PRAN Study

Protocol

Official Title: Evaluation of World Health Organization (WHO) Recommendations on Test and Treat Strategy, Managing Advanced HIV Disease and Rapid Initiation of ART Among People Living With HIV in Nepal: A Cluster Randomized Trial.

Dec 2017

INCLUSION CRITERIA

- Age > 15 years
- Diagnosed with HIV-infection
- ART naive or ART started during study enrollment period
- Consent for study participation

This protocol is a short text compiling essential information for the package of care. It has been edited in collaboration between the National Centre for AIDS and STD Control and Expertise France.

For additional and extended information for clinical management you can refer to “National HIV Testing and Treatment Guidelines 2017” published by the National Centre for AIDS and STD Control.

NOTES

16. Advanced Adherence Support (mHealth and community care support

A. Clinically well PLHIV (WHO Clinical Stage 1 or 2 OR CD4 cell count >200 cells/mm3)

- **Home-based care service** (Make monthly/bimonthly visit plan).
- **ART follow up:** At least after 3 months but make sure to analyze current ART adherence level.
- Link with **Community care center** for transitional shelter during initiation of ART.
- **mHealth Intervention**: Push text messages in mobile for appointment reminders and general awareness through DHIS-2 tracker system. Seek patient consent to push text messages.

B. PLHIV with Advanced HIV Disease (Presence of symptoms of WHO stage 3 or 4 OR CD4 count ≤ 200 cells/mm_3)

- **Community Home based care service** (Make weekly/ biweekly visit plan).
- **ART follow up:** Monthly
- Link with **Community Care Center** for transitional shelter while management of OIs and while observational period during initiation of ART.
- **mHealth Intervention** (Push text messages for appointment reminders, general awareness through DHIS-2 tracker system).

The present study will implement package of care in 10 different sites that are equiped with HIV Care and ART Tracking System (DHIS2 tracker, mHealth and Biometric System):

- Teku hospital, Katmandu; Sukraraj Tropical & Infectious Disease Hospital, Kathmandu
- Bir Hospital, Katmandu
- TU-Teaching Hospital, Katmandu
- Western Regional Hospital, Pokhara
- Rapti Sub-Regional Hospital, Surkhet
- Bharatpur Hospital, Bharatpur
- Seti Zonal Hospital, Dhangadhi
- B.P. Koirala Institute of Health Sciences, Sunsari
- Tikapur Hospital, Kailali and Mahakali Zonal hospital , Kanchanpur

The inclusion criteria in the study are the following:

- Age > 15 years
- Diagnosis of HIV-infection
- Naive of ART or started ART during study enrollment period
- Consent for study participation

The study follow-up of the patients is summarized on the next page.

STUDY FOLLOW-UP					
	Baseline	**Day-15**	**M-3/6**	**M-12**	**M-24**
Inclusion criteria	X				
Demographics	X				
Clinical characteristics	X				
HIV infection details	X				
Biological testing					
• Standard	X		X	X	X
• Specialized	X	X	X	X	X
Radiology testing	X	X			
Treatment (prophylaxis, ART)	X		X	X	X
Outcomes (AIDS, Death, LTFU)			X	X	X

15. Corticosteroids and *Strongyloides stercoralis*

The corticosteroids have a particular and specific association with the development of hyperinfection syndrome and dissemination due to *Strongyloides stercoralis* in PLHIV and in IRIS.

Hyperinfection syndrome has been described regardless of dose, duration, or route of administration of corticosteroids. Even short courses (6–17 days) of steroids in immunocompetent patients without underlying immunosuppressive conditions have even been associated with hyperinfection syndrome and death.

Therefore a preventive treatment of *Strongyloides stercoralis* is recommended in case of corticosteroid use, as follow:

Albendazole	400mg, orally, BD, for 3 days

14. Immune Reconstitution Inflammatory Syndrome (IRIS)

This is a condition that can occur shortly after a person starts HIV therapy for the first time. It occurs in 10–30% of patients initiating ART, usually within first 4–8 weeks but can occur up to six months.

The possible risk factors for IRIS are as shown below:

- People with CD4 counts below 100 before starting therapy;
- People with greater drops in HIV viral load due to therapy;
- People with diagnosis of another infection before starting therapy, the closer the appearance or diagnosis is to starting therapy, the higher the risk;
- Severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatment.

