TB Comorbidities

Several medical conditions are risk factors for TB and poor TB treatment outcomes. Similarly, TB can complicate course of some diseases. It is therefore important to identify these comorbidities in people diagnosed with TB in order to ensure early diagnosis and improved outcome. When these conditions are highly prevalent in the general population they can be important contributors to the TB burden. Consequently, reducing the prevalence of these conditions can help prevent TB. TB share underlying social determinants with many of these conditions. Addressing the social determinants of health is a shared responsibility across disease programmes and other stakeholders within and beyond the health sector.

TB and HIV

The primary impact of HIV on TB is that the risk of developing TB becomes higher in patients with HIV. Overall, HIV-infected persons have approximately an 8-times greater risk of TB than persons without HIV infection. The risk of TB in HIV-infected persons continues to increase as HIV disease progresses and CD4 cell count decreases. While anti-retroviral treatment can substantially decrease the risk of TB, this risk always remains higher than that in HIV negative individuals. Furthermore, among cured TB survivors with HIV infection, the risk of recurrent TB is also quite high.

Similarly, Tuberculosis is the most common opportunistic infection amongst HIV-infected individuals. It is a major cause of mortality among patients with HIV and poses a risk throughout the course of HIV disease.

The presentation of TB in the HIV-infected patient may vary with degree of immune suppression. The diagnosis of TB in PLHIV can be more difficult and may be confused with other pulmonary or systemic infections. As the HIV disease progresses and the individual become more immune-compromised, the clinical presentation is proportionately more likely to be extra-pulmonary or smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality.

It is estimated that there are 2.1 million people living with HIV in India with an estimated adult HIV prevalence of 0.27% (range: 0.2%–0.4%).TB accounts for 25% of deaths among People Living with HIV and AIDS (PLHIV) in India. Although only 5% of incident TB patients are HIV-infected, in absolute terms it means more than 100,000 cases annually, ranks second in the world and accounts for about 10% of the global burden of HIV-associated TB. HIV positivity among PLHIV varies from states /districts in the country, the proportion of HIV positive among TB patients over 10% in high HIV burden states to up to 40% in some high burden districts.

NACP and RNTCP Coordination in India:

To mitigate the effect of dual burden of HIV and TB co-infection, the ministry of Health and Family Welfare, Government of India through its NACO and Central TB Division (Department of Health and Family Welfare) has been undertaking joint collaborative efforts since 2001. While joint HIV/TB activities started with differential strategies based on underlying HIV burden initially, the programme evolved over the years and currently implements uniform HIV/TB collaborative activities across the country. NACP and RNTCP have developed a policy of HIV/TB collaborative interventions based on experience gained during programme implementation in initial years.

The mechanism for collaboration includes coordinated service delivery at field level, and oversight and advisory groups at the district level in the form District Coordination Committee chaired by District Collector. At the state level, a similar mechanism exists in the form of the State Technical Working Group chaired by Director Health Services and State Coordination Committee chaired by Principle Secretary Health. At the National level, TB-HIV coordination committee chaired by Additional Secretary, National AIDS Control Organization [NACO] and technical working group [NTWG] chaired by DDG regularly monitor and provide suggestions on key policy matters related to TB/HIV Collaborative activities. To enable effective coordination, joint trainings, standard recording and reporting, joint monitoring and evaluation and operational research are strategically implemented.

Milestones of TB-HIV collaborative activities in India

- 2001- Basic HIV/TB activities started in six high-HIV burden states.
- 2003 - Pilot for HIV-TB cross-referral in four districts of Maharashtra.
    - Cross-referral started in six HIV high prevalence states.
- 2004 - Cross referral of activities expanded to eight additional states.
- 2005 - Joint training modules developed, joint surveillance initiated.
- 2007- Pilot for Routine referral of TB patients for HIV testing and CPT.
    - National (policy) framework for TB/HIV developed.
- 2008 - National Framework revised.
    - All-India implementation of HIV-TB activities.
    - Intensified Package (IP) rolled out in nine states.
- 2009 - National Framework revised.
    - Intensified Package rolled out in eight more states.
    - Uniform activities at ART centers and ICTCs nationwide for intensified TB case finding and reporting, established.
- 2010 - Intensified package launched in 11 states.
- 2012 - Nationwide coverage achieved.
- 2013 - National Framework for HIV/TB collaborative activities in India developed

