

Side- effects - Sulpha sensitivity Hypersensitivity Exfoliative Dermatitis

Secondary prophylaxis -

Cost: 0/100

2.How will you follow up the treatment? How quickly do you expect a response to treatment?

· 1–2wks /– CT scan changes – 2wks

3. If Mr. G fails to improve what will you do next?

· Pleural biopsy –
· CBC – for TB, Cryptococcal.

FEEDBACK 1.7

1. Mr. G's anti-toxoplasma antibody test could not be done as it was not available. What treatment will you start for Mr. G?

Drugs, dose and duration

Pyramethamine 100-200 mg stat followed by 50-100 mg OD

(Available is Metakelfin -each tablet contains 25 mg Pyrimethamine)

Sulphadiazine 1-1.5 G q6h

Folinic acid 10-15 mg OD (If too expensive T. Folic aicdin higher doses may be used).

All for 3-6 weeks followed by secondary prophylaxis.

Alternative treatment - Co-trimoxazole (TMP 5 mg/Kg BD)

Secondary prophylaxis - Sulphadiazine 500 mg- 1G qid,

Pyramethamine 75-100 mg OD, Folinic acid 10-25 mg OD (life long)

Side effects - Drug rash, drug fever, crystalluria, anemia, bone marrow suppression

Cost: (8 tablets of sulphadiazine + 4 tablets of metakelfin/day for 6 weeks)- Rs. 8048

2. How will you follow-up the treatment? How quickly do you expect a response to treatment?

Follow-up treatment by clinical response

Response is usually seen in 7-10 days. CT scan at 2 weeks is advised if the

test is available and cost of test permits it being repeated.

3. If Mr. G fails to improve what will you do next?

If Mr. G fails to respond it may indicate a diagnosis other than toxoplasma encephalitis. The lesion needs to be biopised using stereotaxic brain biopsy at a higher centre. However studies have shown that the etiological diagnosis obtained through brain biopsy are not readily treatable. Therefore the clinical usefulness of brain biopsy in focal cerebral lesions non-responsive to anti-toxoplasma treatment may be low.

Before doing the next exercise ***study the figure: " Approach to neuropathy with HIV infection" (page 41).*** *On completion of the reading, you can start the next exercise.*

ACTIVITY 1.8

APPROACH TO LIMB PAIN (10 min)

Mr. P. is a bank manager, who was diagnosed to have HIV infection 3 years ago. He was started on highly active antiretroviral therapy (Stavudine, Didanosine and Efavirenz) six months ago. For the past two months, he has noticed burning pain and a sensation of "pins and needles", beginning on the fingers and toes and gradually ascending till the level of the wrists and knees. He is a non-smoker, does not consume alcohol and is not a diabetic or hypertensive.

1. What is the diagnosis that explains Mr. P's symptoms?

- Drug reaction / Peripheral neuropathy
-

2. Mention the differential diagnosis of this neurological syndrome and its most likely etiology?

- Diabetic
- chronic alcoholic
- Toxic
- claudication

FEEDBACK 1.8

1. What is the diagnosis that explains Mr. P's symptoms?

Peripheral neuropathy: paresthesias of glove and stocking pattern

2. Mention the differential diagnosis of this neurological syndrome and its most likely etiology?

Drug induced neuropathy by stavudine and ddI

Other causes- Other ARV drugs, INAH, alcohol, HIV induced neuropathy, CMV induced neuropathy, B12 deficiency, other associated conditions eg. Diabetes Mellitus

ACTIVITY 1.9

NEUROPATHY (10 min)

Refer back to Mr. P's case in activity 1.8.

1. What treatment can you offer for Mr. P?

FEEDBACK 1.9

1. What treatment can you offer for Mr. P?

Provide drug holiday - stop all ARV drugs together.

Reduce dose

Change regimen - use a non-ddI and d4T containing regimen

Loose footwear

Graduated walking

Soaking feet in ice

Drug treatment:

Paracetamol / Non-steroidal anti-inflammatory drugs

Tricyclic anti-depressants

Opioid analgesics

Carbamazepine

ACTIVITY 1.10

APPROACH TO FORGETFULNESS (10 min)

Mr. S., a 28-year old lorry cleaner, was diagnosed to have AIDS 6 months ago when he presented with weight loss and chronic diarrhea due to isosporiasis. He had symptomatic improvement after a course of co-trimoxazole and loperamide treatment. His wife had noticed that the patient had become increasingly forgetful over the last couple of months. She had also noticed slowness of gait,

deterioration of his handwriting and that S. had become very withdrawn. She had not noticed any fever, headache, seizures or neurological deficits like hemiplegia or aphasia. Physical examination revealed a thinly built male, who was conscious and alert. His recent memory was impaired and he had poor attention span and concentration. He was unable to perform fine repetitive movements. There were no focal neurological deficits, papilledema or signs of meningeal irritation.

1. What type of neurological syndrome do you think the patient is suffering from?

2. What is the differential diagnosis of this syndrome in order of probability?

1. Encephalitis / HIV - Dementia
2. - Toxoplasma
3. Drug induced - D
4. ? TB

3. What investigations would you order? Why?

For Meningitis (CSF) / Culture ? MRI contrast

FEEDBACK 1.10

1. What type of neurological syndrome do you think the patient is suffering from?

Dementia - the patient's symptoms are impaired memory, attention and concentration and motor difficulty.

2. What is the differential diagnosis of this syndrome in order of probability?

1. HIV associated dementia complex

Toxoplasmosis, PML and severe depression (pseudo-dementia) can present as dementia like picture

3. What investigations would you order? Why?

CSF - to rule out chronic meningitis

CT scan brain or MRI - to rule out focal cerebral lesion

Before proceeding to the next activity ***read: "AIDS Dementia Complex" (page 42)*** *in the reader. After you complete this go on to your next activity.*

ACTIVITY 1.11

AIDS DEMENTIA COMPLEX (ADC) (10 min)

The CT scan of brain (C+) study did not show any focal lesions. There was bilateral cortical atrophy. The CSF showed 8 cell/mm^3 CSF protein 70 mg/dl and CSF glucose 80 mg/dl.

What treatment may be effective in reversing his dementia?

FEEDBACK 1.11

What treatment may be effective in reversing his dementia?

Highly active anti-retroviral treatment is the only definitive treatment for this condition. AZT and stavudine should be among the drugs that are used as they cross the blood brain barrier more effectively.

NOTES

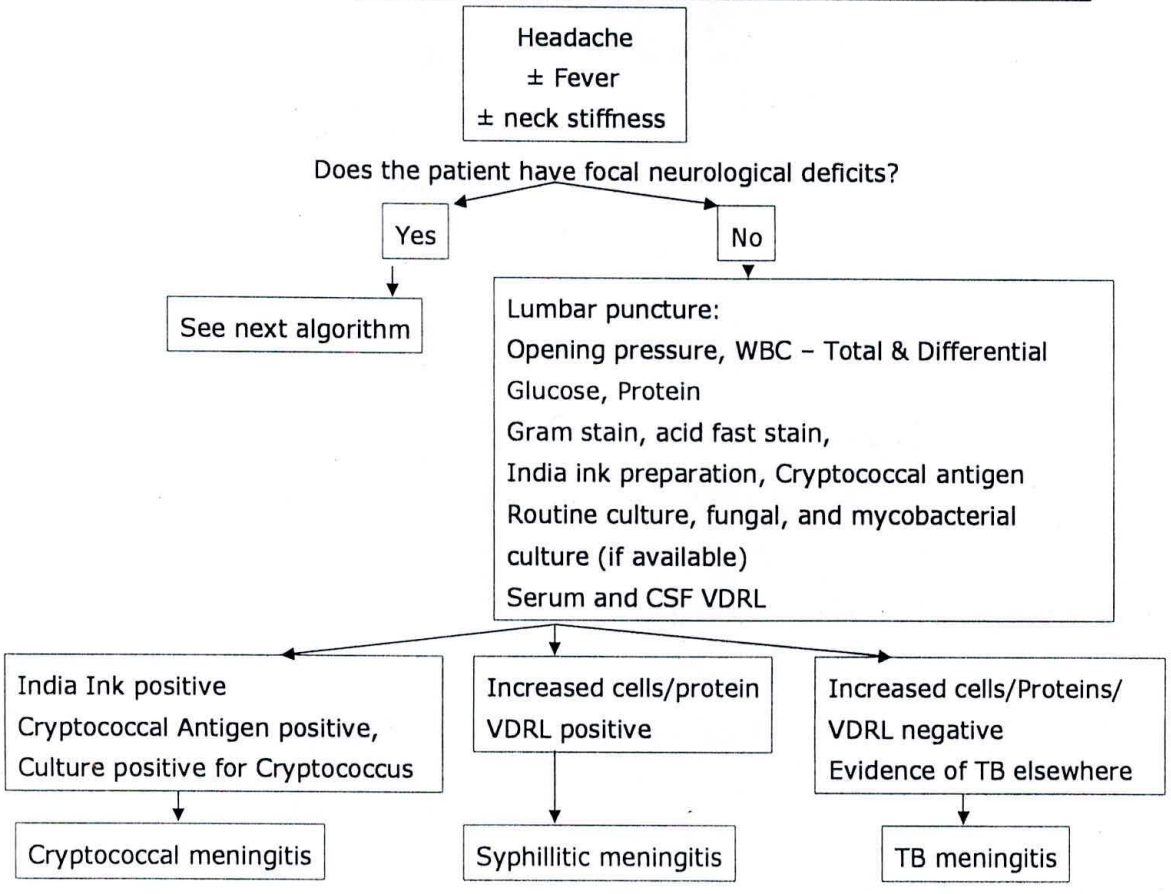
NOTES

READINGS

Table 1 : Neurological Syndromes and Opportunistic Infections in AIDS

Syndrome	Clinical features	Etiology
Meningitis	Headache	Cryptococcosis
	Fever	Tuberculosis
	Nausea/ vomiting	Syphilis
	Altered consciousness	
	Neck stiffness	
Focal cerebral lesions	Headache	Toxoplasmosis
	Focal neurological deficits	Tuberculosis/tuberculoma
	(hemiplegia, hemianopia)	Cysticercosis
	Seizures	Progressive multifocal
		leukoencephalopathy (PML)
		Lymphoma
Encephalitis	Cognitive impairment	CMV
	Psychiatric features	
	Altered consciousness	
Dementia	Cognitive impairment	HIV
	Psychomotor slowing	
	Behavioural disturbances	
Myelitis	Paraparesis	CMV
	Sensory changes	HIV
	Sphincter disturbances	

FIG. 1 - APPROACH TO MENINGITIS IN HIV INFECTION



CRYPTOCOCCAL MENINGITIS

Cryptococcosis is a systemic or CNS fungal infection caused by the organism *Cryptococcus neoformans*. The commonest manifestation is meningitis (cryptococcosis is the most common cause of meningitis in AIDS). Other manifestations are skin lesions (flesh coloured, umbilicated papules resembling molluscum contagiosum), pulmonary manifestations and fungemia.

The organism is ubiquitous, but particularly plentiful in soils enriched with bird droppings.

The incidence of cryptococcal meningitis in PLWHA is estimated to be 6 - 10% in the US. It is much more frequent in Africa and India, probably because of the increased environmental exposure to the pathogen. It occurs in HIV-positive patients with CD4 cell counts <100/μL.

Clinical manifestations and Diagnosis: (See further reading) Patients present with headache, fever, nausea and vomiting. The onset of symptoms is subacute over 7 - 14 days. Confusion and impaired consciousness occur in later stages. Signs of meningeal irritation (neck stiffness, Kernig's sign) are unusual (<40%). The diagnosis is confirmed by CSF examination. Positive India ink staining or CSF cryptococcal antigen will provide rapid diagnosis, which is confirmed by CSF culture. In situations where CSF culture and cryptococcal antigen are not available, India Ink test may be used as the confirmatory test.

Prognosis: It is associated with 100% mortality without specific anti-fungal treatment. Poor prognostic features include a high opening pressure of CSF, low CSF glucose levels, CSF cell count <20 leukocytes/mm^3, altered mental status, positive India ink preparation and cryptococci isolated from extra-neural sites.

Treatment:

a. ***Severe cases*** (high opening pressure of CSF, low CSF glucose levels, <20 leukocytes/mm3, altered mental status,)*:* Admit for 2-week induction with Amphotericin B intravenously, 0.7 mg/kg/day, (with or without flucytosine 100 mg/kg/day in 4 divided doses).

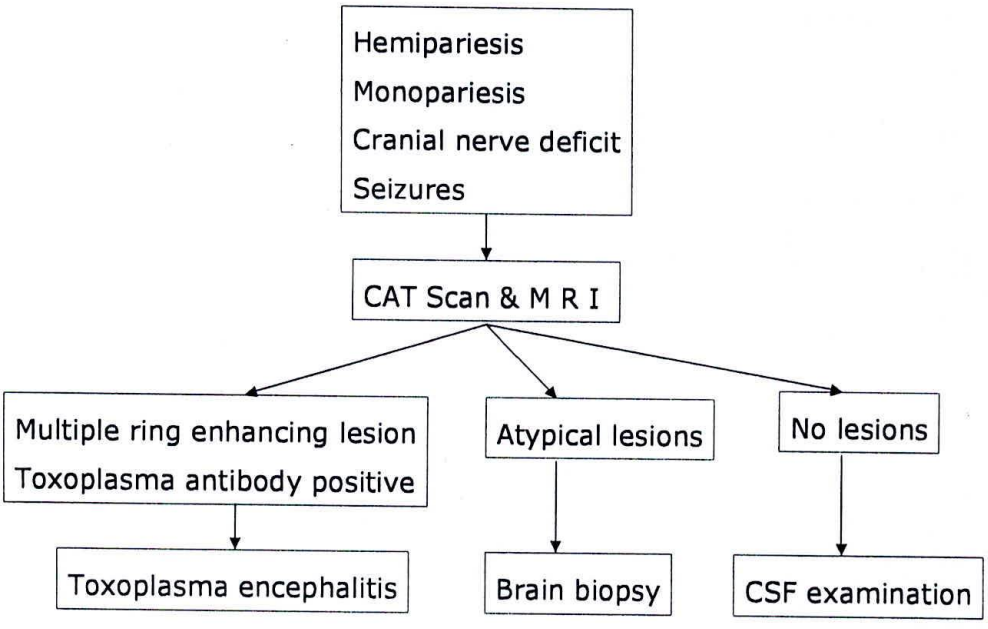
b. ***Mild cases:*** Fluconazole 800 mg p.o. loading dose, followed by 400 mg p.o. once daily x 8 weeks.

Maintenance therapy: Fluconazole by 200 mg once daily (indefinitely)

Management of elevated CSF pressure:

If initial opening pressure >250 mm CSF, repeat LP at 1-3 day intervals as needed for pressure reduction; removing 10-20 ml of fluid may be required. Check closing pressure. Occasionally, lumbar drains or ventricular-peritoneal shunt may be indicated if raised intra-cranial tension is refractory to medical treatment (consult Neurosurgery).

FIG. 2 - APPROACH TO FOCAL CEREBRAL SYNDROME IN HIV INFECTION



TOXOPLASMA ENCEPHALITIS

Toxoplasma gondii is a protozoan parasite which causes latent infection of central nervous system worldwide in the normal population. In patients with severe defects in the cellular immune response such as HIV infection, the parasite can become reactivated. HIV patients are at risk of developing toxoplasma encephalitis at CD count <100/μL. The infection of the CNS is multi-focal causing pathology of enlarging nodules and areas of necrosis with predeliction for the cortex and basal ganglia. The primary neurological presentation of toxoplasma encephalitis (TE) is a focal cerebral syndrome.

Studies from other countries have shown that nearly half of AIDS patients who are toxoplasma antibody positive will develop TE. In our own hospital TE is the fifth most common discharge diagnosis for patients with HIV infection. TE can be effectively prevented by primary prophylaxis with cotrimoxazole or sulphadiazine with pyrimethamine.

Clinical manifestations and Diagnosis:

Toxoplasma encephalitis presents subacutely (over weeks) with symptoms of headache, fever, altered mental status(70%), hemipariesis or other focal signs (60%) and seizures (30%). It occurs in advanced immunodeficiency (CD<100/μL).

The diagnosis is based on: (a) CT/MRI imaging showing multiple ring enhancing lesions in the basal ganglia and cortex often with mass effect and (b) IgG toxoplasma antibody titre positive. A negative CT/MRI scan rules out the diagnosis of TE. The differential diagnosis of ring enhancing lesions includes: lymphoma brain, tuberculoma, cryptococcocis, neurocysticercosis, brain abscess and brain tumours. In patients with advanced HIV infection, TE is the most frequent cause of ring enhancing lesions.

Prognosis: 85% respond to specific therapy usually within 7 days. Failure to respond within 7 days should make you consider an alternative diagnosis and is an indication for brain biopsy.

Treatment:

Pyrimethamine 100-200 mg stat , then 50—100 mg daily

Folinic acid 10 mg OD+ Sulfadiazine 4-6 G/day × 6 weeks

Alternatives-

Pyrimethamine + Folinic acid + Clindamycin or

Primethamine + Folinic acid + Azithromycin or Clarithromycin

Co-trimoxazole (TMP 5 mg/kg BD)

Clinical response usually occurs within 2 weeks

CT/MRI response also occurs within 2 weeks

Corticosteroids are indicated if there is mass effect.

Suppressive treatment (secondary prophylaxis)

Pyrimethamine 25-75 mg daily +

Folinic acid 10 mg OD +

Sulfadiazine 0.5 G Q6H daily life long

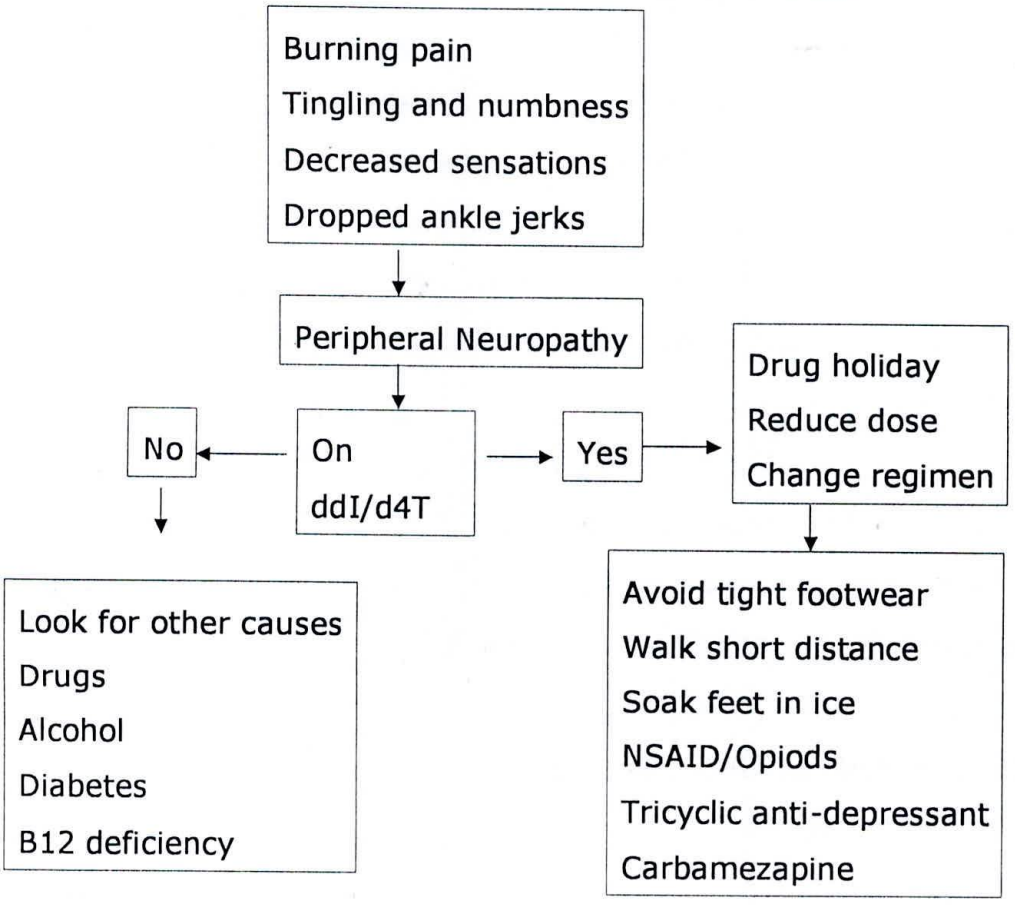
Primary prophylaxis

Indication: IgG Toxoplasma antibody positive & CD 4 < 100

Bactrim DS I daily

Alternative: DDS + Pyrimethamine + Folinic acid

FIGURE 3 - APPROACH TO NEUROPATHY IN HIV



AIDS DEMENTIA COMPLEX (ADC)

HIV virus enters the central nervous system early in the infection and infects macrophages and microglial cells sparing the neurons. The mechanism by which the virus produces damage to the neurons is not known but is thought to be due to secretion of factors (cytokines) by stimulated macrophages which cause neuronal death. As the disease progresses (CD4 count<200/μL), HIV produces a slowly progressive encephalitis manifested by (a) cognitive decline; (b) motor difficulty and (c) behavioral changes. About one-third of adults and half of children develop ADC in western countries.

The common symptoms are: (a) cognitive decline - decreased attention and concentration, forgetfulness and slowing of thought; (b) motor difficulty-slowed movements, ataxia and clumsiness and (c) behavioral changes-apathy, agitation and blunting of personality.

In a patient presenting with these symptoms, chronic meningitis and toxoplasma encephalitis need to be ruled out. The tests of choice are CT/MRI imaging and CSF examination. In ADC there is mild increase in CSF WBC count and elevated CSF protein levels. The CT scan and MRI show cerebral atrophy and the absence of contrast enhancement and mass effect.

The definitive treatment of ADC is HAART with drugs which penetrate the blood brain barrier including zidovudine or stavudine.

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3. Subauste C.S and Remington J.S. (1999) AIDS associated toxoplasmosis. *In* Sande M.A and Volberding P.A. (eds) *The Medical Management of AIDS*. W.B. Saunders Company, Philadelphia.