IRIS is generally self-limiting and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of, or poor adherence to, ART.

Decrease immune response by:

1	Corticosteroids 1 to 2 mg/kg usually for 1 to 2 weeks, decreased by 50% over the next 2 weeks (sometimes up to 12 weeks).
2	Continue HAART and OI therapy + steroids
3	Treatment of OI for standard period or longer

1. Baseline tests, essential for all patient registering in HIV care

Some tests must be performed for every patient at the time of HIV-infection diagnosis. The purpose is to rule out concomitant infections, Opportunistic Infections (OIs) and determine baseline safety parameters.

STANDARD BIOLOGY
TC, DC, ESR, Hb, Platelets
ALT/SGPT, if needed, LFT (Liver function test)
Blood urea, Serum creatinine and if needed, kidney function test (Electrolytes - sodium, potassium)
Urine analysis to assess for proteinuria
Urine pregnancy test as indicated in female
Blood sugar level
ADVANCED BIOLOGY
Hepatitis B serology (HbS Antigen)
Hepatits C serology (IgG)
VDRL titer
Toxoplasmosis IgG, CMV IgG if CD4<350/mm^3
CD4 cell/count
Sputum GeneXpert if TB symptoms. If GeneXpert not available, Sputum AFB for TB
RADIOLOGY
Chest-X-Ray

Some additional tests might be done as per physician's decision depending on clinical presentation, to rule out OIs (eg. USG abdomen, lumbar puncture, etc).

2. Screen for TB

Screening for TB is essential since it is a very common OI that can be revealed by HIV-infection, or be unmasked by ART initiation.

TB screening has to be done at baseline, within 3 days after the first visit and every month until stabilized HIV-infection. It relies on asking systematic questions to the patient:

- Cough?
- Night sweats?
- Weight loss?
- Fever?

If yes to any question for TB: CXR + Sputum GeneXpert

3. When to start ART ?

ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and CD4 count.

The actual « test and treat » strategy implies that every patient newly diagnosed with an HIV-infection should be rapidly initiated on ART after serology result disclosure except in case of suspected or active OIs.

Two situations may be encountered:

1– patient without suspicion or active OI: initiate ART within 7 days after HIV serology disclosure

2– patient with suspicion or active OI: differ initiation of ART by 15 days after OI treatment starting date (4 to 6 weeks in cryptococcal meningitis)

This situations are summarized in the table on the next page.

Cryptococcal therapy	
Step 1: Induction phase *2 weeks until CSF sterile, followed by consolidation phase*	
Repeated Lumbar Puncture **(decrease intra-cranial pressure)**	
Preferred therapy • Amphotericin B, IV 0.7 to 1mg/kg/day • Flucytosine, PO 25mg/kg/ 6 hours	**Alternative therapy - 1** • Amphotericin B, IV 0.7 to 1mg/kg/day • Fluconazole 800mg/day, IV or PO **Alternative therapy - 2** • Flucytosine, PO 25mg/kg/ 6 hours • Fluconazole , IV or PO 800mg/day **Alternative therapy - 3** • Fluconazole , IV or PO 1200mg/day
Creatinine clearance should be monitored	
Step 2: Consolidation phase *8 weeks, followed by maintenance phase*	
Preferred therapy	*Alternative therapy*
Fluconazole 400mg/day if preferred therapy during induction phase	Fluconazole 800mg/day if any alternative therapy during induction phase
Step 3: Maintenance phase *At least one year*	
Fluconazole 200mg/day	

CM treatment is detailed on the next page.

It is important to notice that corticosteroids and mannitol are ineffective to decrease intracranial pressure; therefore they are not recommended for the management of CM. The principal intervention in patients with symptomatic raised Intra-Cranial Pressure (ICP) is repeated Lumbar Puncture (LP):, as follow:

Focal sign	LP contra-indicated CT scan first
No Focal sign	Perform a first LP
CSF Pressure	
<20 mmHg or <25 mmHg without Headaches	No depletion
20—24 mmHg + Headaches	Depletion 30 mL
25—34 mmHg	Depletion 30 mL Control LP after 48H
≥ 35 mmHg	Depletion 30 mL Control LP after 24H

Repeat LP to confirm clearance of infection is not necessary in patients with clinical improvement by 2 weeks of treatment.