National Framework for HIV/TB in India:

Latest revision of National Framework Nov 2013 aimed to incorporate recent policy updates in NACP and RNTCP and align with respective national strategic plan for next 5 year along with recommendations in WHO HIV/TB policy guidelines 2011

The salient features are as below.

1. Emphasis on Integrated TB and HIV services e.g. HIV screening at RNTCP DMC.

2. Focus on early detection and early care:

   a. Early detection of TB in PLHIV:
      i. Early suspicion of TB–symptoms of any duration among PLHIV
      ii. Use of an expanded clinical algorithm for TB screening that relies on presence of four clinical symptoms (current cough, weight loss, fever or night sweats) instead of only cough, to identify patients with presumptive TB
      iii. Strengthen ICF at ART, Link ART centre (LAC) and Targeted intervention projects (TI) for High Risk Group (HRG) specially Injection Drug Users (IDU)
      iv. Offering upfront CBNAAT among presumptive TB cases among PLHIV
      v. Early detection HIV/TB

   b. Enhance HIV testing facilities in settings with lack of co-located HIV and TB testing facilities, by establishing HIV screening services using whole blood finger prick test (WBT)
      i. Strengthen HIV testing of TB patients in high HIV prevalent settings by promoting establishment of Facility Integrated Counselling and Testing Centre(F-ICTC) where DMC exists
      ii. PITCamong patients being evaluated by diagnostic smear microscopy presumptive TB cases in high HIV prevalent settings

   c. Early Care:
      i. Promotion of 'single window delivery services' where in all HIV/TB patients get their TB medications from the ART centres along with ART drugs.
      ii. Strengthened linkage of HIV/TB patients to ART centres through travel support by RNTCP as per NSP (2012-2017) etc.
      iii. ART for HIV infected TB cases irrespective of CD4 count
      iv. Prompt ART initiation- within first 8 weeks of commencing Anti-TB treatment.
      v. Monitoring of timeliness of ART initiation through expanded ART reporting formats

3. Early detection and care of HIV infected Drug Resistant TB patients (DR-TB/HIV):
      i. Strengthen HIV testing in presumptive DR-TB cases (Criteria C)
      ii. Ensure access to culture and drug susceptibility testing for HIV infected TB patients
      iii. Prompt linkage of HIV infected DR-TB cases to ART centres
      iv. Prompt initiation of ART in HIV infected DR-TB cases

4. Prevention of TB among HIV infected adults and children:
      i. Implementation of IPT for all PLHIV (On ART + Pre-ART)
      ii. Strengthen implementation of air borne infection control strategies.

5. Strengthen HIV/TB activities among children and pregnant women

6. Promotion of participation of private, NGO, CBO health facilities and affected communities working with NACP and RNTCP to strengthen HIV/TB collaborative activities.

HIV Screening for TB Patients / Presumptive TB cases-

1. Presumptive / Diagnosed TB patients coming to the ICTCs will be offered counselling and testing as per the norms and standard operating procedures of the National AIDS Control Programme (NACP).
2. All referrals will be recorded in the ICTC counselling register as referrals from RNTCP
3. For patients with HIV positive results, the counselor will link the patient to the nearest ART centre available in the district/state .This will be done by giving a referral form and explaining the patient on how to access the centre. The patient will be given the contact details of the district programme managers for any assistance needed
4. The counsellor will document the HIV status, date of HIV testing and PID number in the RNTCP laboratory form as a feedback to LT of DMC. The counselor will also assist the DMC LT to update the laboratory register with information on HIV status.