Photo 1A

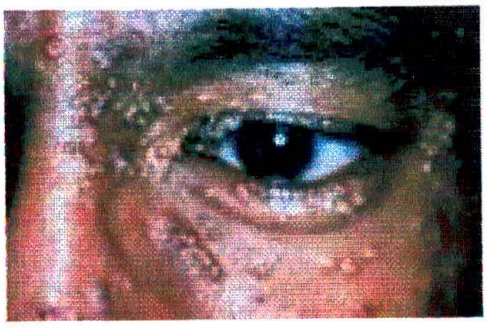


Photo 1B

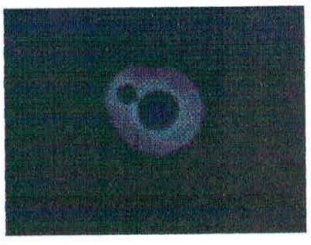
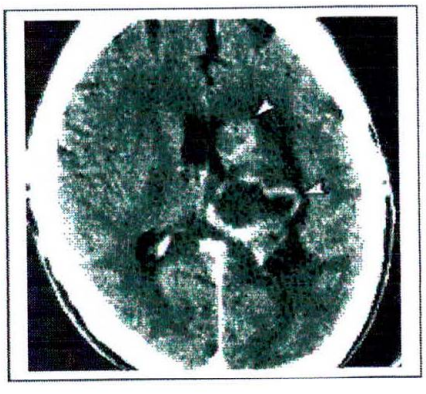


Photo 1C



Dr Mani Kalkeath

HIV Physician Training Course 2002,
Christian Medical College, Vellore

DISTANCE LEARNING COURSE

HIV
AND
WOMEN

Author : Jessie Lionel

Course Organiser : Anand Zachariah

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MODULE 2

INSTRUCTION SHEET- HIV AND WOMEN (MODULE 2)

1. In addition to this module you will find:

Envelope addressed to Course Coordinator, HIV Physician Training Program, CMCH, Vellore-632004 which has stamps required for registered post.

2. After you complete the module tear (a) Tutor marked assignment (page 25); (b) the module evaluation form (at the end of the module) and enclose it in this envelope. Send it by registered post to CMCH by: December 21, 2002.

OVERVIEW

Women comprise 4 % of adults living with HIV/AIDS worldwide. Most women are infected at a childbearing age through heterosexual transmission. In India the prevalence of HIV among pregnant women varies from 0.13 - 1.75 cases/100 pregnant women. The risk of mother-to-child transmission (MTCT) from an HIV infected mother varies from 25 to 35%. Several interventions including antenatal screening for HIV infection, anti-retroviral therapy, caesarian section and avoiding breastfeeding have been shown to reduce the risk of MTCT. Ninety percent of pediatric HIV infection is due to MTCT and this can almost entirely be prevented by these interventions.

HIV affected women are also prone to gynecological problems including infertility, reproductive tract infections and cervical cancer. Special attention has to be paid to the evaluation, treatment and prevention of these disorders. The treatment of STD's in women will be covered in Module 8 HIV and STD's.

This module aims to improve your skills in planning out obstetric and gynecological management of HIV affected women and to develop your clinical services in relation to these.

OBJECTIVES

After completion of this module you should be able to outline:

1.The steps of organizing an antenatal screening program in your own clinic.

2.The approach to pre-test and post-test counselling in the antenatal setting.

3. How to choose appropriate measures to reduce mother to child transmission (MTCT) for an individual patient with HIV infection.

4. The steps of initiating anti-retroviral therapy to reduce MTCT.

5. How to choose appropriate contraception for an HIV affected woman.

6. The approach to routine gynecological care of an HIV affected women.

CONTENTS

*Let us start with a short **reading "HIV screening in pregnancy" (page 27)**. Once you have finished reading this, you should be able to undertake your first activity.*

ACTIVITY 2.1

HIV SCREENING IN PREGNANCY (10 MIN)

Write down the advantages and disadvantages of universal screening in an antenatal clinic.

UNIVERSAL SCREENING

ADVANTAGES	DISADVANTAGES
1. Allows strategies for inducing Bacteriatric Infecti	1. Expensive
2. Even if clients unaware of high risk, program effecti	2. Ethical issues.
3. Institute necessary contraceptive & gynae service	3. Low yield
4. Pre-Post Test counselling	4.

FEEDBACK 2.1

UNIVERSAL SCREENING

ADVANTAGES	DISADVANTAGES
1. Identifies all women affected 2.Required for program to prevent MTCT 3. Prevents horizontal transmission to partner 4. The person can access medical care	1. Costly 2. Requires system for informed consent and counselling 3. Requires system for instituting measures to reduce MTCT 4. Increased stigma and possibility of refusal of care

The next activity aims to help you think about the counselling services that you require in the antenatal clinic of your hospital or institution. To do the next exercise you will need to ***read the following readings.***

1. Guidelines and policies in HIV care, CMCH Hospital Infection Control Committee, Christian Medical College and Hospital 2001.

Page 38-39 Informed consent

Page 28 Patient information sheet

Once you have finished reading this you can undertake the next activity.

ACTIVITY 2.2

COUNSELLING (10 MIN)

Design a patient information sheet on HIV testing for your antenatal clinic based on the information sheet given in the reading. This may be used as a pamphlet; or it can provide key messages for a health education program.

HIV INFORMATION SHEET FOR THE ANTENATAL CLINIC AT _____
Introduction For the evaluation and proper care of your pregnancy, we need to test you for HIV, Hepatitis B and Sexually transmitted diseases. There is a chance of HIV positive person affecting the baby and the partner.
What is an HIV test? HIV test is required to be done for the care of the patient and to manage the risks to the partner and the baby.
Why is it being done? Little blood is removed and tested for the presence of HIV virus. If it shows positive, it is tested again to confirm, and the partner's blood is also tested to identify the HIV status. Results are informed after confirmation
If the test is positive, what treatment can be offered? • Plan and support in the long term treatment of the patient • Treatment for preventing infection of the child • Measures for prevention of infection to the partner if not positive
Reassurance that care will not be refused If the test is positive, the required care will be provided and confidentiality maintained
Options for more detailed discussion with nurse/ counsellor/ doctor If further clarity is required, you may please contact the nurse/doctor.

FEEDBACK 2.2

Design a patient information sheet on HIV testing for your antenatal clinic based on the information sheet given in the reading. This may be used as a pamphlet; or it can provide key messages for a health education program.

Introduction In the evaluation for your pregnancy we require to screen you for the following infections: Hepatitis B, HIV (the infection that causes AIDS) and sexually transmitted diseases. These infections can be transmitted to your husband or partner as well as to your child.
What are these tests: These are screening blood tests that look for evidence of these infections. If they are positive, then you may require other tests to confirm the presence of any of these infections.
Why is it being done If any of these infections are there, we can institute treatments to cure them or precautions to prevent spread to your child and spouse.
Reassurance that care will not be refused If any of these tests are positive, then your results will be kept confidential and will be explained to you or those whom you may want to be informed. We will ensure that all necessary treatments are provided to you.
Options for more detailed discussion with nurse/ counsellor/ doctor If you would like to have more detailed information or discussion please contact the nurse or doctor.

The next activity aims to help you identify the testing protocol that you would like to use in your antenatal clinic of your hospital or institution. To do the next exercise, you will need to read the below readings and also visit the laboratory which does your HIV test. Once you have finished reading this you can undertake the next activity.

1. NACO guideline for HIV testing page 40

Strategies for HIV testing in India page 41

ACTIVITY 2.3

HIV TESTING STRATEGIES (10 MIN)

1. Which of the testing strategies I,II or III of the WHO/UNAIDS recommendations are you using in your laboratory?

Strategy III . Tridot

2. Which type of tests do you use for A1 and A2 or A1, A2 and A3 in your laboratory (eg. Rapid test eg. Tridot, ELISA eg. Genedia, Western blot)?

A_1 – Tridot A_2 – Abbot Strip A_3 – ELISA.

3. If a result is indeterminate what would you do?

4. What is the cost of testing strategy II and III?

Rs 300 + Rs 400.
However patient is charged only Rs 200.

FEEDBACK 2.3

1. Which of the testing strategies I,II or III will you use?

You could use strategy II or III depending on the availability of tests and costs involved.

If you had access only to rapid tests then you would use strategy II.

2. Which tests will you use for A1, A2 and A3?

Strategy II

A1- Rapid test (eg. Tridot, Capillus, HIV spot) or ELISA (eg. Genedia, Detect HIV, Microlisa)

A2 - Rapid test by another method or ELISA by another method

A3- ELISA by a 3rd method or rapid test by a 3rd method or western blot test

The sequence of tests that could be done are:

One rapid test followed by 2 ELISAs (Strategy III)

Two rapid tests followed by 1 ELISA (Strategy III)

Two ELISAs followed by one rapid test (strategy III)

Three ELISAs (Strategy III)

Two rapid tests (Strategy II)

One rapid test and 1 ELISA (Strategy II)

3. What would you do if a result is indeterminate at the end of the algorithm?

Western blot test should be done if you have access to it. Otherwise you could wait for a period of 2-3 months and repeat the HIV test.

What is the cost of testing strategy II and III?

Strategy II
Two rapid tests - Rs.200
One rapid test + 1 ELISA - Rs.150
Strategy III
Two rapid tests + 1 ELISA - Rs.250
Two ELISAs + 1 Western Blot - Rs.1,100
Two ELISAs + 1 rapid test - Rs.200

The next activity will help you explain the risks of mother to child transmission to a HIV affected mother during pregnancy. To do the next exercise you will need to ***study tables: "Mother to child transmission" (page 29) and "Factors which increase risk of MTCT" (page 30)*** *in the reader. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 2.4

MTCT: RISK FACTORS (10 MIN)

Mrs. Saraswathy a 23 year old lady is attending your antenatal clinic for her first pregnancy at 14 weeks of gestation. She had a routine antenatal HIV test and her HIV ELISA was found to be positive. You have initiated her post-test counselling and are reviewing her for the second time after the test report. Mrs. Saraswathy is keen to know what the actual risk of her baby acquiring HIV infection is and what she can do to prevent this from happening.

1. How will you explain to her the risks of mother to child transmission?

Ante-natal	5-10%
During labour	10-20%
After delivery- with breast feeding	5-15
Overall	20-45%.

2. How will you explain to her what she can do to reduce the risk of mother to child transmission?

1. Ant-retroviral treatment (short course)
2. Nutrition and Vit A supplement
3. Regular check, Treatment of STDs.
4. Protected sex.
5. Planned Caesarean
6. Artificial feeding.

FEEDBACK 2.4

1. How will you explain to her the risks of mother to child transmission

Ante-natal	: 5 -10%
During labour	: 10 - 20%
After delivery, with breast feeding	: 5 -10%
Overall	: 30 - 45%

2. How will you explain to her what she can do to reduce the risk of mother to child transmission?

1. Maintain good diet
2. Take vitamins and minerals
3. Continue regular ante-natal care under you
4. Avoid breast-feeding if she can afford to give formula feeding or cows milk.
5. Use barrier method of contraception.
6. Consider the option of anti-retroviral treatment to reduce MTCT.

The next activity will help you to choose the appropriate measure to reduce mother to child transmission. To do the next exercise you will need to ***study tables: "Efficacy of single drug ART to reduce MTCT" (page 31) and "Mother to child transmission-mode of delivery" (page 32) and "Dosing schedules for single drug ART" (page 33)*** *in the reader. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 2.5

PREVENTION OF MTCT (20 MIN)

1. Choose the appropriate treatment modalities to reduce the MTCT for the clinical settings given in the table below, in relation to:(a)ART to mother; (b) Mode of delivery (c) Infant prophylaxis and (d) Infant feeding.

No.	Case scenario	ART to mother	Delivery	InfantProphylaxis	Infant Feeding
1	22-year old primi-gravida with HIV infection at 12 weeks of gestation	AZT 300mg bd till delivery	• AZT 300mg BD • Planned Caesarian or	• AZT 10mg/kg bd x6wk • Nevirapine 200mg. • No breast feeding	• Artificial feeds
2	30-year lady, HIV infected, presenting at 32 weeks of gestation	"	"		
3	Unbooked lady in early labour, rapid HIV test positive	Nevirapine — single dose	Nevirapine or AZT • No Episiotomy or assisted labour (? Caesarian)	"	"

4	Unbooked lady delivered before HIV result became available				

2. Calculate the cost of the treatment for the above cases:

Sl. No.	ART	Delivery	Infant Prophylaxis	Feeding
1				
2				
3				
4				

3. What modifications to the delivery procedure would you undertake to reduce the risk of mother to child transmission?

1.
2.
3.
4.
5.

4. Write down:

(a) Advantages of breast feeding

i. complete nutrition
ii. bonding
iii. Immunity building

(b) Factor which determines advice to breast feed:

© Qualifications to the advice to breast feed.

i. Viral load high.
ii. CD_4 count < 200.
iii. Retroviral Rx to baby 6 wks.

FEEDBACK 2.5

1. Choose the appropriate treatment modalities to reduce the MTCT for the following settings:

No.	Case Scenario	Treatment ART	Mode of Delivery	Infant Prophylaxis
1	Primi gravida at 12 weeks GA.	AZT 300 mg bd from 14 weeks or any time after- wards	Elective C.S. at 38 weeks	Syrup AZT 2 mg/kg Q6H x 6 wk hrs. of birth
2	30 yrs lady at 32 weeks GA.	AZT 300 mg BD from 34 weeks for 4 weeks	Elective C.S. at 38 weeks	Syrup AZT 2mg/kg Q6H x 6 wk hrs. of birth
3	Unbooked lady, early labour	Single dose oral Nevirapine 200 mg stat	Vaginal delivery with all precautions to decrease MTCT	Syrup AZT 2 mg/kg Q6H x 6 wee 8 hrs. of birth
4	Unbooked lady delivered before HIV result	--	--	Syrup AZT 2 mg/kg Q6H x 6 wk hrs. of birth or Single dose 2 mg / Syrup Nevirapine

2. Calculate the cost of the treatment for the above cases:

Sl. No.	ART	Delivery	Infant Pro-phylaxis	Feeding
1	a) From 14 weeks - Rs.7,660 b) From 20 weeks - Rs.5,745 c) From 28 weeks - Rs.3,192	Rs.8-10,000	Rs.403	Rs.1,500 Approx.
2	From 34 weeks - Rs.1,277	Rs.8-10,000	Rs.403	Rs.1,500
3	Nevirapine 200 mg - Rs.19	Rs.2,500	Rs.403	Rs.1,500
4	--	Rs.2,500	Rs.403	Rs.1,500

3. What modifications to the delivery procedure would you undertake to reduce the risk of mother to child transmission?

1. Elective LSCS if patient can afford it and your set up is equipped.
2. Avoid artificial rupture of membranes, perineal tear, episiotomy, fetal scalp monitoring, suction cup, forceps application.
3. Avoid umbilical blood sampling
4. Bathe baby immediately after delivery.
5. Avoid emergency Caeserian section.

4. Write down:

(a) Advantages of breast feeding

i. Good nutrition/well balanced easily digestible

ii. Breast milk protection against gastroenteritis and respiratory infections.

iii. Preservation of gastrointestinal barrier against infection by HIV

(b) Factor which determines advice to breast feed:

Low socio-economic status which may prevent the mother from being able to give sterile and clean formula feeds or cow's milk.

(c) Qualifications to the advice to breast feed.

i. Exclusive breast feeding (no cows milk or formula feeds) for 4 months.

ii. Treat infections of breast, check for cracking of nipples and oral candidiasis in the mouth of the child.

iii. Weaning at 4 months with rice or ragi kangi with palladai or spoon.

The next activity will help you to choose the appropriate method of contraception for an HIV infected woman. To do the next exercise you will need to ***study the table: "Contraception in HIV infection" (page 35)*** *in the reader. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 2.6

CONTRACEPTION (10 MIN)

A 23 year old lady with HIV infection has one 2 year old child. Her husband is also infected. On discussion with her regarding contraception she expresses the desire to adopt a temporary method.

Which contraceptive methods would you choose and explain your reasons.

Method of contraception Reason

FEEDBACK 2.6

Method of contraception:

Barrier method (condoms) with oral contraceptive pills or IUCD

Reason

Of the temporary methods the most safe are barrier methods but their efficacy is not high. In addition barrier methods reduce risk of STD's.

Therefore a combination of hormonal contraception and barriers method may be used. Since it is difficult to sustain motivation to take OCP's everyday, IUCD with a short thread may be inserted. Regular supplementation with iron to correct anaemia is advised.

The next activity will help you to understand the appropriate gynecological care for a HIV infected woman. To do the next exercise you will need to ***read: "Routine Gynecological Care in HIV infection" (pages 36)*** *in the reader. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 2.7

GYNECOLOGICAL CARE (10 MIN)

30 year old Mrs. Revathy was diagnosed to have HIV infection 3 years ago. She presented to the OPD with history of vaginal discharge.
On examination: there is curdy white vaginal discharge and on the vulva there is evidence of external warts.

1. What tests will you do for her?

VDRL test is negative. The gnonococcal smear and wet mount for trichomonas are negative. The KOH test is positive. The pap smear shows evidence of severe atypia.

2. What treatment will you administer?

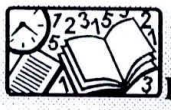
FEEDBACK 2.7

1. What tests will you do for her?

Blood VDRL, urine microscopy, vaginal smear for wet mount, gnonococcal smear, potassium hydroxide (KOH) preparation and pap smear.

2. What treatment will you administer?

1. T. Clotrimazole 100 mg vaginal pessaries I OD for 10 days.
2. Imodium solution or cryotherapy for warts.
3. Refer for colposcopy and biopsy for the severe atypia to rule out cervical intraepithelial neoplasia.



READINGS

HIV SCREENING IN PREGNANCY

Ninety percent of pediatric HIV infection is due to perinatal and MTCT. Pediatric HIV infection can be prevented effectively through strategies to reduce MTCT and perinatal transmission.

Selective or universal screening at antenatal clinics is advised to identify HIV affected women. Selective screening in women who are known to be at risk is advised in low prevalence areas but may miss women who are not aware that they are at risk. Universal screening is advocated in high prevalence areas but is more costly and associated with practical and ethical problems. In our hospital universal screening is performed. In your center you will have to decide your policy based on knowledge of local prevalence, cost and practicality.

HIV PATIENT INFORMATION SHEET IN THE ANTE-NATAL CLINIC

Counselling and voluntary testing is practiced in the Obstetrics and Gynecology department at Christian Medical College and Hospital. In view of the large number of patients, individual pretest counselling for each woman receiving antenatal care is not practical. Therefore printed information sheets (in different languages) are used to provide information about the HIV test to women attending the antenatal clinic. Women who request more information are referred to a counsellor. Any woman who tests positive on an HIV test is referred to a senior obstetrician for disclosure of results, counselling and further management. No woman or her family is discriminated against on the basis of her HIV status. In the case of a women testing positive, screening of the husband/partner is recommended before the woman is informed about the test result. This is done to avoid refusal of screening for HIV by the husband/partner and the possible implications this may have on the woman.

PATIENT INFORMATION SHEET (Guidelines and Policies in HIV CARE)

Among the investigations required for your care, we may need to test you for the presence of HIV and Hepatitis B infection. HIV infection spreads through sexual contact, sharing needles and contaminated blood or blood products. An HIV positive individual can transmit the infection to the husband/wife/partner. A pregnant mother who has the infection can transmit it to her child. Therefore it will help you to know your HIV status and will help us plan your treatment.

We look for HIV infection in your body by testing a sample of your blood. If this test suggests the presence of the virus in your body, you may have to have another test to confirm this. If the first test is positive, then it is advisable that your husband / wife / partner is also tested. Once the test result is confirmed, we will make the result known to you.

Please keep in mind that this test is done for your own and your family's wellbeing. If this test reveals the presence of disease, then you will be advised regarding appropriate treatment. Your care will not be compromised if you test positive. If you have any concerns regarding this test, do not hesitate to discuss them with the doctor treating you.

MOTHER TO CHILD TRANSMISSION

Estimated mother to child transmission (MTCT) rates (%) in breast feeding and non-breast feeding populations who have not received any intervention to reduce transmission.

TIME POINTS	NON-BREAST FEEDING	BREAST FEEDING TO 6 MONTHS	**BREAST FEEDING TO 18-24 MONTHS**
	MTCT rate (%)	MTCT rate (%)	**MTCT rate (%)**
Intrauterine	5-10	5-10	**5-10**
Intrapartum	10-20	10-20	**10-20**
Postpartum (< 2 Months)		5-10	**5-10**
Post-partum (> 2 months)		1-5	**5-10**
Overall	**15-30**	**25-35**	**30-45**

The overall MTCT rate provides the actual rate of transmission according to patient group: non-breast feeding, breastfeeding to 6 months and breast-feeding to 18-24 months. The rate according to different time points in pregnancy: intra-uterine, intrapartum, post-partum (< 2 months and > 2months) are estimated rates.

Source: Modified from De Cook et al 2000

FACTORS WHICH INCREASE RISK OF MTCT

HIV disease	Maternal factors	Obstetric factors	Newborn
• Increased Viral load • Low CD4 count • Advanced disease • Drug resistance	• Malnutrition • Vitamin A deficiency • Cigarette smoking • STD • No regular access to ANC • Unprotected sexual intercourse	• Pre-term labour • Premature rupture of membranes • Invasive fetal monitoring • Uterine manipulation • Abruptio placenta • Episiotomy • Forceps • Vacuum extraction • Emergency caesarian section	• Breast feeding • IUGR • Premature baby

STUDIES OF SINGLE DRUG ART TO REDUCE MTCT

	Drug regimen	MTCT (%)
076 regime (See Article 1 in Readings)	AZT started 14-34 weeks + IV intrapartum + oral neonatal for 6 weeks (non-breastfed)	8.3%
Thai short (See Article 2 in Readings)	AZT started at 36 weeks until delivery (non-breast fed) + Neonatal for 6 weeks (non-breast fed)	8.6%
Nevirapine (See Article 3 in readings)	Single oral dose Mother 200 mg in labour Neonate: 2 mg/kg within 72 hours of birth (breast fed)	15.7%
NY AIDS Institute	Mother: no ART Neonate: AZT within 48 hours for standard duration (Non-breast fed)	9.3%

See references for details of study methodology, control groups and efficacy of reducing MTCT.