A repeated LP may be necessary if new symptoms develop in patients after 2 weeks of treatment; ICP should be assessed and India ink stain repeated on the CSF. Patients failing fluconazole therapy should be treated with amphotericin. Repeated CSF CrAg is not indicated (positive for months).

ART should be started

- After the patient stabilizes to avoid severe IRIS,

Usually after 4 weeks of induction and consolidated treatment with amphotericin B–containing regimens combined with flucytosine or fluconazole.

	Opportunistic infection	
	Not suspected	Suspected OR Active
ART	Rapid ART Initiation (same day/ within a week time)	Delay Initiation *15 days to 6 weeks according to type of OI*
Investigation for OI	According to CD4 count	Yes, systematic
Prophylaxis	Immediate initiation, as follow	Initiation as follow while screening for OI
CPT	CD4<350/mm^3	CD4<350/mm^3 *High dose of Cotrimoxazole if suspicion of PCP / Toxoplasmosis*
IPT	All patients	All patients *ATT if suspicion of TB*
Fluconazole	CD4<100/mm^3 AND Positive blood Cryptococcal Ag	CD4<100/mm^3 AND Positive blood Cryptococcal Ag *Amphotericin B + Flucytosine if suspicion of Cryptococcal meningitis*

4. What to start - 1st Line of treatment?

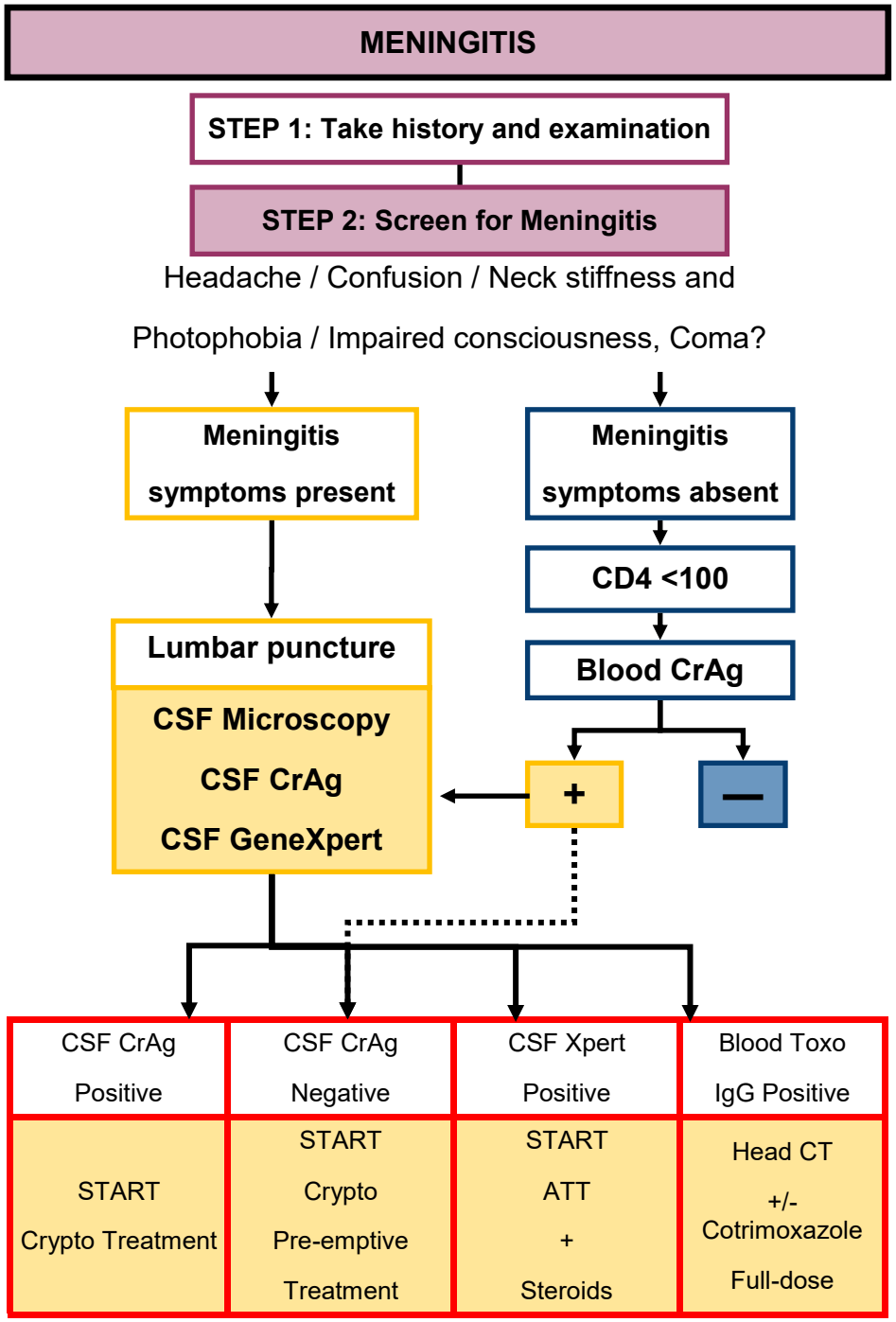
Except for some special conditions, the first line of treatment recommended is the same for adults, pregnant or breastfeeding women, and adolescents.