Intensified TB case finding (ICF) at ICTCs, ART and Community Support Centres (CSCs)
Intensified TB case finding at HIV care settings is an important strategy for early diagnosis of TB among PLHIV.

ICF at ICTCs
All ICTC clients should be screened by ICTC counsellors for presence of TB symptoms at every encounter (pre, post, or follow-up counselling). Clients who have symptoms or signs, irrespective of their HIV status, should be referred to RNTCP diagnostic and treatment facility located in same institution. Therefore, NACP and RNTCP promote establishing co-located facilities, for better coordination between the two programmes. Hence, as network of HIV testing facilities is being expanded, consideration should be given to establish them at sites, which already have RNTCP, designated microscopy centres (DMC).

The referrals of presumptive TB cases from ICTCs to TB diagnosis facility should be recorded on a line list (**Annexure 12A)** to facilitate exchange of information with RNTCP and track the client through the process of TB diagnosis and initiation of TB treatment. To streamline this process further RNTCP programme staff should stay in touch with ICTC counsellors to complete the exchange of information in time. In addition, ICTC counsellors and RNTCP programme staff participate in monthly HIV/TB coordination meeting at district level to validate line-lists and Monthly HIV/TB reports (**Annexure 12B**) and resolve operational issues if any.

ICF at ART Centres
HIV-infected persons attending ART centres for pre-ART registration have a high prevalence of TB disease (6 to 8%). The incidence of TB among ART clients is also very high, even when on ART. Although ART reduces risk of incident TB, it remains many times higher compared to general population. In addition, HIV-infected clients having undiagnosed or untreated TB may seek care at ART centres and thus exposing other HIV-infected persons to the risk of acquiring TB. Therefore active efforts for intensified TB case finding (ICF) at ART centres is critical for early suspicion and detection of TB, linkage to treatment and thus for prevention of transmission of infection to other clients. The national ART guidelines clearly state that all patients coming to ART centres should be actively screened for opportunistic infections, particularly tuberculosis. All people living with HIV should be regularly screened for four symptoms viz., current cough of any duration, fever of any duration, significant weight loss or drenching night sweats, during every visit to a health facility and every contact with a health-care provider. Those with history of coughing blood and sputum and with any pulmonary abnormality in chest X-ray should also be evaluated for TB. Similarly, children living with HIV who have one or more of the following symptoms – failure to thrive, fever or cough of any duration or history of contact with a TB patient should be evaluated for TB.

Screening for TB is important regardless of whether the PLHIV is receiving IPT or ART. The presumptive TB cases identified at ART centres or Link ART centres should be prioritized and "fast-tracked" for evaluation by SMO/MO to minimize opportunities for airborne transmission of infection to other PLHIV.

PLHIVs suspected to have TB by MO, should be subjected to testing of sputum / appropriate specimen from a relevant extra-pulmonary site by CBNAAT at the nearest facility. CBNAAT is the frontline test for diagnosis of TB among PLHIV. If CBNAAT is not available, arrangements have to be made for collection and transportation of sputum specimen to the nearest CBNAAT site. If CBNAAT linkage is not available, then the patient should be evaluated with microscopy and Chest-X ray on the same day.

Clinically dignosed TB and extra pulmonary TB is more common among people living with HIV and therefore a high level of suspicion is required. In the event of suspicion of Extra Pulmonary TB, the diagnostic algorithm as for HIV negative presumptive EPTB patients may be followed. Similarly, refer to diagnostic algorithm for paediatric pulmonary TB.

Preferably, PLHIVs should be offered TB and HIV diagnostic facility at the same premises as a "one-stop service" in order to reduce diagnostic delay and to link those not having any of the four symptom complex to IPT services.

In addition, the referrals presumptive TB cases should be recorded on an ART centre TB-HIV line list (**Annexure 13 A**) to facilitate coordination with RNTCP programme staff and to track the patient closely through the process of TB diagnosis and TB treatment initiation. It is also crucial that ART Centre staff members attend monthly HIV/TB coordination meeting. The HIV/TB monthly reporting format to be generated at ART centres is incorporated into the ART centre monthly report (CMIS) (**Annexure 13 B**).