MOTHER TO CHILD TRANSMISSION: - MODE OF DELIVERY

		Elective LSCS	Vaginal delivery	Emergency LSCS
French cohort	With AZT	0.8%	6.6%	11.4%
Swiss cohort	With AZT	0.1%		
	Without AZT	8.0%	20.0%	
Read et al	With AZT	2.0%		
	Without AZT	8.2%		

DOSING SCHEDULES FOR SINGLE DRUG ART

Drug	Ante-natal	Intra-partum	Neonate (immediately after birth)
Option 1	AZT 300 mg bd from 14 weeks	300 mg q3h during labour	2 mg/kg qid for 6 weeks
Option 2	AZT 300 mg bd from 36 weeks	300 mg q3h during labour	2 mg/kg qid for 6 weeks
Option 3			2 mg/kg qid for 6 weeks
Option 4		T. Nevirapine 200mg stat in labour	Syr. Nevirapine 2mg/kg within 72hr of birth / oral AZT 2mg/kg qid for the infant for 6 weeks

Cost

Tab. AZT 300 mg - Rs.22.80

Tab. Nevirapine (Cipla) 200 mg - Rs.18.86

Syr. AZT (Cipla) 15 mg/5 ml (100 ml) - Rs.100.70

HAART THERAPY IN PREGNANT WOMEN

1. The principles of HAART are the same in pregnancy as in the normal HIV infected patient.
2. The indications of HAART are: (a) clinical deterioration (opportunistic infections, constitutional symptoms); (b) immunological deterioration (CD4 < 500 or < 350 cells/μl); or (c) virological deterioration (>10,000 copies/ml).
3. HAART regimens should consist of 2 nucleoside reverse transcriptase inhibitor (NRTIs) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI).
4. Efavirenz is contraindicated in pregnancy due to its teratogenicity.
5. Nevaripine is better avoided due to increase risk of development of drug resistance.
6. In patients who are on HAART before pregnancy, discontinuation of all drugs together until 14 weeks is advised.

The safety of anti-retroviral drugs in pregnancy is not fully established. Therefore detailed discussion with the patient is required before starting on HAART.

CONTRACEPTION IN HIV INFECTION

	ADVANTAGES	DISADVANTAGES	EFFICACY
HORMONAL	• Easy to use • Reduces anemia • Regular cycles	• Drug interactions • Increased genital HIV shedding • Cervical ectopy • Need to use barrier contraception • Needs motivation to take regularly • Failure due to low compliance	• High
IUCD	• Easy to put in • One time motivation • Small thread reduces ascending infections	• Increased: HIV shedding Anemia STD/PID • Need to use barrier contraception	• High
CONDOM	• Reduces risk of HIV and STD transmission	• Best used with another method	• Moderate
TUBAL LIGATION	• Permanent	• Need to use barrier contraception	• High

ROUTINE GYNECOLOGICAL CARE OF HIV INFECTED WOMEN

1. Perform a pelvic examination and PAP smear every 6 months with careful vulval, vaginal and anal inspection.
2. Refer for colposcopic evaluation women with any atypia, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGCUS), low grade and high grade squamous intraepithelial lesion (SIL)/ cervical intra-epithelial neoplasia (CIN) or persistent inflammation (that is unresolved after treatment for gonococcus or chlamydia) on any Pap smear.
3. Assess and treat vaginal discharge, genital warts, STDs (the treatment of STD's will be covered in more detail in Module 8 ,"HIV and STD's).
4. Counsel on STDs, cervical cancer, human papilloma virus (HPV), contraception, pregnancy and safer sex.

Among the gynecological conditions four are more frequent, more severe and less responsive to treatment.

	Treatment
Genital warts	5 % Imodium solution / Cryotherapy - liquid nitrogen
Vaginal candidiasis	Topical clotrimazole/ miconazole /Nystatin for 10 days Or T. Fluconazole 150 mg weekly/monthly for recurrence of infection (6 doses)
Pelvic inflammatory disease (PID)	Mild infections: Doxycycline 100 mg bd for 1 week ***or*** Tab. Metronidazole 400 mg bd for 5 days ***with*** T. Ofloxacin 400 mg bd for 7 days Acute and severe PID: Admission and parenteral therapy with (Crystalline Penicillin /Gentamycin/Metronidazole)
Cervical intra-epithelial neoplasia (CIN)	Low grade - Electrosurgical excision/ Conisation Recurrent / High grade - Hysterectomy

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2. Pitkin R.M. and Scott J.R. (eds) (2001) HIV and pregnancy. In *Clinical Obstetrics and Gynecology* 44: 1-422.

3. CDC (2001) Revised recommendations for HIV screening of pregnant women. Preinatal counselling and guidelines consultation. *MMWR* 50 (RR19): 59-86.

4. Public Health Service Task Force (2002) Recommendations for use of anti-retroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. http://hivatis.org

5. De Cock K.M., Fowler M.G., Mercier E et al. (2000) Prevention of mother to child HIV transmission in resource-poor countries. Translating research into policy and practice. *JAMA* 283: 1175-1182.

Translating research into policy and practice. JAMA
2000, 283:9 1175-1182.

Informed consent:

Obtaining consent is the basic minimum requirement for HIV testing. Exceptions to this rule are outlined in Chapter 4. In minors, testing should proceed only with the informed consent of a responsible parent or guardian. **Informed consent cannot be implied or presumed**. Obtaining informed consent involves educating, disclosing advantages and disadvantages of testing for HIV, listening, answering questions and seeking permission to proceed through each step of counselling and testing.

The basic steps involved in obtained informed consent **are listed below:**

1. Ensure the competence of the individual to understand relevant information and appreciate consequences.
2. Explain the reasons for HIV testing in that particular instance. E.g.: For prevention of mother to child transmission, clinical indications of HIV related disease, hospital policy for selected surgical procedures.
3. Assess the individual's understanding of the routes of HIV transmission. If needed, educate the patient in this regard. Enquire about the individual's assessment of their risk of being positive for HIV infection and reasons for believing so.
4. Explain the components of HIV testing. E.g.: that a blood test would be done and the details of obtaining the result.
5. Explain that a positive result (or refusal for testing) will not result in refusal of care. Explain that the result would be kept confidential.
6. Ensure that the individual understands the above information.

7. Assess whether the individual has any concerns or questions regarding the above. If the individual does not express any concerns and consent to the test, proceed with the test.

In busy clinics like ours, information about HIV/AIDS and the test can be provided by the use of pamphlets, brochures, information sheets or audio-visual aids. This should be supplemented by one to one communication between the patient and care provider in all instances to ensure opportunities for clarifications and expression of concerns. (Information sheet is given as in Appendix)

The decision of whether to obtain informed consent for HIV testing in writing is left to the individual department /unit. It is good clinical practice to document that consent was obtained for testing after providing relevant information, irrespective of whether the patient signs or not. Observing the spirit of informed consent is more important than merely obtaining the patient's signature.

Informed consent is different from pre-test counselling. The former is essential in all instances when HIV testing is done in the clinical context. Results of sero-surveillance in the institution and surveys of opinions of individuals tested suggest that the majority of patients are not at risk for HIV and readily consent to testing, provided the reasons of testing are explained and confidentiality and the non-discriminatory policies of the institution are emphasised. Not all patients require or want detailed pre-test counselling, provided they understand the details and implications of the test and correctly assess their risk of being positive. It is recommended that all patients detected to be HIV positive are offered post-test counselling and a personalised management plan, either by a senior clinician or by staff at the infectious diseases clinic.

6.12.5 Strategies of HIV testing in India

Because of the enormous risk involved in transmission of HIV through blood, safety of blood and blood products is of paramount importance. Since the PPV is low in populations with low HIV prevalence, WHO/GOI have evolved strategies to detect HIV infection in different population groups and to fulfil different objectives (Annexure 6.1). The various strategies, so designated, involve the use of categories of tests in various permutations and combinations.

1. ELISA/Simple/Rapid tests (E/R/S) used in strategy I, II & III
2. Supplemental test like Western Blot and Line Immunoassay are used in problem cases e.g. in cases of indeterminate/discordant result of E/R/S.

Strategy I: Serum is subjected once to E/R/S for HIV. If negative, the serum is to be considered free of HIV and if positive, the sample is taken as HIV infected for all practical purposes. This strategy is used for ensuring donation safety (blood/blood products, organ, tissues, sperms etc.). The unit of blood testing reactive (positive) is discarded. Donor is not informed.

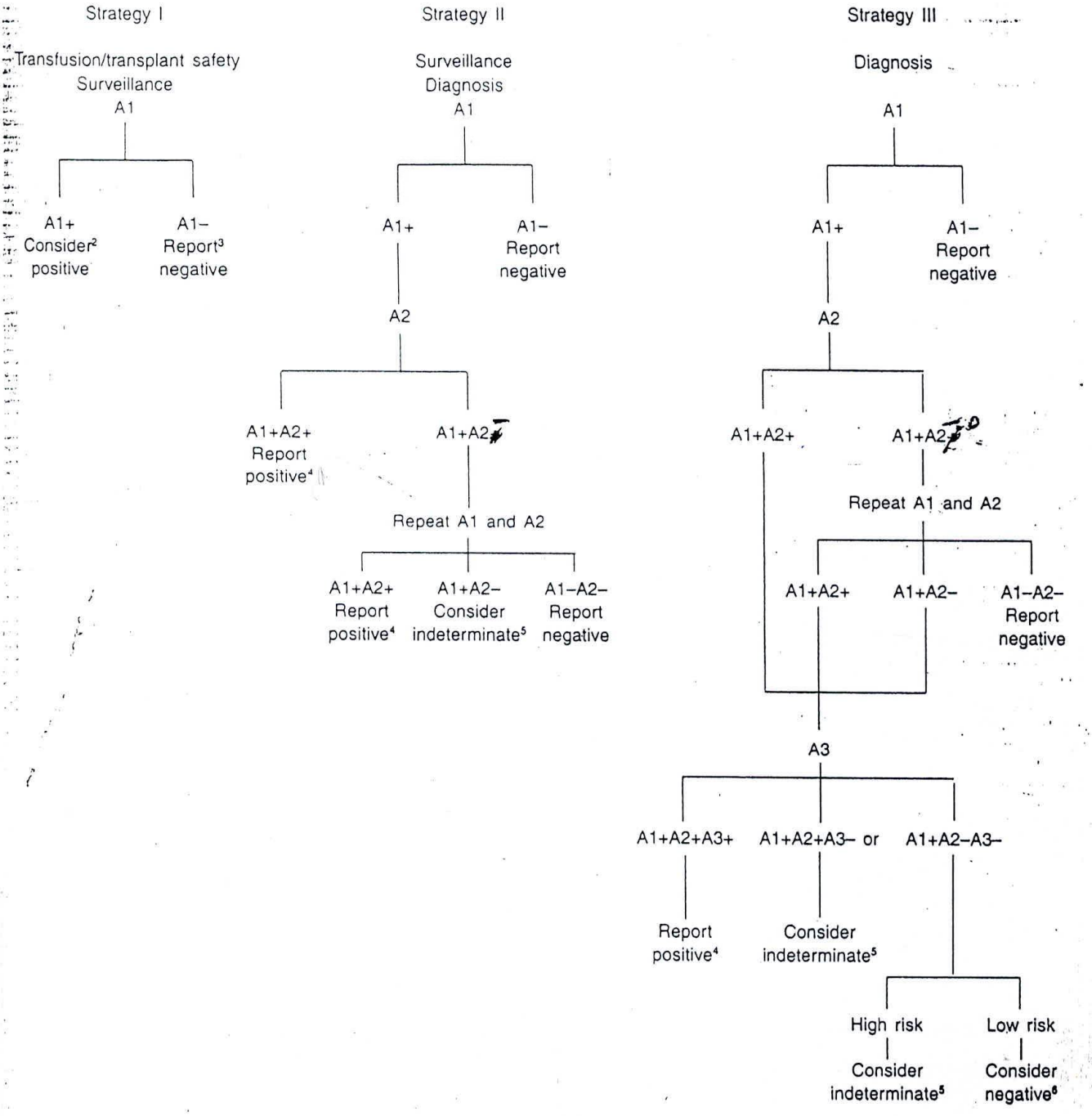
Strategy II: A serum sample is considered negative for HIV if the first ELISA report is so, but if reactive, it is subjected to a second ELISA which utilizes a system different from the first one. It is reported reactive only if the second ELISA confirms the report of the first. This strategy is used for surveillance and for diagnosis only if some AIDS indicator disease is present.

Strategy III: It is similar to strategy II, with the added confirmation of a third reactive ELISA test being required for a sample to be reported HIV positive. The test to be utilized for the first ELISA is one with the highest sensitivity and for the second and third ELISAs, tests with the highest specificity are to be used.

Strategy II & III are to be used for diagnosis of HIV infection. ELISA 2 and ELISA 3 ought to be tests with the highest PPV possible to eliminate any chances of false positive results. Strategy III is used to diagnose HIV infection in asymptomatic individuals indulging in high risk behaviour.

Chapter 6 - Annexure 1

Schematic representation of the UNAIDS and WHO HIV testing strategies



[1]Assay A1, A2, A3 represent 3 different Assays

[2]Such a result is not adequate for diagnostic purposes: use strategies II or III. Whatever the final diagnosis, donations which were initially reactive should not be used for transfusions or transplants.

[3]Report: Result may be reported.

[4]For newly diagnosed individuals, a positve result should be confirmed on a second sample.

[5]Testing should be repeated on a second sample taken after 14 days.

[6]Result is considered negative in the absence of any risk of HIV infection.

Dr Daniel Kalkstein 0301

HIV Physician Training Course 2002,
Christian Medical College, Vellore

DISTANCE LEARNING COURSE

HIV
AND
CHILDREN

Authors : Verghese VP and Cherian Thomas

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This course is supported by the European Commission through grant number IND/B76211/1B/1999/0379 provided to the HIV/STI Prevention and Care Research Programme of the Population Council India.

MODULE 3

INSTRUCTION SHEET- HIV AND CHILDREN (MODULE 3)

1. In addition to this module you will find:
    a. X-rays 3A-C (in 3 covers required for Activity 3.9).
    b. Envelope addressed to Course Coordinator, HIV Physician Training Program, CMCH, Vellore-632004 which has stamps required for registered post.

2. After you complete the module tear (a) Tutor marked assignment (page 35); (b) the module evaluation form (at the end of the module) and enclose it in this envelope. Send it by registered post to CMCH by: December 28, 2002.

OVERVIEW

This module we hope will enable you improve your skills in the clinical management of children of mothers with HIV infection and children having HIV infection. The module aims to enable you to develop your clinical services in relation to these two topics.

In India about 1-2% of pregnant mothers are infected by HIV infection and the rate of perinatal transmission is between 25-35%. Ninety per cent of pediatric infection occurs through mother-to-child transmission. **Paediatric infection may almost entirely be prevented by anti-retroviral therapy during pregnancy and in the perinatal period, elective caesarian section, and avoidance of breastfeeding by the mother.**

The newborn infant of an HIV-positive mother should receive 6 weeks of zidovudine, cotrimoxazole from 6 to 8 weeks of life (PCP prophylaxis) and routine immunizations. Serological testing can confirm the diagnosis of HIV infection only after 18 months of age.

The signs and symptoms in HIV infection in children are non-specific and the **commonest presentations are failure to thrive, tuberculosis, persistent orophryngeal candidiasis and recurrent bacterial infections.** Since the disease progresses faster in children, the affected child may often be the index case in the family. **Maintenance of nutritional status, immunization, treatment of recurrent bacterial infections and PCP prophylaxis are the keys to prolonging life in children.** Most of the opportunistic infections can be diagnosed using clinical criteria and treated with commonly available drugs. **Antiretroviral therapy is recommended for all children with advanced HIV infection and for those with significant immunosuppression** especially those who have access and can pay for the drugs.

OBJECTIVES

After completion of this module you should be able to manage:

1. an infant born of an HIV positive mother

(a) recommendations for breast feeding

(b) opportunistic infection prophylaxis

(c) testing protocol.

2. a child with suspected HIV infection:

Specifically you will learn about

(a) when to suspect HIV infection

(b) how to diagnose HIV infection

(c) how to counsel parents

(d) advice regarding immunization, OI prophylaxis and nutrition

(e) diagnosis and treatment of common opportunistic infections

(f) when to consider initiation of anti-viral therapy

CONTENTS

Let us start with an activity to help you to choose the appropriate anti-viral prophylaxis for a child born of a HIV positive mother. Turn to the reading, ***"Post-exposure prophylaxis for babies born of HIV positive mothers" (page 37)****. Once you have finished reading this you should be able to undertake the following activity.*

ACTIVITY 3.1

POST-EXPOSURE PROPHYLAXIS FOR NEWBORN

(10 min)

23 year old Meena is a known patient with HIV infection who delivered a 2.8 Kg baby boy at home. Meena had not received any anti-viral therapy during her pregnancy or delivery. She has come to the hospital to take your advice regarding care of the child.

1. What anti-viral treatment would you advice for the child?

Drug- Zidovudine (Don't know the efficacy after 48 hrs of delivery — NOT any more post-exposure prophylaxis)

Dose- 2 mg/kg OD or 4 mg/kg bd × 6 wks. To be started within 48 hrs of delivery

Duration-

FEEDBACK 3.1

2. What anti-viral treatment would you advice for the child?

Drug- Zidovudine

Dose- at 2 mg/kg Q6H or 4 mg/kg bd to be started within 48 hours of birth.

Duration- 4-6 weeks

The aim of this activity is to help you develop recommendations for breastfeeding of the newborn child of a HIV positive mother. To do the next exercise, you will need to ***read "WHO/UNICEF/UNAIDS Statement on breast feeding" in reader*** *at the end of this module . Once you have finished reading this you can undertake the next activity.*

ACTIVITY 3.2

BREAST FEEDING OF CHILD OF HIV POSTITIVE MOTHER (15 min)

Refer back to Meena's case in Activity 3.1.

1. Circle below whether you would advise Meena to breast feed or not.

YES / NO

2. What is your reason for providing this line of advice?

The fact that She delivered at home and did not have ART shows she is from poor and marginalized situation. Hence breastfeeding for the nutrition and survival of the child becomes an issue.

3. If your advice is for her to breast feed, what specific instructions would you give Meena?

Breast feeding: Exclusive

Top-up feeds: Nil.

Duration of breast feeding: 3 - 4 months

Weaning: Stoppage of breast feeding with weaning on semi solid adult food

4. If you were to advise her not to breast feed, what specific instructions would you give her?

Type of replacement feeding:
. Cows milk, full strength (? with mild ~~mon~~ woks) with ~~ac~~ hygienic precautions.

Bottle / Paladai: — either method — Paladai preferred.

FEEDBACK 3.2

1. Whether you would advise Meena to breast feed or not.

You would advise <u>not</u> to breast feed.

2. What is your reason for providing this line of advice?

AZT prophylaxis is being used to reduce mother to child transmission. Breast feeding would reduce the benefit of AZT prophylaxis. Therefore breast feeding may be withheld.

3. If your advice is for her to breast feed what specific instructions would you give Meena?

Breast feeding: Exclusive breast feeding

Top-up feeds: No water or milk substitutes

Duration of breast feeding: 4-5 months

Weaning: Abrupt weaning

4. If you were to advise her not to breast feed what specific instructions would you give her?

Type of replacement feeding: Cows milk is a cheaper option than formula feeds.

Bottle / Paladai: Palladai to be preferred to bottle as there is reduced chance of gastroenteritis.

The next activity will help you learn about OI prophylaxis and immunisation for the new born. To do the next exercise you will need to ***read the sections "Pneumocystis carinii prophylaxis in Newborn" (page 37) and "Immunisation for newborn baby of HIV positive mother" (page 38)*** *in the reader at the back of this module. Once you have finished reading this information you can undertake the next activity.*

ACTIVITY 3.3

OI PROPHYLAXIS AND IMMUNISATION OF NEWBORN (20 min)

1. What OI prophylaxis would you give to Meena's baby?

Drug: Trimethoprim - Sulphamethoxazole

Dose: 10 mg/kg/day (of Trimethoprim) in two divided doses daily on ~~alternate~~ 3 days a wk. (alt. days)

Duration: 1 year. starting 6-8 wks.

Infection to be prevented: Pneumocystis Carinii.

2. Indicate with a tick mark which of the following vaccinations you would give the baby:

- ✓ DPT
- ✓ OPV
- ✓ Hepatitis B
- ✓ Haemophilus influenzae type B vaccines
- ✓ BCG vaccination
- ✗ Measles (only at 6-9 months)

FEEDBACK 3.3

1. What OI prophylaxis would you give to Meena's baby?

Drug: Bactrim (trimethoprim-sulfamethoxazole)

Dose: TMP 10 mg/Kg/day, 3 days a week

Duration: From 6-8 weeks to 1 year

Infection to be prevented: P. carini

2. Indicate below which of the vaccinations you would you give the baby?

DPT √

OPV√

Hepatitis B√

Haemophilus influenzae *type b vaccines* √

BCG vaccination√

Measles √ (at 6 and 9months)

The next activity will help you learn about the lab diagnosis of HIV infection in a baby born of a HIV positive mother. To do the next exercise, you will need to ***read the section "Laboratory confirmation of HIV infection" (page 39)*** *in the reader at the end of this module. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 3.4

HIV TESTING IN NEWBORN (15 min)

1. What test would you order and when, to diagnose HIV infection?

18 months age WHO regimen or ELISA & Rapid

2. What advanced test can be used for an earlier diagnosis of HIV infection?

HIV - PCR or HIV culture. done twice.

3. How can you exclude HIV infection earlier than 18 months?

After 4 months if two rapid tests are negative in a non-breast feeding baby

FEEDBACK 3.4

1. What test would you order and when to diagnose HIV infection?

ELISA test at 18 months of age

2. What advanced test can be used for an earlier diagnosis of HIV infection?

PCR test for HIV infection which is positive on 2 separate occasions, the second after 4 months of age.