FIXED DOSE COMBINATION IN A SINGLE PILL		
TENOFOVIR (TDF)	**LAMIVUDINE (3TC) OR EMTRICITABINE (FTC)**	**EFAVIRENZ (EFV)**

5. TDF + 3TC/FTC + EFV toxicities?

3TC and FTC are less at risk of toxicities.

Efavirenz—EFV
Central nervous system toxicity (dizziness, insomnia, abnormal dreams) or Mental symptoms (anxiety, depression, mental confusion)
Convulsions
Hepatotoxicity
Hypersensitivity reaction, Stevens—Johnson
Drug interaction with Daclatasvir (HepC treatment)
Tenofovir—TDF
Chronic kidney disease Acute kidney injury Fanconi syndrome
Dicrease in bone mineral density
Lactic acidosis or severe hepatomegaly with steatosis



13. Cryptococcal Meningitis (CM)

Cryptococcal disease in HIV infected patients is caused by *Cryptococcus neoformans*, a yeast-like fungus.

The incidence of cryptococcal meningitis increases in patient with CD4 <100 cells/mm^3, and most cases occurs when CD4 <50 cells/mm^3.

Cryptococcal disease presentation in PLHIV, is:

- Sub-acute meningitis or meningo-encephalitis with
- Fever,
- Malaise,
- Headache,
- Neck stiffness and photophobia,
- Altered mental status/confusion,
- Personality changes, memory loss,
- Impaired consciousness and coma,
- Focal signs, including cranial nerve palsies.

Diagnosis relies on two components:

1- Blood cryptococcal antigen (Cr Ag): it has to be carried out in patient with CD4 <100 cells/mm^3 and no symptoms of CM.

2- CSF analysis after performing a lumbar puncture:

- CSF opening pressure (usually >200 mm H_2O)
- CSF CrAg (more sensitive than indian ink)
- Indian ink needs to be performed if CSF CrAg is not available
- Fungal culture if available

The screening algorithm for meningitis including cryptococcal meningitis is detailed on the next page.

6. Viral load and CD4 monitoring

CD4 count has to be carried out at baseline, at 6th month, at 12th month and every 6 months thereafter until virologicaly suppressed.

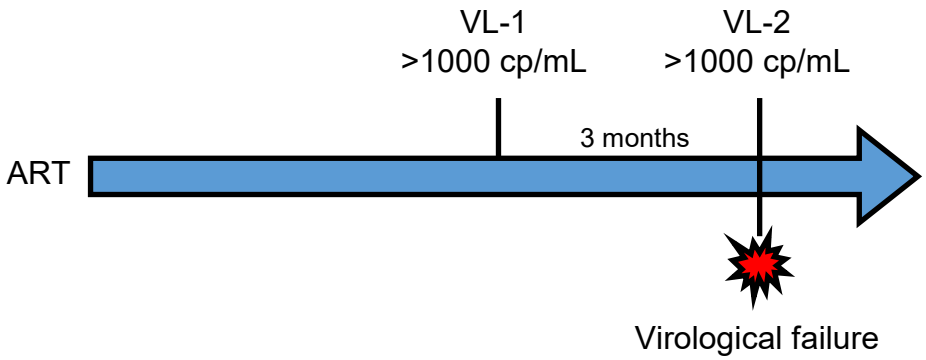
Viral load monitoring can be carried out at 6th month, at 12th month and every 12 months thereafter if the patient is undetectable.