Information of all HIV infected TB patients in HIV care should be recorded in the ART centre HIV/TB register (**Annexure 13 C**). These include TB patients detected by ART centre staff as well as those TB patients found HIV infected while on TB treatment and referred to ART centre by the RNTCP. TB-HIV register is an important monitoring tool to track timeliness of initiation of CPT and ART the TB treatment outcome to modify ARV regimens as per guidelines. It is also important that ART centre staff carry this register when they attend monthly HIV/TB coordination meeting to update information on TB treatment outcome from RNTCP staff and share information pertaining to CPT and ART with them for recording into RNTCP TB registers.
PLHIV diagnosed to be suffering from TB are presumptive MDR cases and need to follow the algorithm for diagnosis of drug resistant TB (Refer Section 5).

ICF at Link ART Centres (LAC)
The ICF activity is also implemented at all Link ART plus and Link ART centres in the country. As in ART centres LAC-Plus and LAC should 1) implement ICF using symptom screening on every encounter 2) promptly refer presumptive TB case to RNTCP diagnostic facilities, and 3) refer the patient to ART centre promptly if TB is detected for initiation of ART or modify current ARV regimen. Similar to ART centre, the LAC staff nurse /counsellor should maintain line-list, exchange with local RNTCP staff to seek information on TB diagnosis and treatment and complete the line-list.

The LAC Plus use same line-list format as the ART centre **(Annexure 13 A)** while at LAC the ICTC line-list format is used (since ICTC counsellor runs the LAC) **(Annexure 12A)**. The completed line-list from LAC-plus is merged with ART centre line-list whereas that from LAC is merged into ICTC line-list for the same period and monthly report is generated accordingly. These mechanisms are designed considering operational feasibility but key point is if TB is detected among patients at LAC plus of LAC, they **must be promptly referred to ART centre** for further management.

ICF among HIV high risk groups (HRG)

Operational research conducted in high HIV prevalent states have shown that HRG's like female sex workers (FSW), men having sex with men (MSM), injection drug users (IDU) etc. are more likely to have tuberculosis compared to general population. In addition, it is known that HIV prevalence among the HRG is several times higher than general population. While NACP provides HIV prevention interventions for the HRG through its targeted interventions, the ICF provides an opportunity to provide additional services to this population. This intervention is likely to help in detection HIV/TB cases early and link to care support and treatment. Among the HRG's, IDU have highest HIV prevalence therefore the programmes aim to provide ICF services and prompt linkage to care support and treatment to IDU as a priority.

ICF at Care and support centres:

TB symptom screening based on 4 symptom complex should also be done by counsellors and outreach workers at Care and support centre in collaboration with SACS.

Treatment of HIV-infected TB

Early diagnosis and effective treatment of TB among HIV-infected patients are critical for controlling the disease and minimizing the adverse impact of TB on the course of HIV. Hence, initiation of treatment is very important soon after the diagnosis of TB. Among HIV-infected persons, treatment of TB is same as that in the HIV-negative TB patients.

Anti-TB Treatment of HIV infected TB patients:

- Based on the clinical history and investigation reports ART MO will categorize patients as Rifampicin sensitive/ rifampicin sensitivity status not known/ clinically diagnosed TB cases, prior history of taking Anti-TB drugs (Cat I /Cat II) accordingly and initiate daily anti TB treatment in Fixed Dosage Combination as per RNTCP guidelines at ART Centre itself.

- All HIV-infected TB patients if not tested already should be tested for drug susceptibility before initiation of treatment. Staff nurse will refer the patient to the nearest drug resistant TB centre in coordination with to RNTCP and record the same in the line list as DRTB /Rif resistant patient. PLHIV with drug resistant TB should be managed by DR-TB center in consultation with ART centre.