3. How can you exclude HIV infection earlier than 18 months?

If 2 ELISA's after 6 months are negative at 1month interval of each other then the diagnosis of HIV infection can reasonably be excluded.

The next activity aims to teach you about initial evaluation of child suspected HIV infection. To do the next exercise, you will need to ***read the sections "Natural History of HIV infection in children" (page 40), "1994 Revised HIV Pediatric Classification System:***

clinical categories" (page 40) and "Clinical and Lab Findings: Suspect HIV Infection" (page 41) in reader at the end of this module. Once you have finished reading these, you can undertake the next activity.

ACTIVITY 3.5

INITIAL EVALUATION OF CHILD (15 min)

5 year old Nesan was brought by his parents with complaints of failure to thrive for the last one year, poor appetite, itchy skin lesions and recurrent respiratory infections.

On examination:

Pallor, oral thrush generalised lymphadenopathy, bilateral parotid enlargement, papular urticaria, hepatosplenomegaly.

Laboratory tests:

Haemoglobin 9 g/dl, Total WBC count 4200 Lymphocytes 25 Neutrophils 70 Eosinophils 3 Basophils 2. Platelet count 20,000/cmm. Total protein 6.5 g/dl. Albumin 3 g/dl.

1. What clinical and laboratory features point to the presence of HIV infection in this boy?

Clinical:

Laboratory:
- Lymphopenia
- Thrombocytopenia
- Hyperglobulinemia
- Anaemia

2.Nesan's Tridot test and ELISA test were positive. Which type of natural history do you think Nesan's illness follows?

Intermediate

3.Which clinical stage of the 1994 Revised HIV Pediatric Classification System do you think he fits into?

B

FEEDBACK 3.5

1.What clinical and laboratory features point to the presence of HIV infection?

Clinical:

failure to thrive

itchy skin lesions-papular urticaria

recurrent respiratory infections.

Pallor-anaemia

Oral thrush

generalised lymphadenopathy

bilateral parotid enlargement

hepatosplenomegaly

Laboratory:

Lymphopenia

Thrombocytopenia

Hypergammaglobulinemia

2.Nesan's Tridot test and ELISA test were positive. Which type of natural history do you think Nesan's illness follows?

Intermediate progression

3.Which clinical stage of the 1994 Revised HIV Pediatric Classification System do you think he fits into?

Category B

The next activity will help you learn about counselling the parents, laboratory testing and treatment of a child with suspected HIV infection. To do the next exercise, you will need to ***read the section "Counselling the family of an HIV positive child" (page 30) in reader*** *at the end of this module. Once you have finished reading this you can undertake the next activity.*

ACTIVITY 3.6

COUNSELLING OF FAMILY

1. How would you counsel the parents of Nesan in the listed areas listed below?

1. Reassurance:
Many things can be done for Nesan to make him healthier — PCP prophylaxis, TB prophylaxis and ~~ART~~.

2. Explaining diagnosis and prognosis:
- Reached B category
- Intermediate progressor

3. Screening of parents/siblings:
Important to screen both, as ~~they~~ parents may and some siblings may be infected. In order to plan for future it is necessary to know.

4. Tests, treatment and followup:
- CD4 count — 6 monthly & follow up
- Prophylaxis, Rx of opportunistic infections and ? HAART

5. Nutrition:
- High calorie, high protein (10 cal/kg, 2gms/kg)
- Micro nutrients - Vit A, Iron, Zinc + Antioxidants?

6. Schooling:
Normal schooling and recreational activity

7. Recreation:

FEEDBACK 3.6

1. How would you counsel the parents of Nesan?

1. Reassurance: regarding diagnosis that it is HIV disease not AIDS; treatment available; disease will not spread to other children
2. Explaining diagnosis and prognosis: Survival up to 8 years; can be improved with treatment
3. Screening of parents/siblings: both parents have to be screened; if parents are positive the other children need to be screened.
4. Tests, treatment and followup: should come for regular followup and treatment; importance of OI treatment and prevention will be stressed.
5. Nutrition: Discussion on good nutrition vitamins and micronutrient replacement in improving immune function.
6. Schooling: Should go to school; need not inform the teacher
7. Recreation: can play all games within physical capacity

The aim of the next activity is to teach you about laboratory testing and treatment of a child with suspected HIV infection. To do the next exercise, you will need to ***re-read the section "Lab Evaluation of the HIV positive child"(page 39) and "Opportunistic infection prophylaxis" (47) in reader*** *at the end of this module. Once you have finished reading these sections you can undertake the next activity.*

ACTIVITY 3.7

LAB EVALUATION OF CHILD OPPORTUNISTIC INFECTION PROPHYLAXIS

1.What further tests would you order for Nesan?

CD4, PPD & chest xray,

2. Nesan's PPD is 6 mm at 48 hours and chest x-ray is normal. He cannot afford to have a CD4 count and viral load test done.
What treatment would you initiate for Nesan?

TB prophylaxis ~ Rifam 10mg/kg OD + INH 10mg/kg

3. What OI prophylaxis would you start?

PCP ~ TMP-Sulf. 10mg/kg OD

FEEDBACK 3.7

1.What further tests would you order for Nesan?

PPD and Chest X-ray

2. Nesan's PPD is 6 mm at 48 hours and chest x-ray is normal. He cannot afford to have a CD4 count and viral load test done.

What treatment would you initiate for Nesan?

Papular urticaria- Liquid paraffin and anti-histamines

Oral candidiasis- Topical clotrimazole or Syr. Fluconazole

3.What OI prophylaxis would you start?

PCP- Bactrim TMP 10 mg/Kg/day in 2 doses for 3 consecutive days/week

TB - Rifampicin 10 mg/Kg/day and INAH 5 mg/Kg/day for 6 months

The next activity will help you to learn about nutritional therapy for a child with HIV infection. To do the next exercise, you will need to ***read the sections "Nutrition of a HIV positive child" (page 44)*** *in the reader at the end of this module. Once you have finished reading these sections you can undertake the next activity.*

ACTIVITY 3.8

NUTRITION FOR HIV POSITIVE CHILD

What nutritional advice would you suggest?

- high calori (100-200 kl/kg/Day) + High Protein 2-3 gm/kg/day
- Milk according to digestibilities and if not lactose allergy (infants)
- Micronutrients & oxidants
- Supported feeding if odynia

FEEDBACK 3.8

What nutritional advice would you suggest?

Nutritional monitoring

Dietary advice -Calories 150-200 Kcal/Kg/day

Protein 2-3 g/Kg/day

Vitamins and micronutrient - Vitamin A, zinc and iron supplementation

Lactose free diet for chronic diarrhea and secondary lactose intolerance.

Nasogastric feeding in a case of severe malnutrition.

The next activity aims to teach you about the clinical diagnosis of common opportunistic infections. To do the next exercise, you will need to ***read the sections "Respiratory Problems" (page 45) in reader*** *at the end of this module. Once you have finished reading these sections you can undertake the next activity.*

ACTIVITY 3.9

RESPIRATORY PROBLEMS - RECOGNITION

1.Read the case scenarios in the second column. Match the case scenarios to the X-ray provided.

	Case History	Study the following x-rays	X-ray image finding	
A	7 year old Vani is brought with a history of failure to thrive for the past 1 year, persistent cough for the past 3 months and gradually increasing dyspnoea for the past 15 days. On examination, she is emaciated, weighing 14 kg and her respiratory rate is 60/minute with no other findings on auscultation. Her oxygen saturation by pulse oximetry is 80% and her serum LDH is > 1000 U/l. Her chest Xray is given alongside. Diagnosis: PC Pneumonia	X-ray 3A (X-ray in cover at end of the module)	. Diffuse infiltrate, No shift of trachea etc	

B	4 year old Radhika comes with a history of persistent fever for a month and cough for the past 10 days. On examination, she has a respiratory rate of 40/min, diminished air entry, dullness on percussion and fine crepitations over the left lung base. Diagnosis: Pulm. T.B	X-ray 3B (X-ray in cover at the end of the module)	(B) Cervical Nodes (C) ↓ in lower lobe consolidation. ? Cavitation (U) lobe.	
C	5 year old Gunasekaran has come with a history of high-grade fever for the past 3 days with cough and breathlessness. On examination he has a respiratory rate of 60/min, and fine crepitations heard over both infrascapular regions. His total WBC count is 20,000/cu.mm. Diagnosis: Bacterial pneumonia	X-ray 3C (X-ray in cover at the end of the module)	(C) ↓ lobe consolidation.	

FEEDBACK 3.9

			Chest X-ray image finding	Diagnosis
Case A	Case history	X-ray 3A	Diffuse infiltrates seen in both lung fields extending to the peripheries.	PCP
Case B	Case history		Bilateral upper mediastinal adenopathy, infiltrates in the left midzone and opacification of the left lower zone with obliteration of the costophrenic angle.	Pulmonary tuberculosis with hilar lymphadenopathy and left lower lobar consolidation with pleural effusion.
Case C	Case history		Right upper lobe consolidation	Bacterial pneumonia probably pneumococcal

ACTIVITY 3.10

TREATMENT OF RESPIRATORY PROBLEMS

Write down the appropriate treatment against each diagnosis.

Condition	Treatment
Bacterial pneumonia	1. Penicillin Crystalline Q6H 2. Amp
Pulmonary TB	• INAH, RIF, Ethambutol, Pyrazinamide for 2 months • INAH RIF x 4 month in those responders for 7 months
Pneumocystis carinii pneumonia	• Co-trimoxazole 15-20mg (TMP) per kg/Day in 4 doses for 3 wks • T. Prednisolone 2mg/kg/kg in 3 doses tapered off in 3 wks

FEEDBACK 3.10

Write down the appropriate treatment against each diagnosis.

Condition	Treatment
Bacterial pneumonia	Conventional antibiotics
Pulmonary TB	INAH/Rifampicin/Pyrazinamide/Ethambutol 2 months, Isoniazid /Rifampicin 4 months, extended upto 7 months in slow responders
Pneumocystis carinii pneumonia	Trimethoprim-sulfamethoxazole (15 - 20 mg/kg per day TMP) in four divided doses for 2 to 3 weeks, T. prednisolone 2 mg/kg/day for 2 weeks tapered and stopped by 3rdweek

The next activity is aimed at teaching you about indications for anti-viral treatment. To do the next exercise you will need to ***read the sections "Anti-viral treatment" (pages46-48) in the reader*** *at the end of this module. Once you have finished reading this, you can undertake the next activity.*

ACTIVITY 3.11

INDICATIONS FOR ANTI-VIRAL TREATMENT

Put a tick mark against the following situations do you think that anti-viral treatment is indicated?

	Case Scenario	Yes /No
1	One year old Arun has tested HIV Elisa-positive twice after the age of 6 months. His parents cannot afford CD4 testing, and virologic testing is not available. Arun has a history of 3 to 4 upper respiratory infections in the past 1 year. On examination, his weight is 9 kg, and he has no lymphadenopathy, oral candidiasis or hepatosplenomegaly. Systemic examination is normal.	No
2	4 year old Ravi has been brought to you with a history of recurrent skin infections and otitis media, and one episode of pneumonia documented on chest Xray 6 months earlier. On examination, he has cervical and axillary adenopathy, enlarged parotids, and a liver palpable 3 cm below the right costal margin. Investigations reveal the following: positive HIV ELISA and Western Blot, CD4 count of 400 cells/cu.mm.	Yes
3	8 year old child is well and has been remarkably aymptomatic. CD 4 count 550/mm3	No
4	3 year old Arun has been brought with a history of regression of milestones over the past 6 months he has lost the ability to run and says only "amma" and "appa" whereas previously he had a large vocabulary. On examination, he has a broad-based ataxic gait and exaggerated deep tendon reflexes in the lower limbs. He was found to HIV ELISA reactive and his CT scan shows bilateral basal ganglia calcifications.	?

? Opportunistic infection ? Cerebral TB / C

FEEDBACK 3.11

Put a tick mark against the following situations for which in your opinion anti-viral treatment is indicated?

	Yes/No
1	No
2	Yes
3	No
4	Yes

For more detailed discussion of neurological manifestations of HIV infection see Verghese VP et al (reference 3).

NOTES

NOTES

READINGS

POST-EXPOSURE PROPHYLAXIS FOR BABIES BORN OF HIV POSITIVE MOTHERS

All newborn babies born of HIV positive mothers should receive ART prophylaxis according to MTCT protocol

(a) *Infants whose mothers have received AZT during pregnancy and labour* should receive Zidovudine (at 2 mg/kg Q6H or 4 mg/kg bd) within 48 hours of delivery for a duration of 4-6 weeks

(b)*Infants whose mothers have received single dose Nevirapine during labour* may receive Nevirapine (2 mg/Kg stat dose) within 72 hours of delivery

or Zidovudine (at 2 mg/kg Q6H or 4 mg/kg bd) within 48 hours of delivery for a duration of 4-6 weeks

© *Infants whose mothers have not received any ART during pregnancy or delivery* should receive Zidovudine (at 2 mg/kg Q6H or 4 mg/kg bd) within 48 hours of delivery for a duration of 4-6 weeks.

PNEUMOCYSTIS CARINII PROPHYLAXIS IN NEWBORN

At 6 to 8 weeks of age prophylaxis for *Pneumocystis carinii* pneumonia (PCP), usually with trimethoprim-sulfamethoxazole (at 10mg/kg/day of Trimethoprim in 2 divided doses daily, 3 days a week) should be started and given until the age of 1 year. Trimethoprim-sulfamethoxazole is avoided in the first few weeks of life as it can cause neutropenia.

IMMUNISATION FOR THE BABY OF A MOTHER WHO IS HIV POSITIVE

- All routine vaccinations as recommended by the WHO need to be given to the baby of a mother who is HIV positive

  DPT

  OPV

  Hepatitis B

  Haemophilus influenzae *type b vaccines*

  BCG vaccination

  (It is usually given in the first 2 months of life. Older children with symptomatic HIV disease should not receive BCG vaccination because of the risk of disseminated tuberculosis.)

- Measles vaccination

  First dose- 6 months of age

  Second dose - 9 months of age

  (measles antibody response to vaccination is lower in HIV-infected children)

- Varicella vaccination may be given to asymptomatic children after 12 to 15 months of age if the family can afford it.
- Pneumococcal vaccine may be given to children older than 2 years of age.

LABORATORY CONFIRMATION OF HIV INFECTION

Child >18 months of age: A positive ELISA or Western blot test is indicative of HIV infection

Child < 18 months of age:

1. A positive ELISA test cannot be used to make a diagnosis of HIV infection in these children.
(Exposed infants and children younger than 18 months of age maintain HIV seropositivity due to the persistence of transmitted maternal antibodies)

2. Two or more negative antibody tests (ELISA or Western Blot) can reasonably exclude HIV infection in non-breastfed infants with no evidence of clinical infection.

- Tests performed beyond 6 months of age
- Interval of 1 month between assays

3. Definitive diagnosis can be made in case of perinatal transmission if two HIV PCR assays drawn at separate times are positive. This can be performed as early as the first 48 hours of life using HIV DNA PCR or HIV culture, both of which are very sensitive and specific in determining HIV infection.
4. Negative PCR assays after 4 months of age can exclude HIV infection in the absence of breastfeeding.

NATURAL HISTORY OF HIV INFECTION IN CHILDREN

	Proportion (%)
Rapid progression (AIDS in 2 years)	20
Intermediate progression (AIDS in 7-8 years)	60-75
Slow progression (AIDS>8 years)	5-10

median survival time of perinatally HIV-infected children- 8 to 9 years

(not on antiretroviral therapy)

1994 REVISED HIV PEDIATRIC CLASSIFICATION SYSTEM: CLINICAL CATEGORIES

Category A	Category B	Category C
Mildly Symptomatic	Moderately symptomatic	Severely symptomatic
Lymphadenopathy Hepatomegaly Dermatitis Parotitis Recurrent/ persistent URI, sinusitis or otitis media.	Recurrent or chronic Diarrhea Failure to thrive Persistent oropharyngeal candidiasis Anaemia, neutropenia thrombocytopenia Bacterial meningitis Pneumonia Sepsis Cardiomyopathy Hepatitis Recurrent herpes stomatitis Multi-dermatomal herpes zoster Complicated chickenpox Lymphoid interstitial pneumonia (LIP) Persistent fever (> 1 month)	Serious bacterial infections Esophageal candidiasis Cryptococcal meningitis Diarrhea > 1 month Encephalopathy Persistent HSV ulcer (> 1 month) Tuberculosis, disseminated or extrapulmonary *Pneumocystis carinii* pneumonia Salmonella (nontyphoid) septicemia, recurrent Cerebral Toxoplasmosis

Category N: Not Symptomatic

In situations where CD4 testing is not available or affordable, the presence of a Category B or Category C illness may be taken as an indirect indicator of the presence of moderate or severe immunosuppression, for purposes of monitoring disease progression and deciding when to start PCP prophylaxis in children older than 18 months of age (unpublished data).

CLINICAL AND LAB FINDINGS: SUSPECT HIV INFECTION

Clinical suspicion of HIV infection

The following clinical manifestations and laboratory findings should lead to the suspicion of HIV infection in children, especially when present in combination and where other causes cannot be found. It must be emphasized that many of these manifestations may also be seen in children in developing countries due to other infections or illnesses in the absence of HIV infection.

History of

- Failure to thrive
- Recurrent bacterial infections (pyoderma, sinusitis, otitis media, pneumonia, meningitis)
- Recurrent or chronic diarrhea
- Recurrent or persistent oral candidiasis
- Developmental delay or loss of milestones
- Progressive respiratory distress during the first 6 months (PCP)
- Recurrent vaginal candidiasis (older girls)
- Bruising or epistaxis
- Recurrent varicella or herpes zoster
- Mycobacterial infections

Examination Findings

- Generalized lymphadenopathy
- Unexplained hepatomegaly, splenomegaly or both
- Chronic or recurrent enlargement of parotid glands
- Oral thrush
- Papular urticaria (HIV dermatitis)
- Hyperreflexia, spasticity, rigidity, increased muscle tone
- *Candida* dermatitis
- Bruising or petechiae
- Unexplained digital clubbing
- Chronic lung disease or lymphoid interstitial pneumonitis (LIP)
- Unexplained congestive heart failure
- Renal failure or nephrotic syndrome

Laboratory Findings

- Unexplained anemia, neutropenia or thrombocytopenia
- Hypergammaglobulinemia (frequent)
- Hypogammaglobulinemia (in advanced disease)

- Failure to form antibodies following vaccination
- Increased liver transaminases
- Increased amylase (due to parotitis)
- Increased lactic dehydrogenase levels (in LIP and PCP)
- Persistently abnormal chest X ray

COUNSELLING THE FAMILY OF AN HIV POSITIVE CHILD

Child

Preschool

Encourage the child to ask about the tests and procedures and attempt to allay fears about the same. Use simple diagrams to explain issues like injections, and health consequences and steps that have to be taken.

School age

Plan information commensurate to the developmental level.

Adolescents

Try to establish a sense of trust with a view towards therapy and its compliance.

At all ages encourage recreational activities that health permits.

Regular follow up with developmental and neurological assessments.

Continue school.

Family

Parents

Understand the despair and anxiety and allow them to speak about their concerns.

Educate them regarding injections and treatments to help them to move towards acceptance and realistic expectations.

Tackle parental guilt and help them to understand that it was not their intent to cause harm to the child.

If depressed or in suicidal risk treat depression and seek psychiatric help.

Assess stresses on other members of the family like the grand parents.

Check both the parents for HIV status if it is unknown.

Siblings

Assess fears in the siblings.

Encourage older children to help in the care of the affected child.

Check the siblings for HIV infection.

LAB EVALUATION OF THE HIV POSITIVE CHILD

Mantoux testing and a radiograph of the chest are essential in the initial evaluation of the HIV-infected child. Annual TB testing with PPD and chest roentgenogram is recommended for both HIV-infected and non-infected siblings. A PPD reaction of 5 mm or greater should be considered positive in HIV-infected children. A positive PPD with a normal chest X-ray indicates infection with TB but not disease. A positive PPD is an indication for initiating TB prophylaxis with Rifampicin 10 mg/Kg/day and Isoniazid 5 mg/Kg/day for 6 months.

Other investigations may be done as clinically indicated.

NUTRITION OF THE HIV POSITIVE CHILD

Nutritional support in the HIV-positive child include:

- Monitoring weight and height at each visit to identify growth failure
- Diet providing 150 –200 Kcalories/kg/day, and 2-3 gm protein/kg /day
- Caloric density may be increased by the addition of fats such as coconut oil that are easily digested
- Lactose-free formula in the infant with lactose intolerance secondary to chronic diarrhoea.
- Predigested milk formula (Pregestemil) in the infant with chronic diarrhoea and no lactose intolerance
- Micronutrient supplementation with Vitamin A, iron and zinc
- Antioxidants such as Vitamin E, selenium, glutathione and beta-carotene .
- Nasogastric tube feeding may be used in the child with odynophagia or anorexia
- Appetite stimulants such as cyproheptadine may be tried
- Gastrostomy feeds/total partenteral nutrition may be tried in specialized centers for children who do not respond to all other interventions.

RESPIRATORY PROBLEMS		
INFECTION	CLINICAL CRITERIA	TREATMENT
Pneumocystis carinii	Persistent cough/dyspnoea minimal findings Diffuse bilateral interstitial infiltrates (CXR) Hypoxemia (pulse oximetry) Serum LDH level > 2 to 3 times normal Response to co-trimoxazole therapy	Trimethoprim-sulfamethoxazole (15 - 20 mg/kg per day TMP) in four daily doses for 2 to 3 weeks T. prednisolone 2 mg/kg/day for 2 weeks tapered and stopped by 3rdweek
Bacterial pneumonia	Acute onset high fever leukocytosis with shift to the left Lobar consolidation (CXR) Positive blood cultures	Conventional antibiotics
Pulmonary TB	Fever>1 month Weight loss Cough Close contact with TB Positive PPD > 5 mm AFB positive Histology of TB Radiology suggestive of TB Response to ATT	INAH/Rifampicin/Pyrazinamide/Ethambutol 2 months Isoniazid /Rifampicin 4 months Extended upto 7 months in slow responders (sputum positivity or persistence of signs or symptoms after the initial 2 months). Extrapulmonary disease: Continuation phase for 7 months (total therapy 9 months)
Lymphoid interstitial pneumonia	Bilateral reticulonodular infiltrates (CXR) Serum LDH elevated to within 2 to 3 times normal Elevated immunoglobulin levels No response to therapy with antibiotics/ATT	Bronchodilator therapy In case of hypoxia treat with steroids

INDICATIONS FOR ANTI-VIRAL TREATMENT

CRITERIA	INDICATION
CLINICAL:	Category C
LABORATORY:	Any clinical category (N,A,B,C,) with CD4 count < 15% (See page 49 for age-specific counts)

As many of the symptoms of HIV disease overlap with symptoms seen in children without HIV disease in resource-limited settings, initiation of ART in children < 18 months of age should not be considered in the absence of viral load assays and CD4 counts.