7. Treatment / virological failure

HIV viral load is the preferred monitoring approach to diagnose and confirm treatment failure.

Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/mL measured on two different samples within a 3-months interval and at least 6 months after starting a new ART regimen.

In case of a first positive viral load: viral load as to be repeated 3-months after.



8. Second line of treatment

The second line of treatment is mostly based on protease-inhibitors (PI) containing regimen.

Active TB and Anti-Tuberculosis Treatment (ATT) intake can be a challenging situation will being on a PI-based regimen.

In case of ATT without Rifabutin available, Raltegravir-based regimen might be used.

The different options are displayed in the following table.

ART: second line	
Without ATT	Switch EFV to:
	Atazanavir / ritonavir — ATV / r Lopinavir / ritonavir — LPV / r
With ATT	Switch EFV to:
Rifabutin available	Atazanavir / ritonavir — ATV / r Lopinavir / ritonavir — LPV / r
Rifabutin not available	Raltegravir — RAL LPV / r, double dose *LPV 800mg/200mg twice daily*

The treatment of TE and PCP is detailed in the table below.

Pneumocystosis and Toxosplamosis **Induction therapy**	
Cotrimoxazole IV **TMP 15 to 20 mg/kg/day** **SMX 75 to 100 mg/kgday** *Given q6h or q8h* *Switch to PO after clinical improvement*	
Pneumocystosis	**Adjunctive Corticosteroids :(moderate to severe PCP) - PREDNISONE** - Day 1 to 5: 40 mg, PO, BID - Day 6 to 10: 40 mg, PO, QD - Day 11 to 21: 20mg, PO, QD **Induction duration = 21 days**
Toxoplasmosis	**Induction duration = at least 6 weeks** Followed by chronic maintenance therapy: ***TMP-SMX (****160 TMP/800 SMX)* ***DS 1 tablet BID 6 weeks*** *Until CD4>200 cells/mm^3 for more than 6 months after ART start. Then switch to CPT.*

In the absence of treatment, disease progression results in seizures, stupor, coma, and death.

Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can occur but are rare in patients with AIDS.

CT scan or MRI of the brain will typically show

- Multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia,
- Often with associated edema.

TE treatment is detailed on the next page.

Note that after induction phase, chronic maintenance therapy is necessary. It can be stopped in patients that have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increase in their CD4 counts to >200 cells/mm^3 after ART that is sustained for more than 6 months. After stopping chronic maintenance therapy, CPT must be introduced.

Induction therapy, 6 weeks
Cotrimoxazole IV
TMP 15 to 20 mg/kg/day + SMX 75 to 100 mg/kgday
Given q6h or q8h
Switch to PO after clinical improvement
Chronic maintenance therapy, usually 6 weeks
TMP-SMX (160 TMP/800 SMX) **DS 1 tablet BID**
CPT
TMP-SMX (160 TMP/800 SMX) **DS 1 tablet daily**

9. Prophylaxis and Pre-emptive therapies

OIs are the most important cause of morbidity and mortality in PLHIV.

Cotrimoxazole (TMP/SMX) prophylaxis is effective against common bacterial infections, diarrhoea (including *Isospora belli*), Malaria, Toxoplamosis (primary or recurrent), Pneumocystis pneumonia (PCP, primary or recurrent). In case of intolerance, Dapsone or desensitization to TMP/SMX might be used.

CD4<350/mm3 ± **WHO stage** + **No suspicion**

Isoniazid Preventive Therapy (IPT) is used in individuals with latent TB infection, regardless of CD4 count or ART status. After screening and exclusion for active TB, IPT should be proposed to all patients for 6 months.

All patients + **No suspicion**

Fluconazole is a drug of choice for treatment of candidiasis and pre-emptive therapy of cryptococcal meningitis. It should be proposed in all patients with CD4 count <100/mm^3 with positive blood cryptococcocal antigen (Cr Ag) after excluding positivity of Cr Ag in the cerebro spinal fluid (CSF).