ANTI-RETROVIRAL REGIMENS

REGIMEN	NRTIs	NNRTI / PI
FIRST-LINE	ZDV + 3TC	NVP or EFZ
	ZDV + 3TC + ABC	
SECOND-LINE	d4T + ddI	IDV
	d4T + ddI	NVP/EFZ(if first 3 NRTIs)

OPPORTUNISTIC INFECTION PROPHYLAXIS

PCP prophylaxis beyond 1 year of age is also given to all children with a previous episode of PCP and those with evidence of severe immunosuppression (CD4 count < 500 between 1-5 years age or < 200 between 6-12 years age). In the absence of CD4 testing all children with a history of Clinical Category B or C illness may be considered candidates for PCP prophylaxis.

APPENDIX: ANTIRETROVIRAL DRUGS

Nucleoside analogues inhibiting HIV-1 reverse transcriptase (NRTIs):

Drug	Dosage	Major toxicity
Zidovudine (ZDV/AZT)	180 mg/M^2 bd; 4mg/kg bd in neonates	Bone marrow suppression
Didanosine (ddI)	90 - 150 mg/ M^2 bd; 50 mg/M^2 bd in neonates	Pancreatitis, hepatitis Peripheral neuropathy
Lamivudine (3TC)	4 mg/kg bd; 2 mg/kg bd in neonates	Pancreatitis, hepatitis Neutropenia
Stavudine (d4T)	1 mg/kg bd	Pancreatitis, hepatitis Peripheral neuropathy
Zalcitabine (ddC)	0.005 to 0.01 mg/kg tid	Mucocutaneous eruptions
Abacavir (ABC)	8 mg/ kg bd (in > 3 mo. age)	Life-threatening hypersensitivity

Non-nucleoside analogues inhibiting HIV-1 RT (NNRTIs)

Drug	Dosage	Major toxicity
Nevirapine (NVP)	120 mg/M^2 od x 2 wks then 200 mg/M^2 bd	Severe skin rash Hepatitis
Delavirdine (DLV)	**Dose unknown**	Mild skin rash GI symptoms
Efavirenz (EFV)*	200 -600 mg od in > 3 yrs age	Skin rash CNS symptoms

*Efavirenz pediatric dose: No data for children younger than 3 years.
By body weight, once-a-day dosing as follows:
10 to <15 kg: 200 mg, 15 to <20 kg: 250 mg
20 to <25 kg: 300 mg, 25 to <32.5 kg: 350 mg
32.5 to <40 kg: 400 mg, >/= 40 kg: 600 mg.

Inhibitors of HIV-1 protease (PIs):

Drug	Dosage	Major toxicity
Indinavir (IDV)	500 mg/M2 tid	Indirect hyperbilirubinemia; kidney stones, GI symptoms,
Ritonavir (RTV)	350 - 450 mg/M2 bd	GI symptoms, hyperlipemia Hepatitis, pancreatitis
Saquinavir (SQV)	*Dose unknown*	GI symptoms, Hyperglycemia
Nelfinavir (NFV)	55 mg/kg bd; 40 - 50 mg/kg tid < 1 yr age	GI symptoms, rash Hyperglycemia
Amprenavir (VZX 478)	20 mg/kg bd in > 4 yrs age	GI symptoms, hyperlipemia, rash, mood disorders

1994 Revised Pediatric HIV Classification System: Immunologic Categories Based on Age-Specific CD4+ Lymphocyte Count and Percentage

	Age of Child		
Immune Category	</= 12 months	1-5 years	6-12 years
	Cells/mm³ (%)	Cells/mm³ (%)	Cells/mm³ (%)
Category 1: No suppression	>/= 1,500 (>25)	>/= 1,000 (>25)	>/= 500 (>25)
Category 2: Moderate suppression	750-1,499 (15 - 24)	500- 999 (15 - 24)	200-499 (15 - 24)
Category 3: Severe suppression	< 750 (<15)	< 500 (< 15)	< 200 (< 15)

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WHO, UNICEF, UNAIDS Statement on Current Status of WHO/UNAIDS/UNICEF Policy Guidelines on breastfeeding

A recent early report of evidence that HIV is less likely to be transmitted through exclusive breastfeeding does not warrant a change in existing WHO/UNICEF/UNAIDS policy.

In the last ten years, evidence has accumulated that HIV can be transmitted through breast-milk. WHO and UNAIDS currently estimate that a child breastfeeding from a mother who is HIV positive has a 15% risk of infection by this route. Every year 200,000 infants may acquire HIV in this way. Where resources permit, many HIV-positive mothers now choose to feed their babies artificially, and to avoid breastfeeding altogether. In resource poor settings,where the risks of artificial feeding may be particularly high, the decision for both individual mothers and policy-makers is more difficult. The situation has led in some settings to a loss of support for initiatives to promote breastfeeding, and to some women avoiding breastfeeding even if they do not know their HIV status.

In 1997, UNAIDS, WHO and UNICEF issued a joint policy statement on HIV and infant feeding, which stated that - "As a general principle, in all populations, irrespective of HIV infection rates, breastfeeding should continue to be protected, promoted and supported" and - "Counselling for women who are aware of their HIV status should include the best available information on the benefits of breastfeeding, on the risk of HIV transmission through breastfeeding, and on the risks and possible advantages associated with other methods of infant feeding" and - "It is therefore important that women be empowered to make fully informed decisions about infant feeding, and that they be suitably supported in carrying them out."

In 1998, WHO, UNICEF and UNAIDS held a technical consultation on HIV and Infant Feeding, and issued guidelines with a human rights perspective, based on the joint policy statement (1). These guidelines call for a strengthening of initiatives to protect, promote and support breastfeeding among mothers who are HIV negative or of unknown HIV status, and they describe several infant feeding options for consideration by HIV-positive mothers. These include:

- replacement feeding with commercial formula or home prepared formula
- breastfeeding in the way generally recommended
- breastfeeding exclusively and stopping early
- use of heat treated expressed breast-milk
- wet-nursing,

in all cases with timely and adequate complementary feeding. There is no attempt to favour any one of these options over the others, as the principle recommendation is for mothers to receive counselling that will enable them to make a fully informed decision appropriate to their situation and resources. The responsibility of the policy-maker and health care manager is to provide the necessary support to enable mothers to make and carry out their choice, whether to breastfeed or to use replacement feeds.

The studies on which existing estimates of transmission are based do not distinguish between infants who are exclusively breastfed and those, usually the majority, who are both breastfed and receive other foods or drinks. A recently published early report (2) suggests that exclusive breastfeeding, that is, when an infant is given no other food or drink of any sort, may be less likely to transmit infection than mixed feeding, possibly because other foods can damage the infants gut, and make it easier for the virus to cross the intestinal mucosa. This report has raised the hopes of many health workers, who are concerned about the adverse effects on child health of decreasing rates of breastfeeding. The question has been raised as to whether or not WHO should revise its infant feeding recommendation.

The information contained in this early report is interesting and important. However, because of limitations of the study size and design, firm conclusions cannot be drawn without further research. That such research should be conducted as a matter of urgency is clear, and has been identified by WHO as a priority.

The current guidelines clearly indicate that for HIV-positive mothers who choose to breastfeed, the safest option is to breastfeed exclusively to minimise the risk of other childhood infections such as diarrhoea, using a good technique to reduce the risk of mastitis and nipple damage which could increase transmission of HIV. Stopping breastfeeding when the infant is 3-6 months old is an option to avoid late postnatal transmission, and at this older age the health hazards for the child, and the social difficulties for the mother associated with not breastfeeding are fewer.

Short term exclusive breastfeeding is already included in the WHO/UNICEF/UNAIDS guidelines as one of the feeding options. The information in the early report, if confirmed, would strengthen the case for choosing it as both feasible and effective. However, there can be no justification for dropping replacement feeding as one of the options, for mothers who wish to use it, while there is any possibility of transmission of HIV through breastmilk.

The existing WHO/UNICEF/UNAIDS/ policy and guidelines remain appropriate according to existing scientific evidence, and there is no present indication that they should be changed. The guidelines accommodate all reasonable infant feeding options for mothers with HIV, and support a fully informed choice, which will allow mothers to be provided with better information as it becomes available.

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Tuberculosis in Children

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Tuberculosis with Human Immunodeficiency Virus Infection

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Abstract. Tuberculosis is the commonest opportunistic infection in HIV-infected patients in developing countries including India. The seroprevalence of HIV among tuberculosis patients in various parts of India has been increasing steadily. Children who are HIV-infected have a higher risk of progression after primary infection. Children born to HIV positive parents who are not infected themselves are also at higher risk of acquiring tuberculosis because of exposure. The clinical and radiological manifestations of tuberculosis are similar to those seen in HIV-uninfected individuals, except in those with advanced immunodeficiency. Most patients respond well to standard chemotherapy but mortality remains high because of other opportunistic infections. Preventive treatment with isoniazid for 6-12 months is effective in reducing those with latent infection.

Key words : *HIV infected; Latent infection.*

The HIV epidemic started a new era in the history of mycobacterial disease in humans, both in developed and developing countries. There has been a resurgence in the number of cases of active tuberculosis worldwide. More ominous has been the emergence of multi-drug resistant tuberculosis. The significance of tuberculosis in the natural history and progression of HIV infection is now well recognized. Extrapulmonary tuberculosis was classified as an AIDS defining illness in children in 1987[1]. In the most recent classification system for HIV infection in children, extrapulmonary tuberculosis is included as a category C condition, i.e. defining severe symptomatic HIV infection[2].

Epidemiology of HIV and Tuberculosis

Using estimates of prevalence of tuberculosis and HIV in various regions, it has been observed that by mid-1994 there were 5.6 million persons co-infected with HIV and tuberculosis worldwide; more than 1.15 million of these live in Southeast Asia (including India[3]). It is estimated that deaths from tuberculosis will increase from 2.5 million annually in 1990 to 3.5 million annually in 2000. The proportion of HIV -attributable tuberculosis deaths will increase from 4.6% to 14.2%. In the developed countries, the increasing rates of tuberculosis have been reversed with effective tuberculosis control programs. In India, the rates of HIV-tuberculosis co-infection are steadily increasing. Here tuberculosis is the commonest opportunistic infection in HIV infected. Close to 60% of adults with symptomatic HIV infection have tuberculosis[4,6]. The seroprevalence of HIV antibody among tuberculosis patients throughout India has increased significantly in the past few years. In Pune, the prevalence of HIV infection among tuberculosis patients increased from 3.2% in 1991 to 20.1% in 1996[7].

Most available data on HIV and tuberculosis is from adults. It is not surprising that tuberculosis is more common among HIV-infected adults than children since there is a cumulative increase in the risk of tuberculosis with age. Adults may develop disease from progression of a primary infection as well as reactivation of latent infection. Disease in children, on the other hand, usually follows progression of primary infection. Though the proportion of HIV-infected children with tuberculosis is lower than HIV-infected adults, the number of children with HIV-attributable tuberculosis is rapidly increasing. It is estimated that worldwide there will be over 56,000 cases of HIV-attributable tuberculosis annually in children by the year 2000[8]. A study from Mumbai showed a prevalence of HIV of 18% among children with CNS tuberculosis or miliary tuberculosis; the prevalence of HIV seropositivity among children with chronic diarrhea in the same study was 24%[9]. In our cohort of 49 children with HIV infection, seven (14%) were diagnosed to have tuberculosis (unpublished data).

Copathogenicity of Tuberculosis and HIV Disease

The association between HIV and tuberculosis is not surprising because of the overlap in the populations at greatest risk for infection with both these organisms and the importance of cell mediated immunity in controlling tuberculosis. Thus, those with HIV infection are more likely to develop active disease when infected with *Mycobacterium tuberculosis* and, consequently, more likely to spread the infection to their close contacts. Areas of the world with

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the highest rates of tuberculosis (>100 cases per 100,000 population) are the same regions where HIV is rapidly increasing. In these areas transmission of HIV is predominantly heterosexual and HIV infection in children puts them at high risk for co-infection with *M. tuberculosis*, following which they also have a higher risk of progression to active disease; the risk of active disease in children with HIV is 5-10 times higher than those without HIV[9].

Children born to HIV-infected mothers, but who are not themselves infected, are also at higher risk for acquiring tuberculosis because of the increased risk of exposure to tuberculosis from their parents. It is estimated that tuberculosis rate in the first four years of life among children born to HIV-infected mothers is 10 times higher than in non-HIV-infected and 30 times higher in HIV-infected children, respectively, as compared to other children[10].

While it is clear that HIV infection increases the risk of tuberculosis, it is now becoming increasingly clear that the reverse is also true. Immunologic and virologic evidence indicates that the immune response to tuberculosis enhances HIV replication, accelerating the progression of the infection[11]. Therefore, prevention and early treatment of tuberculosis is very important in HIV-infected patients.

Infection with *M. tuberculosis* most often occurs via the respiratory tract. After infection, alveolar macrophages present the mycobacterial antigens to CD 4 positive T-cells. This results in the release of interferon gamma (IFN_γ), which in turn activates macrophages to control the mycobacterial infection. However, the activated macrophages also release interleukin-1, which enhances HIV replication[12,13]. Mycobacteria also enhance HIV replication by inducing nuclear factor Kappa-B, the cellular factor that binds to the promoter region of HIV[14,15].

Clinical Manifestations of Tuberculosis in Patients with HIV Co-infection

In majority of the adults (>15 years) with HIV infection, the clinical and radiological manifestations of tuberculosis are similar to those seen in non-HIV infected adults[16,17]. Studies in Kenya and Tanzania have shown that 88-92% of HIV seropositive adults with tuberculosis had only pulmonary involvement whereas 0.6 to 3% had both pulmonary and extrapulmonary involvement and 8-12% had only extrapulmonary involvement[16]. Of those with extrapulmonary involvement, 85% had lymphadenopathy (mainly cervical)[16]. Miliary tuberculosis was uncommon and found in only 1.7% of 1722 tuberculosis patients with HIV in Kenya[16]. Though many HIV-infected adults have typical clinical and radiological manifestations of tuberculosis, atypical presentations do occur frequently, especially in those with low CD4 counts. Thus, cavitatory upper lobe tuberculosis is more common in those with CD4 counts> 200/mm^3, whereas hilar/mediastinal adenopathy and diffuse pulmonary infiltrates (without cavitation) are more common in those with CD4 counts<200/mm^3[18].

Data from children co-infected with HIV and tuberculosis also suggest that the clinical and radiological manifestations do not vary significantly from those who are HIV seronegative[19]. However, one study from Zimbabwe showed that lobar infiltrates, especially those involving the lower lobes were more common in the HIV seropositive children[20]. In the cohort of 31 HIV seropositive children with tuberculosis in Cote d'Ivoire, nine (29%) had extrapulmonary disease[19]. This was not significantly higher than in HIV seronegative children, 26% of whom had extrapulmonary disease[19]. The common extrapulmonary manifestations were lymphadenopathy, pleural effusion and miliary tuberculosis, the latter seen more frequently in the HIV-infected cohort[19].

In our own experience, all seven children co-infected with HIV and tuberculosis had pulmonary disease. All of them presented with prolonged fever, weight loss and failure of the pulmonary signs and symptoms to subside despite adequate antibiotic therapy. Chest radiographs showed only hilar adenopathy in one, lobar infiltrates with or without hilar adenopathy in four (fig. 1) and diffuse infiltrates in two children, respectively.

The clinical features of tuberculous meningitis in children who are seropositive for HIV are also not significantly different from those in seronegative children. However, ventriculomegaly, gyral enhancement and cortical atrophy on CT scan are more common in HIV seropositive children[21]. Also, mortality and the incidence of severe neurological sequelae are more common in HIV seropositive children. Co-existing HIV encephalopathy and diminished immune function may account for the poorer prognosis[21].

Laboratory Diagnosis

In children the majority of tuberculosis cases are diagnosed clinically without microbiological confirmation. The diagnosis is based mainly on clinical suspicion and radiological manifestations.

The tuberculin skin test is often negative, especially in those with more advanced HIV disease. Only one-third to less than half of children co-infected with tuberculosis and HIV have a positive tuberculin test[19, 20, 22]. Because of the higher risk of tuberculosis in children living in households with HIV-infected adults and because of diminished immune responses in children with HIV infection, the American Academy of Pediatrics recommends using induration $\geq$ 5 mm as the criterion for diagnosis of tuberculous infection[23]. These criteria have not been

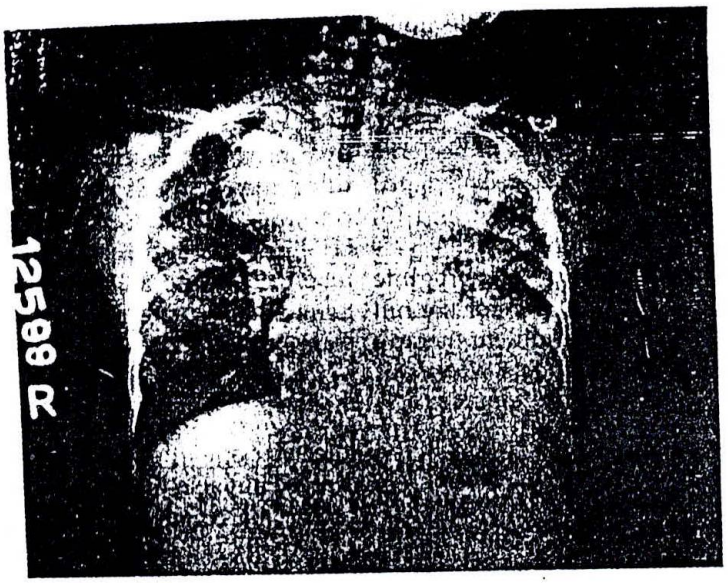

Figure 1: Chest radiograph of a child with tuberculosis and HIV co-infection showing mediastinal lymphadenopathy and lobar infiltrates.

adequately evaluated in developing countries, especially in those where BCG vaccination is part of routine childhood immunization.

Contrary to what one would expect, smears and cultures are more often negative in HIV-infected adult patients with tuberculosis[24]. Similar findings are reported among children with co-infection[19,20]. Despite this, it is recommended that aggressive attempts be made to obtain a positive culture to differentiate between *M. tuberculosis* and other mycobacteria, as well as to determine the antimicrobial susceptibility.

Smears from needle aspiration and Ziehl-Neelson staining are often negative in HIV patients who have tuberculous lymphadenitis[25]. Hence, biopsy with histopathological examination and culture of the lymph node tissue are recommended to establish the diagnosis.

Newer diagnostic modalities including molecular methods of diagnosis of tuberculosis may yield better results than routine smear and culture in the HIV-infected population, but these methods need further evaluation. Moreover, these methods for diagnosis are seldom available in regions where the two infections most frequently co-exist.

Treatment

The treatment of tuberculosis in HIV-infected individuals has been extensively reviewed in a recent publication from the Centres for Disease Control and Prevention (CDC), Atlanta, USA[26]. Readers are advised to consult this document for the latest treatment recommendations.

Pulmonary tuberculosis : For drug-susceptible pulmonary tuberculosis, standard 6-month therapy with isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) daily for the initial two months followed by INH and RIF, daily or twice weekly, for at least 4 additional months, is recommended. Conversion from sputum positive to sputum negative with this regimen is similar in HIV seropositive and seronegative patients with tuberculosis. However, it is not known if relapse rates are higher in HIV-infected patients. Hence, some experts recommend extending the treatment to 9 months. The CDC recommends a minimum of 6 months therapy, with extension to 9 months in those who show slow response. Slow response is defined as sputum positivity or persistence of signs and symptoms of disease after 2 months of therapy[26]. Directly observed therapy is recommended, wherever possible.

Extrapulmonary tuberculosis : The drug regimen and duration of treatment used for pulmonary tuberculosis are generally adequate to treat most forms of extrapulmonary tuberculosis. However, for certain forms of tuberculosis, such as meningitis and bone and joint tuberculosis, a 9-month regimen of a rifamycin-containing regimen is recommended[26].

Drug resistant tuberculosis : The risk of drug resistant tuberculosis is higher among those co-infected with HIV[27]. The reasons for this are not clear, but this might reflect the

fact that a higher proportion of tuberculous disease in HIV-infected individuals follows recently acquired infection.

In recent years there had been an increasing number of reports of rifampicin monoresistance in HIV co-infected patients. The reasons for this are also not fully understood. Possible reasons include (1) increased rates of bacterial replication in an environment of suppressed cell mediated immunity, (2) selective drug malabsorption and (3) inadequate tissue penetration of the drug.

For isoniazid-resistant tuberculosis, a regime containing RIF, PZA and EMB may be used for the full duration of treatment (6-9 months). Intermittent therapy may be used after daily therapy for the initial 8 weeks.

For tuberculosis resistant only to rifampicin a 9-month regime consisting of INH, EMB, PZA and streptomycin for the initial two months, followed by INH, PZA and streptomycin for the next 7 months is recommended.

In multidrug resistant tuberculosis (i.e. resistant to INH and RIF), aggressive treatment with a regime that contains an aminoglycoside or capreomycin and a fluoroquinolone is recommended. The duration of therapy must be at least 24 months after culture conversion.

Paradoxical reactions to treatment : Patients who receive antituberculosis treatment along with anti-retroviral therapy may manifest a paradoxical worsening of symptoms, which are attributable to a recovery of tuberculin hypersensitivity as a result of therapy[28]. Such patients manifest with hectic fevers, lymphadenopathy, worsening chest radiographic findings (e.g. miliary infiltrates and pleural effusion) and worsening of original tuberculosis lesions. Discontinuation or changes in tuberculosis or antiretroviral therapy is rarely required in most situations. A short course of steroids to suppress the immune response may ameliorate some of the signs and symptoms, such as lymphadenopathy.

Interaction between rifamycins and anti-retroviral drugs : Some of the newer anti-retroviral drugs interact with the rifamycin group of anti-tuberculosis drugs, further complicating treatment. Rifampicin induces the enzyme CPY 450 that increases the metabolism of protease inhibitors (PIs) resulting in lower serum levels of these drugs. Since PI resistant mutants of HIV may emerge if optimal levels of the drug are not maintained during therapy, concomitant therapy with rifampicin and PIs is not recommended[26]. On the other hand the protease inhibitor ritonavir inhibits CPY 450, which results in increased concentration of rifabutin and resultant toxicity. Since current evidence indicates that the anti tuberculosis activity of rifabutin is equal to that of rifampicin, it is recommended that this drug be used instead of rifampicin in the treatment of tuberculosis in patients receiving PIs; the PI ritonavir should not, however, be used in treatment regimes containing rifabutin.

Outcome of therapy : When tuberculosis develops in HIV-infected individuals, the prognosis is poor, despite treatment. The 1-year mortality for treated HIV-related tuberculosis is 20-35% both in developed and developing countries[26]. The observed mortality in co-infection with HIV and tuberculosis is four times higher than in tuberculosis without HIV[29]. Although death may be due to tuberculosis, more often it is due to other HIV-related complications[30].

Prevention

Chemoprophylaxis : Prevention of tuberculosis in the HIV-infected population not only prevents progression of HIV disease but also limits the spread of tuberculosis among susceptible contacts.

Several studies have documented that six or 12 months of INH given to tuberculin test positive patients resulted in a 70-83% reduction in incidence of tuberculosis. A multicentric trial in the United States, Brazil, Mexico and Haiti showed that 2 months of RIF and PZA was equivalent to 12 months of INH alone. There is no comparison between a 6-month and 12-month regime of INH, but treatment beyond 12 months does not seem to provide additional benefit. The duration of the protective effect of prophylaxis is not known and the effect on mortality and progression of HIV appears to be limited.

Based on these studies, the CDC currently recommends prophylaxis for all HIV-infected individuals with a tuberculin skin reaction ≥ 5 mm[26]. INH prophylaxis has not been found beneficial in anergic HIV-infected patients. However, some experts recommend prophylaxis for anergic or tuberculin negative HIV-infected individuals with high risk for exposure to tuberculosis. These recommendations hold true for children as well. Yearly tuberculin testing and prophylaxis is recommended for all HIV-infected children.

Non-HIV-infected children of parents with tuberculosis are also at high risk for developing tuberculosis. Once a year tuberculin testing and prophylaxis if they become tuberculin sensitive is recommended[23].

As has been stated earlier, mortality in treated tuberculosis patients co-infected with HIV is largely due to other opportunistic infections rather than reactivation of tuberculosis. This is especially true in patients in developing countries who are not receiving antiretroviral therapy. A recent study from Cote d'Ivoire has shown that cotrimoxazole prophylaxis, started after completion of a 6-

month course of antituberculosis treatment in patients co-infected with HIV, resulted in significantly lower mortality and hospital admissions during a 10-month follow up period[31].

BCG vaccination : There are a few case reports of disseminated BCG infection in individuals with HIV. However, several studies in developing countries have documented that adverse reactions following BCG vaccination in HIV-infected infants are no higher than in non-infected infants[32]. Therefore, BCG vaccination is recommended for infants of HIV-infected mothers in countries where it is part of the routine immunization schedule, provided the children do not have evidence of advanced immunodeficiency. However, the efficacy of BCG in HIV-infected children is not known. One small case-control study showed no efficacy in HIV-infected children compared to 59% efficacy in uninfected children of HIV seropositive mothers[33].

Conclusion

Tuberculosis is the commonest opportunistic infection in the HIV-infected population in developing countries, including India. There has been an increase in the incidence of tuberculosis following the HIV epidemic. The clinical and radiological manifestations of tuberculosis are similar to those seen in HIV-uninfected individuals, except in those with advanced immunodeficiency, where atypical presentations may be seen. Most patients respond well to standard chemotherapy, but mortality remains high primarily because of other opportunistic infections. Prophylactic chemotherapy is effective in reducing the incidence of tuberculosis in those with latent infection. BCG vaccination is recommended in infants born to HIV seropositive mothers unless they have evidence of advanced immunodeficiency. However, the efficacy of BCG in preventing tuberculosis in these children in not known.

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Clinical Manifestations of HIV-1 Infection

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The global pandemic of acquired immunodeficiency syndrome (AIDS) has already claimed an estimated five million lives(1). Pediatric AIDS threatens much of the progress made in child survival in developing countries over the past ten to fifteen years. The earliest reports of AIDS in Indian children have come from multi-transfused thalassemic children(2). More recent reports have described the clinical manifestations in children with perinatally acquired infection(3,4). This report describes the mode of transmission, clinical manifestations and outcome of HIV/AIDS among children diagnosed at our hospital, to add to the emerging description of clinical manifestation of HIV infection among children in India.

Subjects and Methods

The clinical case records of children diagnosed to have HIV infection at our hospital from January 1988 to March 2001 were reviewed. All children had a detailed history and clinical examination performed at the first visit. Serological testing was performed in 45 children because of symptoms suggestive of HIV infection, in 35 children because their parents had positive HIV ELISA tests, and in 8 children as part of preoperative screening. HIV infection was defined using the revised surveillance case

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definition for HIV infection(5), and children were classified into clinical categories using the revised CDC classification of 1994(6). Children younger than 18 months were considered HIV-infected if they tested positive on HIV RNA-PCR assay, or, in addition to positive serology (repeatedly reactive ELISA and confirmatory Western Blot), they had increased serum immunoglobulins, depressed CD4 lymphocyte count and manifested evidence of symptomatic HIV infection (AIDS-indicator conditions diagnosed definitively or presumptively, or recurrent bacterial infections) that met criteria included in the 1987 pediatric AIDS surveillance case definition(7).

Serological diagnosis of HIV infection was made on repeatedly reactive ELISA testing (UBI HIV 1/2 EIA, Beijing United Biomedical Ltd., China; DETECT HIV, Biochem Immunosystems Inc., Canada; ABBOTT EIA PLUS, Abbott, USA) and confirmed by Western blot (HIV Blot 2.2 Gene Labs, Singapore; IMMUNOBLOT INNOLIA, Immunogenetics, Belgium). HIV RNA testing was done using an RT-PCR assay (Amplicor HIV 1 Monitor Test Version 1.5, Roche Diagnostics, NJ, U.S.A.). CD4 lymphocyte subset testing was done using a flowcytometer (Becton Dickinson Facscan, USA) or using an ELISA test (Capcellia CD4/8, Sanofi Diagnostics Pasteur, France). Addtional investigations were done as clinically indicated.

Microbiological confirmation of diagnosis of tuberculosis and *Pneumocystis carinii* pneumonia (PCP) was not always possible. In such cases guidelines from the 1987 CDC surveillance case definition were used. PCP was diagnosed based on findings of persistent cough and/or tachypnea with minimal findings on auscultation, hypoxemia on pulse oximetry or arterial blood gas monitoring, elevated serum lactate dehydrogenase (LDH), presence of diffuse infiltrates on the chest radiograph and response to co-trimoxazole(7,8); in one child who failed to respond to co-trimoxazole, diagnosis was confirmed by post-morterm lung biopsy. Lymphoid interstitial pneumonia (LIP) was diagnosed on the basis of chronic cough and presence of reticulonodular opacities on the chest radiograph, with or without hilar lymphadenopathy, persisting for more than 2 months and unresponsive to antimicrobial or antituberculous therapy(7). Esophageal candidiasis was diagnosed in the presence of recent onset of retrosternal pain on swallowing and oral candidiasis(7) and resolution of symptoms with fluconazole therapy; diagnosis was confirmed with a barium swallow in one of the 4 patients. Tuberculosis was diagnosed on the basis of chronic cough and fever, failure to thrive and weight loss, persistent radiographic findings despite adequate antibiotic therapy; and clinical and radiological improvement with antituberculous therapy(9). Encephalopathy was diagnosed using CDC criteria(6).

Only 7 children were started on antiretroviral therapy owing to cost constraints. Coexisting infections were treated using appropriate antimicrobial drugs. All severely immunosuppressed children and, after 1995, all HIV-exposed infants aged 6 weeks to 12 months received prophylaxis against *Pneumocystis carinii* (10). Data from the questionnaires and clinical case records was entered and analyzed using the software SPSS for Windows (Version 7.5).

Results

Eighty-eight children, 50 boys and 38 girls, were included in the study. Seventy-seven (87%) of the 88 had acquired infection by perinatal transmission. Nine children

(10%) acquired infection following blood transfusion. Three children with thalassemia, one with Fanconi anemia and one with classical hemophilia developed infection following multiple blood transfusions that started between 1986 to 1993; of these, one child acquired the infection as late as 1998. Three children were transfused with their fathers' blood in the neonatal period in 1989, 1990 and 1994, respectively; the fathers were later found to be HIV positive and the mothers HIV negative. The ninth child was transfused with an unrelated donor's blood in 1994 following a road traffic accident; both parents were HIV negative. In two children the mode of transmission could not be ascertained. In a 15 month old child infection was proved by HIV RNA testing but both parents were negative on repeated testing using both ELISA and Western Blot and there was no definite history of blood or blood product transfusion. In another 10-year-old asymptomatic girl whose mother was HIV negative sexual abuse was considered. Her father had died a year previously reportedly with tuberculosis and genital ulcers.

The median duration of follow up was 8 months (range 1 to 156 months). Twenty-seven children are still on regular follow up. Ten children died, and 51 children were lost to follow up at varying periods following diagnosis of HIV infection.

Twelve children were asymptomatic (category N). Seventy-six children were symptomatic, with 18 children in category A, 27 in category B and 31 in category C. The age at onset of symptoms ranged from 1 month to 10 years. Thirty six of the 76 (47%) became symptomatic before 12 months of age; all but 3 were infected perinatally. The remaining 40 became symptomatic at 20 to 120 months of age; 35 were infected perinatally.

Table I enumerates the various clinical manifestations seen in these children. Organisms isolated from pus culture from abscesses and suppurative foci were Group A beta-hemolytic streptococci, enterococci, coagulase-negative staphylococci and *Staphylococcus aureus*, and from ear pus in children with recurrent otitis media were *Pseudomonas aeruginosa, E. coli* and *Proteus mirabilis*.

Of the 23 children with recurrent diarrhea, enteric pathogens were isolated in only five (*Salmonella typhimurium,* enteropathogenic *E.coli, Vibrio cholerae* (2 children) and *Shigella sonnei*). The organisms isolated in blood culture from the six children with documented septicemia were *Staphylococcus aureus* (2 children), coagulase-negative staphylococci, *Enterococcus faecalis* (2 children), *Salmonella typhimurium,* and *Pseudomonas aeruginosa.* In all three children with meningitis no organisms were isolated on CSF culture, and antigen detection for *H. influenzae* type b, pneumococcus and cryptococcus were negative.

All 12 children diagnosed to have tuberculosis (11 pulmonary and 1 miliary) had parents with pulmonary tuberculosis. The Mantoux test was positive (10 × 10 mm) in only two; induration was less than 5 mm in the remaining children. Acid fast bacilli (AFB) were seen in smear and isolated in culture from fasting gastric juice in only 4 children though at least three specimens were collected from each child with suspected tuberculosis. Radiographic findings in the 11 children with pulmonary tuberculosis revealed only a right hilar node in 1 child, diffuse infiltrates in 4 children, and segmental or lobar lesions in 6 (of whom 2 had pleural effusions and 2 had hilar adenopathy in addition). Of the 12 children, 3 have completed therapy, 4 are still on treatment and

TABLE I–*Frequency of Clinical Manifestations of HIV Infection*

	Number	Percentage
Category A Symptoms		
Hepatomegaly	55#	72
Lymphadenopathy	46	60
Splenomegaly	33*	43
Papular urticaria	23	30
Pyoderma (recurrent)	19	25
Dermatoses (other)	19+	25
Otitis (recurrent)	16	21
Parotitis (recurrent)	12	16
Category B Symptoms		
Failure to thrive	44	58
Recurrent diarrhea	23	30
Candidiasis (oral)	20	26
Pneumonia (single episode)	13	17
Pulmonary tuberculosis	11	14
Septicemia	6	8
Meningitis	3	4
Giant molluscum contagiosum	3	4
Lymphoid interstitial pneumonia	2	2.6
Hepatitis	2	2.6
Cardiomyopathy	1	1.3
Category C Symptoms		
Encephalopathy	21 (Progressive 11)	28
Pneumonia (recurrent)	14	18
Pneumocystis carinii pneumonia	6	8
Esophageal candidiasis	4	5
Pyopericardium	1	1.3
Septic arthritis	1	1.3
Miliary tuberculosis	1	1.3
CMV pneumonia	1	1.3

includes 3 children with hepatomegaly due to thalassemia.

* includes 2 children with splenomegaly due to thalassemia.

+ seborrheic dermatitis, viral warts, varicella zoster, oral herpes simplex, pediculosis, icthyosis: 1 patient each; 2 patients with herpes zoster and tinea infection, 11 patients with scabies.

regular follow up and are responding, 4 children were lost to follow up and one child died due to fulminant hepatitis 2 weeks after initiating anti-tuberculous therapy.

Six children were presumptively diagnosed to have PCP; CD4 counts done in 4 of these children showed evidence of severe immunosuppression in 3. All six had oral candidiasis. Two died in hospital; one was 4½ months old and the other 2½ years old; post-mortem lung biopsy done in one showed presence of *P. carinii* cysts in the alveolar spaces.

Of the 21 children with evidence of encephalopathy by CDC criteria, 11 had progressive encephalopathy, with regression of milestones, spasticity and hyperreflexia; one had dysarthric speech, two had ataxia, two had hemiplegia and two had well-controlled seizures in addition. We were able to obtain CT scans in only two children; both showed evidence of cortical atrophy and one child had basal ganglia calcifications in addition.

Ten children died. Six of the ten were younger than 12 months, and the oldest was 50 months old at death. Documented (by post-mortem biopsy) causes of death in 4 of the 6 children who died in hospital were *Pneumocystis carinii* pneumonia in one, cytomegaloviral (CMV) pneumonia in one, dilated cardiomyopathy in one, and fulminant hepatitis in one. The fifth child died in hospital following an attack of cholera with persistent acidosis and hypokalemia, and in the sixth a clinical diagnosis of PCP was made, but we were unable to confirm the diagnosis as the parents refused permission for post-mortem lung biopsy. Four children died at home; one had acute watery diarrhea, two died of bronchopneumonia that did not respond to oral antibiotics, and the fourth died

at home with severe progressive encephalopathy.

Discussion

Though our data show that the mode of acquisition and clinical manifestations of pediatric HIV/AIDS in India are not substantially different from that reported in other countries, there are several important aspects of the disease that we would like to highlight.

Transfusion-associated transmission of HIV continues to occur in India despite regulations requiring screening of donors, either because screening procedures are not being followed or because transmission may occur despite screening. The former is likely in the case of the children infected from transfusions from their fathers. Many small hospitals without access to blood banks may transfuse patients with blood from a close relative without screening in the mistaken belief that the blood would be safe. Our data shows that this is not necessarily true and that unscreened blood must not be used, irrespective of the donor.

Our data also shows that a bimodal progression occurs in Indian children, as described in other countries(11). A significant proportion of patients present in infancy and have severe disease and early death, while children surviving beyond 5 years of age tend to have only moderate signs and symptoms and have longer survival.

The common clinical manifestations of HIV infection such as hepatomegaly, generalized lymphadenopathy and splenomegaly, and skin infections, recurrent diarrhea, and failure to thrive are the same as in studies of HIV-infected children in both Western(12) and tropical countries(13), and in recent reports from India(3,4). Papular urticaria, thought to be due to a hypersensitivity reaction to environmental factors or allergens such as insect saliva or mosquito bites, was commonly seen in our patients. This condition has been described as one of the initial manifestations of HIV infection in Haitian adults and children(13,14).

Respiratory infections were a common problem in our series. Microbiological confirmation of tuberculosis and *Pneumocystis carinii* penumonia was not always possible, and diagnosis was often presumptive, based on clinical criteria and response to therapy. As in other studies from India and other tropical countries(4,13), bacterial pneumonia occurred more frequently than PCP and LIP. This may reflect the greater importance of bacterial infections in tropical countries as well as limited diagnostic options for the diagnosis of PCP and LIP. A recent Indian study has shown a 4% incidence of PCP when confirmed with bronchoalveolar lavage(4). In India, where definitive diagnosis using bronchoalveolar lavage or lung biopsy are seldom feasible, using presumptive criteria for early diagnosis of *Pneumocystis carinii* pneumonia and PCP prophylaxis in infants of HIV-positive mother may prevent one of the major causes of death in infancy.

Our experience is similar to other studies showing that HIV-infected children with tuberculosis often have a negative tuberculin test(3,15), the proportion of children with positive smears or cultures is low(16), and that clinical and radiological features do not differ from children without HIV infection.

The high incidence of encephalopathy in this series of children is comparable to other studies in both developed(17) and developing countries(4,18), and highlights the need for developmental and neurological assessment of the HIV-infected child at each visit.

Key Messages

- Though the predominant route of transmission of HIV infection is vertical, transmission via blood transfusion still takes place.
- There was evidence of a bimodal progression of disease due to HIV infection.
- Clinical manifestations of HIV infection were similar to those described in developed countries. except that bacterial infections were commoner than opportunistic infections.
- In the absence of easily affordable antiretroviral therapy, prompt diagnosis and treatment of bacterial infections, and PCP prophylaxis may be the keys to prolonging life and ensuring optimal health in children with HIV infection.

Among the 10 children who died, the predominant causes of death were respiratory. Since a proportion of these could be due to PCP, prophylaxis for all HIV-exposed infants from 6 weeks to 12 months of age may be important in reducing mortality.

Contributors: VPV and TC designed the study, enrolled the patients, carried out follow up, analyzed the data and prepared the manuscript. AJC helped with patient enrolment and follow up. PGB performed the serology. TJJ, CK and PR assisted in patient enrollment, data analysis and manuscript preparation.

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Evaluation of Chronic Cough in Children: Clinical and Diagnostic Spectrum and Outcome of Specific Therapy

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Cough may be voluntary or involuntary, infrequent and hardly noticeable or painful, disruptive and debilitating. Cough may be viewed as a continuum of health through disease and is a useful host defense mechanism. Cough gives protection to the tracheobronchial tree from potentially injurious substances and by removal of endogenous secretions and other materials, such as pus, necrotic tissue and foreign bodies(1).

Chronic cough needs to be evaluated for the underlying disease in a systematic manner regarding the nature of cough, timing of cough, onset of cough, site of pathology, associated clinical features, response to

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WORLD HEALTH ORGANIZATION ■ FAMILY AND COMMUNITY HEALTH CLUSTER ■ DEPARTMENT OF HIV/AIDS

Contents

2. Use of antiretroviral drugs for MTCT-prevention

Primary prevention of HIV infection among future parents and avoidance of unwanted pregnancies among women infected with HIV are fundamental long term strategies in the prevention of transmission of HIV to infants. However, many HIV-infected women become pregnant and others may acquire HIV infection during pregnancy. The use of antiretroviral drugs during pregnancy and delivery has been shown to be effective in reducing the transmission of HIV from mothers to infants. These regimens reduce the risk of MTCT by decreasing viral replication in the mother and through prophylaxis of the infant during and after exposure to the virus.

This section reviews the evidence available to date on efficacy and safety of antiretroviral regimens, including those based on nevirapine, for MTCT-prevention.

2.1 Efficacy

Remarkable reductions in paediatric HIV infection rates have been observed in industrialized countries since 1994 when the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 showed that administration of zidovudine to women from the fourteenth week of pregnancy and during labour, and to the newborn decreased the risk of MTCT by nearly 70% in the absence of breastfeeding.[6] When combined with elective caesarean section this regimen resulted in a transmission rate of 2% or less, in non-breastfeeding populations.[7,8] The use of combination antiretroviral regimens, known as highly active antiretroviral therapy or HAART, for the treatment of HIV-infected individuals has resulted in similar low vertical transmission rates when used by pregnant women.[9]

The cost and complexity of these regimens have restricted their use in resource-poor settings.

However, from 1998, a shorter zidovudine alone regimen starting from 36th week of pregnancy was shown to reduce the risk of transmission of HIV at 6 months by 50% in a non-breastfeeding population[10] and by 37% in breastfeeding populations.[11,12] Other clinical trials have shown that short course antiretroviral regimens using the combination zidovudine and lamivudine,[12] or nevirapine alone[13] also substantially decrease the risk of HIV transmission (Table 3).