CD4<100/mm3 + **Blood CrAg positive** + **CSF CrAg negative**

Preventive and pre-emptive therapies dosasges are summarized in the following table

Preventive / Pre-emptive therapies dosages	
Cotrimoxazole (TMP/SMX) • CD4 <350 cells/mm^3 • WHO stage 3 / 4	*One DS tablet* (160TMP/800SMX) per day ———————— *Two SS tablets* (80TMP/400SMX) per day
Continue until evidence of stable on ART with evidence of immune recovery and viral suppression	
IPT • Isoniazid • Vitamin B6 (Pyridoxine)	*For 6 months:* • 300mg per day • 25mg per day
Avoid IPT if liver disease, active alcohol use, jaundice, habitual treatment defaulter, prior Isoniazid resistance, peripheral neuropathy.	
Fluconazole (cryptococcal pre-emptive)	*Initial:* 800mg per day for 2 weeks, 400mg per day for 8 weeks, *Maintenance:* 200mg per day
Continue for at least one year: • If no viral load monitoring: until CD4≥200 cell/mm3, two times 6 months apart. • If viral load monitoring: until CD4≥100 cell/mm3, two times 6 months apart, AND viral suppressed viral load.	

TMP/SMX is the treatment of choice for PCP. Patients with moderate-to-severe PCP should received corticosteroids as early as possible. It is detailed in the table of treatment recommended for PCP and Toxoplasmosis.

ART initiation: within 2 weeks of PCP diagnosis and treatment.

Secondary PCP prophylaxis with TMP/SMX should be initiated immediatly upon successful completion of therapy.

12. Toxoplasmic encephalitis (TE)

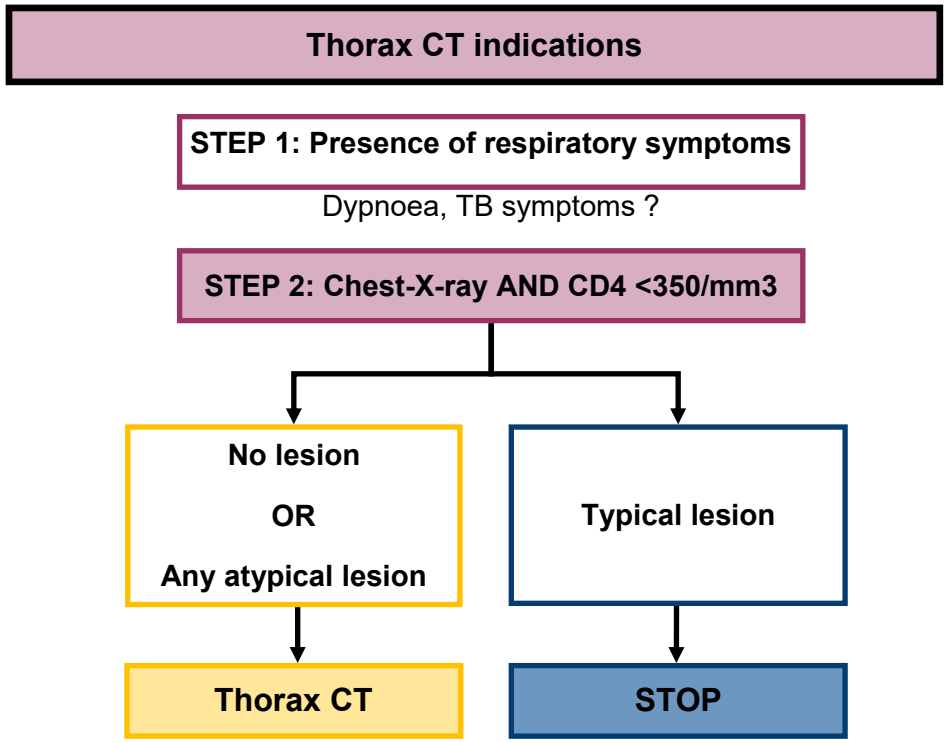
A low incidence of toxoplasmosis is seen in patients who are seronegative for *T. gondii*. Most Toxoplasmosis cases are reactivation of latent disease in individuals seropositive for *T. gondii*. Clinical disease is rare among patients with CD4 cell counts >200 cells/mm^3.