Not a good paper · 67

Table 3. Use of antiretroviral regimens for MTCT-prevention

Regimen (Reference)	Schedule	Cost	Efficacy	Practicality	Efficacy*/Transmission Rates/Comments
NON-BREASTFEEDING POPULATIONS					
ACTG076/ ANRS024[6] ZDV	**Pregnancy: from wk 14** 100mg 5 times dly, **Intrapartum:** 2mg/kg intravenous (IV) infusion over 1 h, continuous hly IV infusion of 1 mg/kg **Postpartum Infant:** 2 mg/kg orally 6 hly for 6 wks	+++	++++	+	18-mth efficacy 68% 18-mths transmission rate 8% Original regimen. Requires extensive resources.
'Thai short course'[10] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum:** 300mg 3 hly	++	+++	+++	6-mth efficacy 50% 6-mths transmission rate 9%
PHPT, Thailand[12] ZDV	Long-Short, Long-Long **Pregnancy: from wk 28** 300mg twice dly **Intrapartum:** 300mg 3 hly **Postpartum Infant:** 2mg/kg 6 hly for 3 days or 6 wks	++	+++	++	6-mths transmission rate 6% May be slightly better than 'Thai short course'
	Short-Long **Pregnancy: from wk 35** 300mg twice dly **Intrapartum:** 300mg 3 hly **Postpartum Infant:** 2mg/kg 6 hly for 6 wks	++	+++	+++	6-mths transmission rate 8% Similar to 'Thai short course'
BREASTFEEDING POPULATIONS					

BREASTFEEDING POPULATIONS

CDC, W Africa[12] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum:** 300mg 3 hly	++	++	+++	6-mth efficacy 37% 3-mths transmission rate 17%
DITRAME/ ANRS 049a W Africa[11] ZDV	**Pregnancy: from wk 36** 300mg twice dly **Intrapartum**: 600mg **Postpartum mother:** 300mg twice dly for 1 week	++	++	++	6-mth efficacy 38%; 6 mths transmission rate 18% Pooled 24-mth W African data CDC/DITRAME: 28% efficacy and transmission rate 22%
PETRA Arm A[13] ZDV+3TC	**Pregnancy: from wk 36** ZDV+3TC twice dly **Intrapartum**: ZDV 3hly/ 3TC twice dly **Postpartum mother:** ZDV+3TC twice dly for 1 wk **Postpartum Infant:** ZDV+3TC twice dly for 1 wk	++	+++	++	6-wk efficacy 54% 6-wks transmission rate 7%
PETRA Arm B[13] & **SAINT**[18] ZDV+3TC	**Intrapartum**: ZDV 3hly/ 3TC twice dly **Postpartum mother:** ZDV/3TC twice dly for 1 wk **Postpartum Infant:** ZDV+3TC twice daily for 1 wk	++	++	+++	PETRA: 6-wk efficacy 39% 6-wk transmission rate 10% SAINT: 6-wk transmission rate 10% Programmatically attractive because of simplicity and relatively low cost.
HIVNET 012[14] & **SAINT**[18] NVP	**Intrapartum**: 200mg at start of labour (HIVNET) or at hospital intrapartum (SAINT) **Postpartum mother:** 200mg stat (SAINT only) **Postpartum Infant:** 2mg/kg stat within 48 hrs (SAINT) or 72 hrs (HIVNET 012)	+	++	++++	HIVNET 012: 14-16-wk efficacy 47%; 6-wks transmission rate 12% 12-mth efficacy 42%; 12-mths transmission rate 16% SAINT: 8-wks transmission rate 13% Programmatically very attractive because of simplicity and very low cost. Concerns over drug resistance in women who have access to ARV therapy.

Efficacy: Percentage reduction in HIV transmission rate in active arm compared with placebo, except for NVP which was compared in HIVNET012 with a probably ineffective regimen consisting of intrapartum ZDV for the mother and 1 week post-partum for the infant

ZDV: Zidovudine **3TC**: Lamivudine **NVP**: Nevirapine **ARV**: Antiretroviral

Adapted from: Efficacy of Antiretroviral Regimens for the Prevention of Mother to Child Transmission of HIV and Some Programmatic Issues : Farley T, Buyse D, Gaillard P, Perriens J. Background documents for WHO Technical Consultation October 2000.[1]

Short term efficacy as determined by infant's infection status at 6-8 weeks of life has been demonstrated for the short course prophylactic regimens comprising zidovudine alone, zidovudine plus lamivudine, or nevirapine alone. Long term efficacy as determined by the child's infection status at 24 months of age has been evaluated for the short course zidovudine regimen, and at 18 months of age for the nevirapine regimen, in breastfeeding populations.[15,16] Available data indicate that the proportion of children acquiring HIV through breastfeeding was comparable in both these regimens and the early difference in reduction of HIV transmission persisted despite continued exposure to HIV through breastfeeding. Assessment of the long-term efficacy of the zidovudine plus lamivudine regimen in such populations is still in progress.

All regimens include an intrapartum component, with varying duration of antepartum and/or postpartum prophylaxis. While the efficacy of the more complex regimens which include antepartum, intrapartum and postpartum components is somewhat higher, the single dose nevirapine regimen provided during labour to the mother and postpartum to the infant has also been shown to be efficacious and is more practical.

2.2 Safety

For women and infants who are offered antiretroviral prophylaxis of MTCT, the risk associated with exposure to one or more drugs must be weighed against the benefit of reducing the risk of transmission to infants of a fatal infection. Short-term safety and tolerance of the antiretroviral prophylactic regimens has been demonstrated in all the controlled clinical trials on MTCT-prevention. Collection of data on long-term safety and on patterns of resistance to the antiretroviral drugs is ongoing.

2.3 Choice of antiretroviral regimen(s)

The choice of regimen(s) to be included in a MTCT-prevention programme should be determined by assessment of feasibility, efficacy, acceptability and cost. However, it should be noted that drug costs may represent only a fraction of the costs of the services that are required for an effective MTCT-prevention programme.

Practical considerations in choosing antiretroviral regimens for MTCT-prevention

Good article

Quality of antenatal care
Proportion of births occurring in health care facilities
Access to early postnatal care
Acceptability and ease of dosage schedules
Access to and cost of drugs

2.4 Use of nevirapine for MTCT-prevention

In recent years, the use of nevirapine has attracted considerable attention because of its demonstrated efficacy in clinical trials in reducing MTCT, low cost and ease of use in MTCT-prevention programmes. Further information about its use for this purpose is provided below.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds directly to HIV-1 reverse transcriptase, slowing the rate of viral DNA synthesis and thereby inhibiting viral replication. Nevirapine is rapidly absorbed when given orally to adults, and has a long elimination half-life $t_{1/2}$ of approximately 40 hours. Nevirapine crosses the placenta efficiently after a single oral 200 mg dose to the mother at the onset of labour. In infants, median $t_{1/2}$ ranges from 45 to 72 hours for elimination of the maternal nevirapine, and from 37 to 46 hours for the elimination of a single 2mg/kg neonatal dose.[19]

Short-term safety and tolerance of single dose nevirapine has been demonstrated in clinical trials. Data from 38 women and infant pairs enrolled in the initial phase I trials, PACTG 250 and HIVNET 006, showed no rash or serious adverse events detected either through laboratory tests of through observation of clinical symptoms in women or infants, attributable to nevirapine. In the HIVNET 012[14] and SAINT studies,[18] 960 women and infant pairs were exposed to the intrapartum/newborn nevirapine regimen; there were no significant differences in serious toxicity, occurrence of rash, anaemia, liver abnormalities or death between nevirapine and short course regimens of zidovudine or zidovudine/lamivudine in women or infants. In the PACTG 316 study, 1506 women receiving antiretroviral treatment (usually combination therapy) were randomized to receive extra dose of nevirapine or placebo at the time of delivery. There was no difference in maternal or infant toxicity between the two study arms.[20] Collection of long-term safety data following administration of single dose nevirapine is ongoing.

Selection of resistant virus has been observed among some women and infants who received single dose nevirapine[21,22] or lamivudine.[22,23] for preventing MTCT. The resistant virus will revert to wild type susceptible strains within 12 to 24 months after stopping the treatment with nevirapine. The clinical

significance of the emergence of resistance in the context of MTCT prevention programmes is as yet unknown, particularly with regard to future treatment options for the mother or the child, or to the outcome of prophylaxis during a subsequent pregnancy if the same drug is used. The WHO Technical Consultation in October 2000 carefully reviewed the available information and concluded that the benefit of decreasing mother-to-child HIV transmission with these antiretroviral drug prophylaxis regimens greatly outweighed concerns related to development of drug resistance.[1]

Nevirapine and zidovudine were included in the WHO Model List of Essential Drugs in 1999, solely for the indication of MTCT prevention of HIV.[24] The HIVNET 012 regimen of nevirapine used for MTCT-prevention is a single 200 mg oral tablet to be taken by the mother at the onset of labour and a single oral dose of nevirapine in suspension (2 mg/kg) to be given to the newborn within 72 hours of birth.

Experience in the field suggests that the oral tablet for the mother can be taken at home at onset of labour. However, it is essential that the child should be brought to a health facility within 72 hours of birth for the oral dose of nevirapine in suspension.

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DISTANCE LEARNING COURSE

SAFE BLOOD BANKING

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Course Organiser : Anand Zachariah

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This course is supported by the European Commission through grant number IND/B76211/1B/1999/0379 provided to the HIV/STI Prevention and Care Research Programme of the Population Council India.

MODULE 4

OVERVIEW

This module will help you examine blood safety procedures in your institution's blood bank or that in your locality and to consider what improvements are needed in blood banking in your own situation.

Millions of lives are saved by blood transfusion. However people who receive blood that has not been properly collected or tested are at risk of developing transfusion transmissible infections (TTI) including HIV, Hepatitis B, Hepatitis C and malaria. In India it is estimated that 0.8 % of all HIV infection is transfusion-related (24,000 cases of estimated 3,000,000 HIV positive individuals). The problem of transfusion-related hepatitis C is even greater.

A safe blood supply can be achieved only if:

(a) Blood donors are volunteers and not paid to donate blood and a large pool of such volunteers is maintained.

(b) Potential donors are interviewed by trained staff to exclude those who are at high risk of harboring TTIs.

(c) All blood is screened appropriately for TTIs including HIV, Hepatitis B and C and malaria.

(d) Unnecessary blood transfusions are avoided by educating medical staff on the transfusion guidelines.

All blood banks should aim to achieve these standards of blood safety.

OBJECTIVES

After completion of this module you should be able to:

1. Understand the advantages of voluntary donation and consider ways of increasing your local volunteer donor pool.

2. Outline the procedure for donor evaluation and to exclude individuals at high risk of TTIs.
3. Enumerate the appropriate tests for screening for transfusion transmissible infections (TTIs) and their standards.
4. List indications for use of blood and blood components.
5. Examine your set-up with regard to blood safety and consider ways in which existing safety standards can be improved.

CONTENTS

Before you start Activity 4.1 we would like you perform Activity 4.3 "Finding out about your local blood bank. You will need to visit your local blood bank for this. Only after completing this should you come back to Activity 4.1.

The aim of the first activity is to help you think about the different types of blood donors and the advantages of voluntary donation. To do the next activity you will need to study the tables, ***"Types of blood donors-India" Page 31), "Prevalence of TTIs -Type of donor" (page 32) and "Professional Blood Donors" (page 32)*** *in the readings. Once you have finished reading these tables you can undertake the next activity.*

ACTIVITY 4.1

VOLUNTARY BLOOD DONATION (15 min)

What are the advantages of using voluntary donors as the main source of blood compared to family and replacement donors?

1. Hidden payment may be present in family and replacement donor (as voluntary donor is - illegal)
2. If paid - malnourished → low useful
3. Higher risk of T.T.I. (table)

FEEDBACK 4.1

What are the advantages of using voluntary donors as the main source of blood?

1. Voluntary donors have a lower incidence and prevalence of TTIs than family/replacement donors or paid donors.
2. Voluntary donors are more likely to be willing to donate blood regularly and in case of emergency.
3. Voluntary donors are not likely to be prone to anemia due to frequent donations.

The aim of the next activity is to help you consider ways of increasing your local volunteer donor pool. To do the next activity you will need to study, ***"Safe blood starts with me"*** *(page 34) in the readings. Once you have finished reading this section you can undertake the next activity.*

ACTIVITY 4.2

CREATING A VOLUNTEER POOL (15 min)

The authorities in your hospital have been trying to encourage the local NCC to enrol their cadets as volunteer blood donors in your blood bank. Your blood bank has requested you to give a talk to the NCC cadets on the topic, "Why should I be a voluntary blood donor?". List the points that you would present in your talk:

1. Greatest gift – gift of life, more than one life
2. Blood cannot be manufactured / or use animal blood
3. Constant need for blood – accidents, cancers, blood disorders
4. Healthy person donate 3/12 C out harm
5. No risk of contracting any illness as hygienic practi
6. If you have suffered from TB you should not
7. It takes 10 min, but keep aside 1 hr – drink some food.

FEEDBACK 4.2

List the points that you would present in your talk.

1. One unit of blood can save more than one life.
2. Blood is a drug for which there is no other substitute.
3. Voluntary blood donors have been found to have healthy lifestyles and hence lower rates of transfusion transmissible infections.
4. Blood volume regenerates in 2 hours, blood cells in 2 weeks and iron stores in 2 months. Therefore donating blood does not result in adverse health problems.
5. If you have any condition which makes the blood that you donate unsafe, then you need to inform the doctor who is screening you.
6. You have no risk of acquiring HIV infection by donating blood.
7. A qualified doctor will examine you before blood donation and check you for any condition that may make blood donation unsafe for you.
8. Donating blood is a good will gesture, a way of sharing your life with another person.

The next activity is aimed at helping you find out information about your blood bank or any nearby blood bank.

For this activity you will need to make a 15-30 minute visit to the blood bank of your hospital. If you do not have a blood bank then phone or visit the person in charge of the nearest blood bank which your institution uses. The information obtained in this activity will be essential to the completion of subsequent activities in this module. After completing this activity you will be required to tear out the 2 sheets of this activity and send it with your tutor marked assignment to Vellore.

ACTIVITY 4.3

FINDING OUT ABOUT YOUR LOCAL BLOOD BANK

(60 min)

For this exercise you need to go to your institution's blood bank or alternately, speak on the telephone to the person in charge of the blood bank nearest to your place.

Find out the following information from the bank:

1.What is the volume of blood supplied by your bank?

_____No. of units/year

2. Which of the following does your bank transfuse:
(*tick against those items that are applicable*)

Whole blood

Packed cells

Platelet-rich concentrate

Cryoprecipitate

Plasma

3. What is the proportion of different donors?

	Proportion (%)
Voluntary non-remunerated donations	
Family/Replacement donations	
Paid donations	

4. Does your blood bank have an officer?

Yes / No

5. Identify:

a. Which of the following screening tests are used in your blood bank.

b. Which kits are used.

c. Look at the literature on the pamphlet of the kit to determine the sensitivity of the tests.

d. Find out the rate of infection by these tests in the donor population (during a recent period).

Test	Kit used	Sensitivity of the test	Rate of infection in donors
HIV ELISA			
HbsAg			
Ant-HCV			
Malarial smear			

6. Does your bank conduct education campaigns to encourage volunteer donation?

Yes / No

7. Does your bank have a register of volunteer donors who can be contacted?

Yes /No

8. Does your blood bank have written guidelines regarding indications for blood and component transfusion?

Yes/ No

FEEDBACK 4.3

This information will be needed as you do the subsequent exercises and we will come back to these shortly. **After completing this activity you will need to tear out the 2 sheets of activity 4.3 and send it along with your tutor marked assignment in the addressed envelop.**

This activity aims to improve your knowledge in relation to donor evaluation and develop a protocol for donor evaluation. Before doing the activity, read ***"Criteria for exclusion of blood donors" (page 38)*** *in the reader. Once you have finished reading the criteria you can undertake the next activity.*

ACTIVITY 4.4

DONOR EVALUATION (20 min)

Prepare a donor evaluation form for your blood bank using the format given below. Use the history and examination sub-headings to list your points.

HISTORY * Recent * Past * Personal * Family * Treatment * Systems review
— Recent inf. / — Cer. Resp / Cardiac / Neurological / renal - Diabetic / Anemic — On long drugs (except Ethanol, Contraceptive) — Past HBV, HCV, HIV. Personal — Sexual practice — Multiple Female & Male. Treat — Acupuncture, Tattoing, Blood transfusion

• EXAMINATION * General * Abdomen * Cardiac * Respiratory
Appearance / Jaundice, Tattoos, BP, Drug use Records etc Abd – Liver spleen. Cardiac Respir.

FEEDBACK 4.4

Prepare a donor evaluation form for your blood bank using the format given below.

HISTORY
Recent - Fever, infections, weight loss, genital ulcer, genital discharge, gland enlargement, jaundice. Past - Jaundice, TB, major illness, anaemia, cancer, STDs, cardiac or lung condition , recurrent diarrhoea. Personal - number of sex partners, IV drug use, MSM (men who have sex with men) behaviour, alcohol abuse. Treatment - Drugs being received, history of blood donation, received blood transfusion, frequent injections, surgeries, previous medical diagnosis. Systems review - Hepatic or haematological problems.
EXAMINATION
General: Pallor, skin lesions, jaundice, oral candida, tattoo marks, IV drug use marks, high and low blood pressure Abdomen: Liver, spleen enlargement. Cardiac: Evidence of cardiac disease. Respiratory: Evidence of respiratory disease.

The next exercise helps you examine the risk of TTI despite adequate blood screening and how this may be reduced. In order to do this exercise read ***"Risk of TTI from adequately screened blood" (page 39)*** *from the reader. Once you have read this you can undertake the activity.*

ACTIVITY 4.5

BLOOD SCREENING FOR TTIs (30 min)

1. Calculation of risk of infection from transfusion of adequately screened blood in your blood bank:
Use the data from the above reading and the total volume of blood transfused in your blood bank in a year to calculate the risk of infection from transfusion.
Eg. Risk of transfusion for HIV 1/ 493,000

If total number of units transfused = **N**,

Risk of HIV from adequately screened blood in your blood bank = **N** x 1/493,000

Risk of infection from transfusion in 1 year:

HIV-

Hepatitis C -

Hepatitis B -

2. What is the ideal sensitivity of a test to be used for screening in blood bank?

99.99%

3. Give the reasons why there are small risks of transfusion despite properly screened blood.

1. Window Period
2. Best sensitivity 99.99% .
3. Human error .

4. What are ways of further reducing the risks of transfusion?

1. Screening donors. (voluntary donation)
2. Increasing awareness on vol. donation
3. Improved kits
4. ?

FEEDBACK 4.5

1. Calculation of risk of infection from transfusion of adequately screened blood in your blood bank:

Risk of infection from transfusion in 1 year -

HIV - N/493,000

Hepatitis C - N/103,000

Hepatitis B - N/63,000

(N = Number of transfusions in a year)

These figures may not be accurate for your blood bank because they are derived from the results of another study.

2. What is the ideal sensitivity of a test to be used for screening in blood bank?

> 99%

3. The reasons why there are small risks of transfusion despite properly screened blood.

1. Donation during window period
2. Errors in the test
3. Clerical errors

4. What are ways of reducing the risk of transfusion further?

1. Using higher sensitivity tests which further reduce the window period
2. Rejection of donors who may be at high risk of infections
3. Ensure that kits are in good condition
4. Maintain a quality control system for the tests and also check that Drug Controller of India has approved the tests.
5. Better systems to reduce clerical errors.

This activity aims to improve your knowledge regarding the clinical guidelines for blood and blood component transfusion. Before doing the activity, ***read "Definition of blood components" (page 41-42) and "Clinical transfusion guidelines" (page 41) in the reader.*** *Once you have finished reading these you can undertake the next activity.*

ACTIVITY 4.6

CLINICAL TRANSFUSION GUIDELINES (30 min)

Study the following clinical scenarios.

(a) Indicate in column 2 whether transfusion is indicated (b) Indicate which blood product you would use in your set up.

	Case Scenario	transfusion Indicated	Type of blood product
1	A 45 year old woman presents with tiredness O/E koilonychias, pallor, no signs of cardiac failure. Haemoglobin 6 g% Microcytosis ++ Hypochromia ++	Yes (N)	Whole blood or Packed cells
2	A patient following a road traffic accident has external haemorrhage and is found to be in shock	Yes	- Whole blood - Packed cells & Colloid solution
3	A patient with chronic liver disease comes to the OPD with ascites. Prothombin time (PT): 30 seconds, control -14 seconds. Partial thromboplastin time (PTT): Patient - 50 seconds, control - 30 seconds.	Yes (N)	- Frozen Fresh Plasma - Cryoprecipitate
4	A patient presents with snake bite and massive haematemesis. Prothombin time (PT): Patient 2 min, control-14 seconds. Partial thromboplastin time (PTT): Patient - 3 minutes, control - 30 seconds.	Yes	- Fresh plasma - Packed whole blood - Cr...
5	A patient with Idiopathic thrombocytopenic thrombocytopenia (ITP) c/o Purpura. No evidence of clinical bleeding. Platelet count 25,000/cmm .	Yes (N)	Cryoprecipitate
6	A patient with aplastic anaemia presents with echymoses and nose bleeds. Hb 3 g%, Platelet count 10,000/cmm.	Yes	- fresh blood - fresh frozen plasma

FEEDBACK 4.6

	Indicated	Type of blood product	Explanation
1	No		There is no evidence of haemodynamic instability and the anemia can be treated haematenics.
2	Yes	Whole blood	Acute blood loss with hypovolemia is a definite indication for whole blood transfusion.
3	No		Coagulopathy without bleeding does not require FFP transfusion.
4	Yes	Fresh blood or FFP with packed cells	Coagulopathy with bleeding is a definite indication for FFP therapy.
5	No		Thrombocytopenia without life threatening bleeding does not require platelet transfusion.
6	Yes	Platelet rich concentrate and packed cells as needed. Or Fresh blood	Use specific components in this situation: packed red cells for anemia and platelet rich concentrate for thrombocytopenia. In case the components are not available then fresh blood may be used.

The next activity aims at helping you think about ways that you can educate your staff regarding rational drug use. Refer back once again to the ***"Clinical transfusion guidelines" (Page 41-42)*** *before you start this activity.*

ACTIVITY 4.7

STAFF EDUCATION IN TRANSFUSION GUIDELINES

(15 min)

You have been concerned regarding the inappropriate use of blood products in your hospital. Your department has asked you to prepare a pamphlet for doctors working in your hospital to encourage the rational use of available blood and blood components.

Use the template on the next page to guide you.

PAMPHLET ON RATIONAL BLOOD USE

Introduction

Component	Composition	Appropriate Use	Inappropriate use
Whole blood	· Fresh blood 450 ml · Preservative (citrate) 63 ml	- Hypovolaemia - Replacement transfusion - When packed cells not available	- Overload - cardiac failure
Packed cells	· 200 ml cells	· Severe anaemia · Hypovolaemia when mixed in colloid volume expander	
Fresh frozen plasma	· 300 ml · Frozen at -25°C within 6 hrs	· DIC (after starting treatment) · Thrombotic Thrombocytopaenia · Liver disease · Malignancy	- volume expansion - Routine I.V. cover - protein source
Cryo precipitate	· Factor VIII & Fibrinogen	· Genetic clotting disease · Fibrinogen deficiency	
Platelets	Pooled units	· Platelet defect · Thrombocytopaenia	- DIC - Septicaemia

FEEDBACK 4.7

Introduction

Avoid unnecessary transfusions because of transfusion-associated risks.