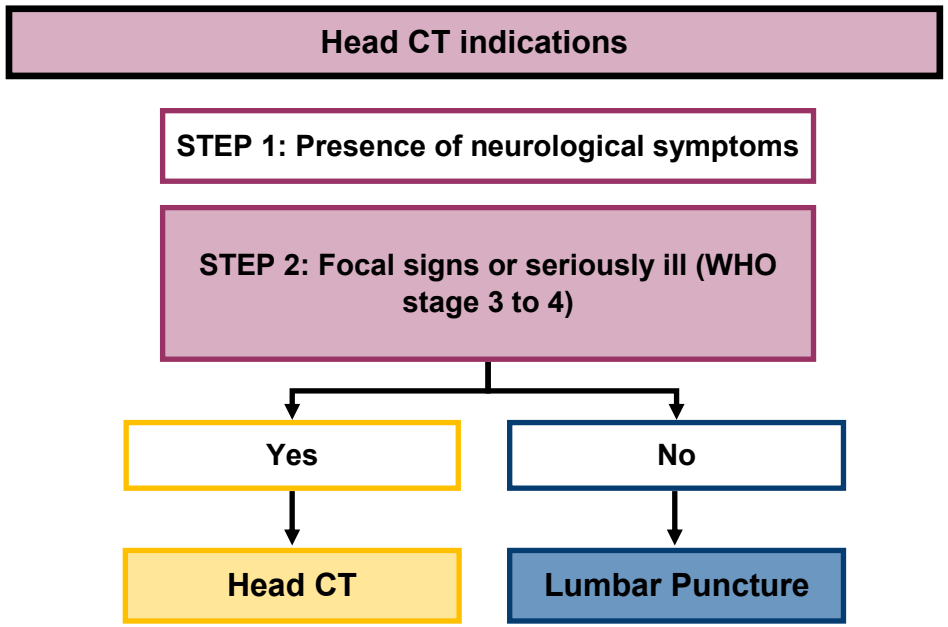
Clinical presentation of *T. gondii* infection is:
- Focal encephalitis with headache,
- Confusion, or motor weakness
- Fever

Patients may also present with non-focal manifestations, including:
- Non-specific headache
- Psychiatric symptoms.

TE diagnosis is often presumptive and requires 3 conditions:

Positive *T. gondii* IgG + **Compatible Clinical symptoms** + **Compatible Imaging**





10. Active Tuberculosis (TB)

All patients with active TB should be initiated on ATT immediatly.

ART should be started regardless of CD4 count, even in patients with drug-resistant TB.

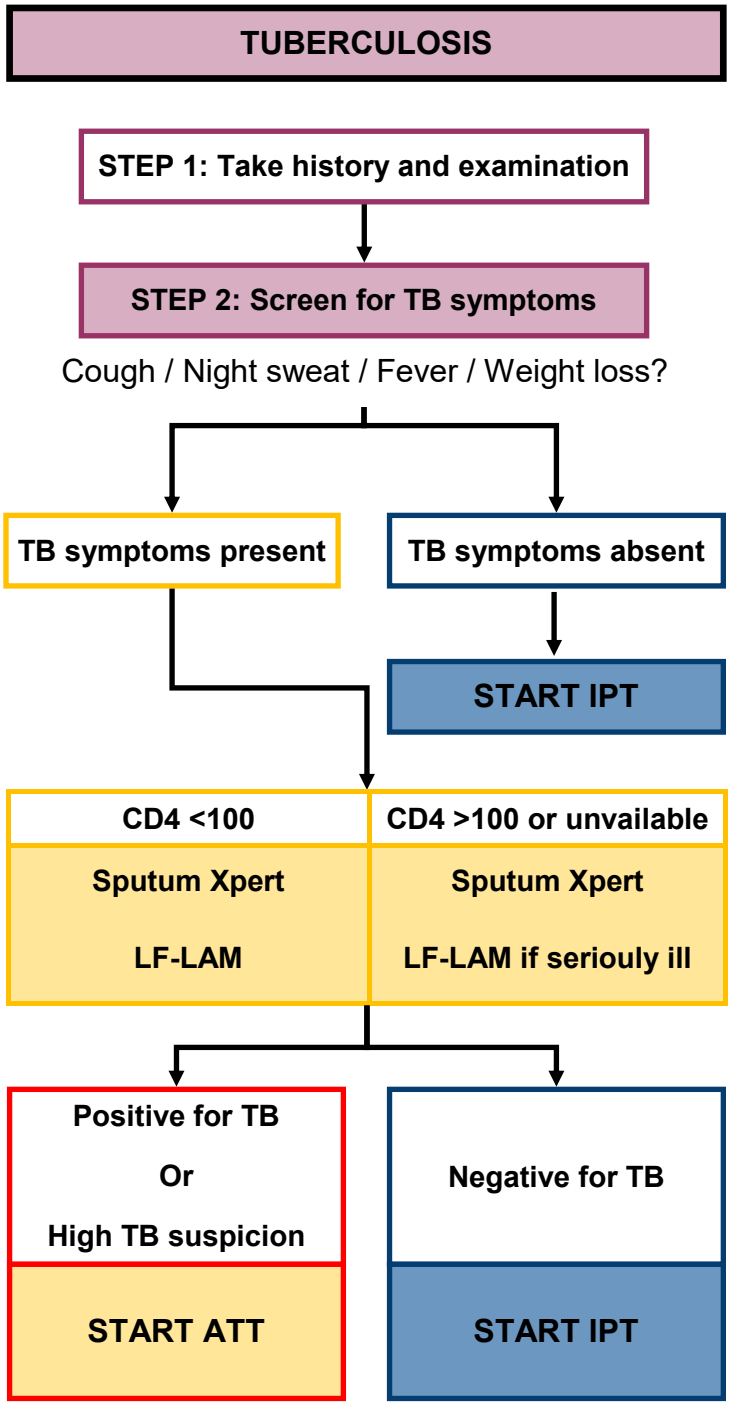
ATT should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (**2 weeks if CD4<50 cells**).

IRIS may occur after initiation of ART. Both ART and ATT should be continued while managing IRIS (Cf. IRIS part)

Tuberculosis screening algorithm is available on next page.

Hepatotoxicity is frequent during ATT and has to be managed as follow:

Transaminases x ULN	No symptoms	Symptoms (nausea, vomiting, abdominal pain, jaundice)
1.25 to 2.5 (grade 1)	No change	No change
2.5 to 5 (grade 2)	• Continue ATT • Check ALT at next visit	Discontinue ATT
5 to 10 (grade 3)	Discontinue ATT	Discontinue: • ATT • EFV or RAL • Cotrimoxazole
> 10 (grade 4)	Discontinue all drugs	Discontinue all drugs



11. Pneumocystis Pneumonia (PCP)

The most common clinical manifestations of PCP are

- Subacute onset of progressive dyspnea
- Fever,
- Non-productive cough,
- and chest discomfort that worsens within days to weeks.

Hypoxemia, can range from

	Mild	Moderate	Severe
PaO2	>70 mmHg		<45 mmHg
SpO2	>90%		

Chest radiograph:

- Diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern.
- Chest-X-ray may be normal in patients with early disease.

Thin-section computed tomography (CT) is a useful adjunctive test, since CT scan will be abnormal, demonstrating “ground-glass” attenuation that may be patchy, while a normal CT has a high negative predictive value.

Additional diagnostic tests are listed below:

Thorax CT-scan	Very sensitive High negative predictive value
Induced sputum	50 to 90%
Bronchoalveolar lavage (BAL)	90 to 99%
LDH dosage	Expected to be >500 UI

Additional monitoring is required for patients experiencing Hepatotoxicity. The following table presents the additional measures requested according to the severity of the Hepatotoxicity:

Grade 1	Check drug dosage according to patient weight
Grade 2	
Grade 3 5 to 10 x ULN	If EFV is discontinued: Continue TDF and 3TC for 2 weeks. Check ALT weekly. When ALT <2.5 and symtoms resolves: Re-introduce drugs as in the following table.
Grade 4 > 10 x ULN	Check ALT twice a week

For patient experiencing Grade 3+ Hepatotoxicity we recommend to comply with the scheme presented in the following page and summarizing how to reintroduce ATT, ARV and CPT.

	Week 1	Week 2	Week 3	Week 4	Week 5
Ethambutol	15-20mg/kg	15-20mg/kg	15-20mg/kg	15-20mg/kg	15-20mg/kg
Rifampicin	10mg/kg	10mg/kg	10mg/kg	10mg/kg	10mg/kg
Isoniazide		5mg/kg	5mg/kg	5mg/kg	5mg/kg
Pyrazinamide			(25-35mg/kg)*	(25-35mg/kg)*	(25-35mg/kg)*
TDF-3TC	Stop after Week 1			300/300mg	300/300mg
EFV or RAL				600 QD (EFV)	600 QD (EFV)
TMP/SMX					Reintroduce

*** Do not reintroduce Pyrazinamide in case of Grade 4 hepatotoxicity.**