Blood is a scarce commodity and should be used sparingly.

Components are preferred to whole blood where possible.

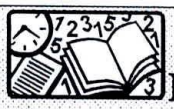
If components are used, many patients can benefit from a single donation.

Check details on blood bag before transfusing to prevent transfusion-associated mishaps.

Component	Composition	Appropriate Use	Inappropriate use
Whole blood	Red cells Plasma Platelets	Acute blood loss Exchange transfusions	Chronic anemia without symptoms Small volume intra-operative blood loss
Packed cell	Red cells	Acute blood loss Symptomatic anaemia Severe pre-operative anaemia Significant Intra-operative blood loss	Chronic anemia without symptoms Small volume intra-operative blood loss

Platelet rich concentrate	Platelets	Thrombocytopenia with bleeding Functional platelet disorders with bleeding	Thrombocytopenia without bleeding (eg. ITP with purpura)
Fresh frozen plasma	Protein Coagulation factors	Replacement of multiple coagulation factors Eg. Snake bite, DIC, liver disease with bleeding Treatment of bleeding in a Haemophiliac when specific factor concentrates are not available	Volume expansion Protein source Routine pre-operative and post-operative cover

NOTES



READINGS

TYPES OF BLOOD DONORS-INDIA

The cornerstone of a safe and adequate supply of blood and blood products is the recruitment, selection and retention of voluntary, non-remunerated blood donors from low risk populations.

There are three types of blood donors:

1. Voluntary non-remunerated donor:

A donor who gives blood freely and voluntarily without receiving money or any other form of payment.

2. Family or replacement donor: A donor who gives blood when it is required by a member of the patient's family or community. This may involve a hidden paid donation system in which the patient's family pays the donor.

3. Commercial or professional donor:

A donor who gives blood for money or other form of payment

The following table provides the proportion of different donors based on a national survey of blood banks in India.

	Proportion
Voluntary non-remunerated donations	39.3
Family/Replacement donations	58.0

The below tables shows the rates of TTIs in different donor groups.

Transfusion Transmissible Infection ?

PREVALENCE OF TTIs–TYPE OF DONOR

	Prevalence (per 1000 units screened)		
	Hepatitis B	Hepatitis C	HIV
Voluntary donations	2.57	0	0.279
Family/Replacement donations	3.52	0.328	0.461

PROFESSIONAL BLOOD DONORS

Professional blood donation is currently illegal. Therefore blood bank statistics do not show the extent of the problem of professional donation. However professional donors may masquerade as relative replacement donors.

Paid donors present a major risk to the safety of the blood supply for the following reasons.

1. Paying donors to give blood undermines the voluntary non-remunerated system of blood donation which is the foundation of a safe blood supply.

2. The highest incidence and prevalence of transfusion-transmissible infections are generally found among commercial or paid donors.

3. They are often undernourished, in poor health and may donate their blood more frequently than is recommended. This may have harmful effects on their own health as well as presenting either a risk to the recipients of their blood or providing them little or no benefit.

4. If donors are paid, it is usually necessary to charge patients for the blood they receive. Poor families may not be able to afford to pay for blood when they need it.

5. The ethical basis of paying individuals to provide blood (or any tissue or organ) is a cause of concern in many countries. The commercial procurement of blood, plasma and organs often leads to serious abuses and may result in adverse consequences. These include the transmission of serious infections both to patients and to the donors themselves through improper collection methods.

SAFE BLOOD STARTS WITH ME

Donation of blood is a gesture of goodwill and care for the fellow human beings. There is no gift more valuable than a Gift of Blood, as it is actually a Gift of Life for the person who receives it.

A safe blood is the one that does not harm the donor, is free from infection or other harmful agents, that does no harm to the recipient and that is used for the benefit of the patients health and well being.

The slogan **Safe Blood Starts With Me** denotes that it is me who is the donor of safe blood. This unit of your blood will save life of more than one patient. As a member of the society it is your responsibility to donate blood.

You can go to the nearest government approved blood centre, which is based on voluntary non-remunerated blood donation and make your significant contribution to saving life of a patient by donating blood. Your contribution is extremely valuable to us.

One unit of donated blood can help save lives of more than one person. One unit of blood can be separated into several components (such as red cells, platelets and plasma) which can meet the needs of many patients. For example, red cells can be given to patients with severe anaemia and platelets can be given to cancer patients.

Trauma victims, cancer patients and patients with inherited blood disorders require most of the blood.

There is no substitute of blood available. Human blood cannot be manufactured and human beings are the only source of blood, which can be used for humans.

Animal blood cannot be used in place of human blood.

Although the **requirement** of blood is alike throughout the year, there is usually a **seasonal shortage** of blood during summer and winter

months as schools and colleges are closed, people go on vacations and there are fewer available donors. There is an increased need for blood donation during these times to maintain an adequate blood supply for all patients needing life-saving blood transfusions.

Blood cannot be stored indefinitely, for example red blood cells can only be stored for about 5 weeks at a temperature of 4-6^{0}C and platelets survive only for 5 days at 22-24^{0}C. The need for a regular blood donation becomes important in view of the limited shelf-life of blood and blood components.

People who are anaemic cannot donate blood. However, they should undergo treatment for anaemia and can donate blood once the haemoglobin is within normal range.

Whole blood donation can be made safely at an interval of 3 months if the donor has no anaemia risk particularly iron deficiency. Repeated blood donation at this interval does not cause any sort of weakness. As pre-menopausal women are more prone to iron deficiency their donation interval is usually longer.

There is absolutely no risk of getting AIDS or any other disease (such as hepatitis B and hepatitis C) from donating blood. The blood is collected using sterile equipment. A new blood bag with attached sterile disposable needle is used for each blood donor and the needle is destroyed immediately after the donation.

You can give blood from the age of 18 years to 60 years safely without any risks at all to your health. It may be a little earlier or later according to national standards.

You are examined before giving blood about your suitability to give blood. If there is any risk to your health due to blood donation or there is any risk to the recipient on receiving the blood, your blood will not be collected.

You must know that many tests need to be done before blood can be transfused. It may take about 3 days to do all these tests. If you only want to donate blood for your family members or friends in need, there may be no time in emergency situations to collect, test and issue your blood for a particular patient. Therefore, there is a need to have sufficient blood available to tackle any emergencies. This is only possible if healthy volunteers donate blood on a regular basis.

Donating blood does not take a long time. The actual blood collection procedure takes about 8-10 minutes. Donors are however, encouraged to spare about one hour for the whole process. The safety of blood actually depends on answering the donor selection questionnaire sincerely and honestly. After the donation you must take rest for 10 minutes at least and have a drink to replenish the fluids.

Individuals who have ever suffered from hepatitis B, hepatitis C or AIDS at any time in their life **should not donate blood.** Those who practice high-risk sexual behaviour or abuse intravenous drugs should also not donate blood. ***Please remember a little of your time can save someone's life.***

Give blood voluntarily As a blood donor, it is your moral responsibility to make sure that the blood, which you donate, is safe and it not likely to transmit any infection, which you may be carrying. To ensure good donor selection, you will be asked few questions in confidence about your life style and your sexual history. The purpose of asking these questions is to select healthy and safe donor for the needy and sick patients, and collect blood, which is safe and unlikely to transmit any infection. You must listen to these questions and answer them as correctly as possible, because we know that you too want to help a patient who is in real need rather than harming a patient.

Please go and enrol yourself as a voluntary donor. You can either donate blood at a blood centre or at any of the mobile donor sessions organised by the blood service.

CRITERIA FOR EXCLUSION OF BLOOD DONORS

1) Age <17, > 60 years.
2) 16 weeks between donations < 3 donations/year.
3) Significant cardiovascular, respiratory, renal disease and neurological disease requiring treatment, insulin dependent diabetes mellitus, cancer and pregnancy.
4) Donors taking potentially teratogenic drugs or drugs that accumulate over a long time. Avoid donors taking any drug except Eltroxin and oral contraceptive pills.
5) Acute bacterial infections and short duration fevers.
6) HIV , Hepatitis B and Hepatitis C.

Risk groups:

7) Those who have received a transfusion of blood or blood products
8) Those who have had acupuncture
9) Those who have had tattooing
10) Men who have sex with men
11) Those who have multiple sex partners
12) IV drug abusers
13) Those who have a history of alcohol abuse
14) Anemia

(The above is not a comprehensive list of exclusion criteria.)

RISK OF TTI FROM ADEQUATELY SCREENED BLOOD

HIV- 1 in 493,000 units transfused

Hepatitis C – 1 in 103,000 units transfused

Hepatitis B- 1 in 63,000 units transfused

(The risk of transfusion associated hepatitis. From: New England Journal of Medicine June 27, 1996)

DEFINITION OF BLOOD AND BLOOD COMPONENTS

Blood product: Any therapeutic substance prepared from human blood

Whole blood: Unseparated blood collected into an approved container containing an anticoagulant-preservative solution

Blood component

1 A constituent of blood, separated from whole blood,
such as:

- Red cell concentrate
- Red cell suspension
- Plasma
- Platelet concentrates

2 **Plasma or platelets** collected by apheresis*

3 **Cryoprecipitate**, prepared from fresh frozen plasma,
which is rich in Factor VIII and fibrinogen

4 **Plasma derivative Human plasma proteins** prepared under
pharmaceutical manufacturing conditions, such as:

- Albumin
- Coagulation factor concentrates
- Immunoglobulins

* Apheresis: a method of collecting plasma or platelets directly from the donor, usually by a mechanical method

CLINICAL TRANSFUSION GUIDELINES

Component	Indications	Contraindications
Whole blood	_ Red cell replacement in acute blood loss with hypovolemia _ Exchange transfusion _ Patients needing red cell transfusions where red cell concentrates or suspensions are not available	Risk of volume overload in patients with: - Chronic anaemia - Incipient cardiac failure
Red Cell Concentrate	_ Replacement of red cells in anaemic patients _ Use with crystalloid replacement fluids or colloid solution in acute blood loss	Same as red cell concentrate
Red cell suspensions	Same as red cell concentrate	Red cells suspended in additive solution are not advised for exchange transfusion of neonates.
Leucocyte reduced blood	Minimizes white cell immunization in patients receiving repeated transfusions but, to achieve this, all blood components given to the patient must be leucocyte-depleted _ Reduces risk of CMV transmission in special situations _ Patients who have experienced two or more previous febrile reactions to red cell transfusion	Will not prevent graft-vs-host disease, although it can improve: for this purpose, blood components should be irradiated where facility is available (radiation dose: 25–30 Gy)
Platelet concentrates	_ Treatment of bleeding due to: — Thrombocytopenia — Platelet function defects _ Prevention of bleeding due to thrombocytopenia, such as in bone marrow failure	_ Not generally indicated for prophylaxis of bleeding in surgical patients, unless known to have significant pre-operative platelet deficiency _ Not indicated in: — Idiopathic autoimmune thrombocytopenic purpura (ITP) — Thrombotic thrombocytopenic purpura (TTP) — Untreated disseminated intravascular coagulation (DIC) — Thrombocytopenia associated with septicaemia, until treatment has commenced or in cases of hypersplenism
Fresh Frozen	_ Replacement of multiple	* Volume expansion

Plasma	coagulation factor deficiencies, e.g.: —Liver disease —Warfarin anticoagulant overdose —Depletion of coagulation factors in patients receiving large volume transfusions. _ Disseminated intravascular coagulation (DIC) _ Thrombotic thrombocytopenic purpura (TTP)	* Protein source * To improve wound healing
Liquid plasma (Bank plasma)	Deficiencies of liver dependent (stable) coagulation factors	* Volume expansion * Protein source * To improve wound healing
Cryoprecipitate	_ As an alternative to Factor VIII concentrate in the treatment of inherited deficiencies of: —Von Willebrand Factor (von Willebrand's disease) —Factor VIII (haemophilia A) —Factor XIII _ As a source of fibrinogen in acquired coagulopathies: e.g. disseminated intravascular coagulation (DIC)	

CHARACTERISTICS OF SELECTED BLOOD PRODUCTS

1. WHOLE BLOOD (CPD-Adenine-1)

Data for a 450 ml (10%) donation volume. Whole blood may contain an alternative anticoagulant/ additive solution.

Description

- Up to 510 ml total volume (this volume may vary in accordance with local policies)
- 450 ml donor blood
- 63 ml anticoagulant
- Haemoglobin approximately 12 g/ml
- Haematocrit 35 (45%)
- No functional platelets
- No labile coagulation factors (V and VIII)
- Unit of issue 1 donation, also referred to as a 'unit' or 'pack'

Infection risk

- Not sterilized, so is capable of transmitting any agent present in cells or plasma which has not been detected by routine screening for transfusion-transmissible infections, including:
  - _ HIV-1 and HIV-2
  - _ Hepatitis B and C
  - _ Other hepatitis viruses
  - _ Syphilis
  - _ Malaria
  - _ Chagas disease

Storage

- Between +2°C and +6°C in an approved blood bank refrigerator, ideally fitted with a temperature chart and alarm
- May be stored up to 35 days if collected in a suitable anticoagulant such as citrate phosphate dextrose with added adenine (CPDA-1) _ During storage at +2°C to +6°C, changes in composition occur resulting from red cell metabolism

Indications

- Red cell replacement in acute blood loss with hypovolaemia
- Exchange transfusion
- Patients needing red cell transfusions where red cell concentrates or suspensions are not available

Contraindications

- Risk of volume overload in patients with:
  Chronic anaemia
  Incipient cardiac failure

Administration

- Must be ABO and Rh compatible with the recipient
- Complete transfusion within 4 hours of commencement
- Never add medication to a unit of blood

BLOOD COMPONENTS

2. RED CELL CONCENTRATE

May also be called 'packed red cells', 'concentrated red cells' or 'plasma-reduced blood'.

Description

- 150–200 ml red cells from which most of the plasma has been removed
- Haemoglobin approximately 20 g/100 ml (not less than 45 g per unit)
- Haematocrit 55–75%
- Unit of issue 1 donation
- Infection risk same as whole blood
- Storage same as whole blood

Indications

- Replacement of red cells in anaemic patients
- Use with crystalloid replacement fluids or colloid solution in acute blood loss

Administration

- Same as whole blood
- To improve transfusion flow, normal saline (50–100 ml) may be added using a Y-pattern infusion set

3. RED CELL SUSPENSION

Description

- 150–200 ml red cells with minimal residual plasma to which approximately
- 110 ml normal saline, adenine, glucose, mannitol solution (SAG-M) or an equivalent red cell nutrient solution has been added
- Haemoglobin approximately 15 g/100 ml (not less than 45 g per unit)
- Haematocrit 50–70%
- Unit of issue 1 donation
- Infection risk same as whole blood
- Storage same as whole blood

Indications

- Same as red cell concentrate

Contraindications

- Red cells suspended in additive solution are not advised for exchange transfusion of neonates. The additive solution may be replaced with plasma, 45% albumin or an isotonic crystalloid solution, such as normal saline

Administration

- Same as whole blood
- Better flow rates are achieved than with red cell concentrate or whole blood

4. LEUCOCYTE-DEPLETED RED CELLS

Description

- A red cell suspension or concentrate containing <5 x 10 6 white cells per pack, prepared by filtration through a leucocyte-depleting filter
- Haemoglobin concentration and haematocrit depend on whether the product is whole blood, red cell concentrate or red cell suspension
- Leucocyte depletion removes the risk of transmission of cytomegalovirus (CMV)
- Unit of issue 1 donation
- Infection risk same as whole blood
- Storage depends on production method: consult blood bank

Indications

- Minimizes white cell immunization in patients receiving repeated transfusion but, to achieve this, all blood components given to the patient must be leucocyte-depleted
- Reduces risk of CMV transmission in special situations
- Patients who have experienced two or more previous febrile reactions to red cell transfusion

Contraindications

- Will not prevent graft-vs-host disease, although it can improve: for this purpose, blood components should be irradiated where facility is available (radiation dose: 25–30 Gy)

Administration

- Same as whole blood

- A leucocyte filter may also be used at time of transfusion if leucocyte-depleted red cells or whole blood are not available

Alternative: Buffy coat-removed whole blood or red cell suspension is usually effective in avoiding febrile non-haemolytic transfusion reactions. The blood bank should express the buffy coat in a sterile environment immediately before transporting the blood to the bedside. Transfusion should start within 30 minutes of delivery with the use, where possible, of a leucocyte filter. Transfusion should be completed within 4 hours of commencement.

5. PLATELET CONCENTRATES (prepared from whole blood donations)

Description

- Single donor unit in a volume of 50–60 ml of plasma should contain:
- At least 55×10^9 platelets
- $<1.2 \times 10^9$ red cells
- $<0.12 \times 10^9$ leucocytes

Unit of issue may be supplied as either:

- Single donor unit: platelets prepared from one donation
- Pooled unit: platelets prepared from 4 to 6 donor units 'pooled' into one pack to contain an adult dose of at least 240×10^9 platelets

Infection risk

- Same as whole blood, but a normal adult dose involves between 4 and 6 donor exposures
- Bacterial contamination affects about 1% of pooled units

Storage

- 20°C–24°C (with agitation) for up to 5 days in specialized platelet packs, although some centres use ordinary plastic packs which restrict storage to 72 hours
- Longer storage increases the risk of bacterial proliferation and septicaemia in the recipient

Indications

- Treatment of bleeding due to:
  - Thrombocytopenia
  - Platelet function defects
  - Prevention of bleeding due to thrombocytopenia, such as in bone marrow failure

Contraindications

- Not generally indicated for prophylaxis of bleeding in surgical patients, unless known to have significant pre-operative platelet deficiency
- Not indicated in:
  - Idiopathic autoimmune thrombocytopenic purpura (ITP)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Untreated disseminated intravascular coagulation (DIC)
  - Thrombocytopenia associated with septicaemia, until treatment has commenced or in cases of hypersplenism

Dosage

- 1 unit of platelet concentrate/10 kg body weight: in a 60 or 70 kg adult, 4–6 single donor units containing at least 240 x 10^9 platelets should raise the platelet count by 20–40 x 10^9 /L
- Increment will be less if there is:
  - Splenomegaly
  - Disseminated intravascular coagulation
  - Septicaemia

Administration

- After pooling, platelet concentrates should be infused as soon as possible, generally within 4 hours, because of the risk of bacterial proliferation
- Must not be refrigerated before infusion as this reduces platelet function
- 4–6 units of platelet concentrates (which may be supplied pooled) should be infused through a fresh standard blood administration set
- Special platelet infusion sets are not required. Platelet concentrates should be infused over about 30 minutes
- Platelet concentrates prepared from Rh D positive donors should not be given to a Rh D negative potential child-bearing female
- Platelet concentrates that are ABO compatible should be given whenever possible

Complications

- Febrile non-haemolytic and allergic urticarial reactions are not uncommon, especially in patients receiving multiple transfusions.

6.FRESH FROZEN PLASMA

Description

- Pack containing the plasma separated from one whole blood donation within 6 hours of collection and then rapidly frozen to -25°C or colder temperature.
- Contains normal plasma levels of stable clotting factors, albumin and Immunoglobulin
- Factor VIII level at least 70% of normal fresh plasma level

Unit of issue

- Usual volume of pack is 200–300 ml
- Smaller volume packs may be available for children

Infection risk

- If untreated, same as whole blood
- Very low risk if treated with methylene blue/ultraviolet light inactivation (see virus 'inactivated' plasma)

Storage

- At -25°C or colder for up to 1 year

Indications

- Replacement of multiple coagulation factor deficiencies, e.g.:
  - —Liver disease
  - —Warfarin anticoagulant overdose
  - —Depletion of coagulation factors in patients receiving large volume transfusions.
  - _ Disseminated intravascular coagulation (DIC)
  - _ Thrombotic thrombocytopenic purpura (TTP)

Dosage

- Initial dose of 15 ml/kg

Administration

- Must normally be ABO compatible to avoid risk of haemolysis in recipient
- No crossmatching needed
- Before use, should be thawed in water which is between 30°C and 37°C. Higher temperatures will destroy clotting factors and proteins
- Once thawed, should be stored in a refrigerator at 2°C–6°C

- Infuse using a standard blood infusion set as soon as possible after thawing
- Labile coagulation factors rapidly degrade; use within 6 hours of thawing

Precautions

- Acute allergic reactions are not uncommon, especially with rapid infusions
- Severe life-threatening anaphylactic reactions occasionally occur
- Hypovolaemia alone is not an indication for use

7. LIQUID (Bank) PLASMA

Plasma separated from a whole blood unit and is stored at +4°C. No labile coagulation factors: i.e. Factors V and VIII.

8. CRYOPRECIPITATE

Description

- Prepared from fresh frozen plasma by collecting the precipitate formed during controlled thawing and resuspending it in 10–20 ml plasma
- Contains about half of the Factor VIII and fibrinogen in the donated whole blood: e.g. Factor VIII: 80–100 i.u./pack; fibrinogen: 150–300 mg/pack

Unit of issue

- Usually supplied as a single donor pack or a pack of 6 or more single donor units that have been pooled

Infection risk

- As for plasma, but a normal adult dose involves at least 6 donor exposures

Storage

- At –25°C or colder for up to 1 year

Indications

- As an alternative to Factor VIII concentrate in the treatment of inherited deficiencies of:
  - —Von Willebrand Factor (von Willebrand's disease)
  - —Factor VIII (haemophilia A) [where factor concentrates are not available]
  - —Factor XIII
  - ---As a source of fibrinogen in acquired coagulopathies: e.g. disseminated intravascular coagulation (DIC)

Administration

- If possible, use ABO-compatible product
- No compatibility testing is needed
- After thawing, infuse as soon as possible through a standard blood administration set
- Must be infused within 6 hours of thawing

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