- The STS of TU where ART Centre / CBNAAT site is located (nodal TU) will link the patient to the concerned TU based on the residence of the patient for TB treatment provision and follow up as per RNTCP guidelines. STS (nodal TU) will also be responsible to get the registration details from the concerned TU. Overall

- Responsibility of this linkage and coordination lies with District HIV –TB and PMDT coordinator.

- TB patients living with HIV infection should receive the same duration of TB treatment with daily regimen as HIV-negative TB patients.

- If drug sensitive TB patient and on second line ART, Rifampicin should be replaced with Rifabutin 300 mg three times a week or 150 mg daily.

- TB Treatment card for these patients will be prepared by staff nurse in duplicate and will be duly signed by medical officer. One copy of the TB treatment card is to be handed over to the patient. Patient will be registered , allotted TB Number and Nikshay ID by STS of the concerned TU as per the RNTCP guidelines within one month and nodal TU will be informed

- Pharmacist will maintain the inventory of stocks of Anti-TB drugs at ART centre. District HIV-TB and PMDT coordinator should ensure availability of adequate stock of Anti-TB drug and logistics in coordination with ART centre, District TB Officer ,District Drug store pharmacist.

- RNTCP will identify local treatment supporter for all HIV –TB co-infected patients. Anti TB treatment will be supervised by the local treatment supporter and any adverse drug reactions should be informed immediately to local medical officer at PHI and ART medical officer.

- Regular follow up of the patients, testing for sputum as per RNTCP Guidelines and adherence to ATT & ART treatment is to be ensured by the treatment supporter, STS, STLS, ART MO. ART Counsellor should ensure proper counselling in all the HIV-TB co-infected patients regarding adherence and possible side effects to ART and ATT.

- A mechanism of ensuring and checking adherence has been instituted by sending a missed call by patient to pre-printed phone numbers hidden behind selected pills after taking dose. As the sequence of hidden numbers cannot be predicted by patients, but are known by the system for each month of medication prescribed, the system offers high confidence that patients who respond correctly have indeed taken their medication.

- PLHIV with drug resistant TB should be managed by DR-TB center in consultation with ART centre. The treatment of HIV positive individual with MDR-TB is the same as for HIV negative patients. However treatment is more difficult and adverse events more common. Due to the increased frequency of adverse drug events, rigorous monitoring in this particular group of patients is required in order to ensure adherence to treatment, early identification and treatment of adverse events and reduce lost to follow up.

Anti-retroviral therapy and co-trimoxazole prophylactic therapy in HIV infected TB patients:

In addition to TB treatment, all HIV-infected TB patients must be provided access to care and support for HIV disease, including co-trimoxozole preventive therapy and antiretroviral therapy. ART reduces TB case fatality rates and the risk of recurrent TB. Co-trimaxazole preventative therapy has been shown to reduce mortality among PLHIV by preventing opportunistic infections.

- **Anti-retroviral therapy** must be offered to all patients with HIV and TB as well as drug-resistant TB, irrespective of CD4 cell-count, as early as possible (after 2 weeks) following initiation of anti-TB treatment. Appropriate arrangements for access to anti-retroviral drugs should be made for patients. However, initiation of treatment for TB should not be delayed.

Table: Initiation of first-line ART in relation to anti-TB therapy

Clinical staging	CD4 cell count (cells/mm3)	Timing of ART in relation to initiation of TB treatment	ART Recommendations
Start ART irrespective of any clinical stage	CD4 count of any value	• Start ATT first • Start ART as soon as TB treatment is tolerated(between2 weeks and 2 months)	Start ART Regimen TLE for patients not on ART. Forpatients already on 1st line ART, ZLN,shift to ZLE & continue ZLE even after ATT is stopped.
Rationale for ART recommendation during TB treatment : In the absence of ART, TB therapy alone does not significantly increase the CD4 cell count. Nor does it significantly decrease the HIV viral load. Thus, CD4 counts measured during active TB are likely to reflect the actual level of immune suppression The use of HAART in patients with TB can lead to a sustained reduction in the HIV viral load. It can also facilitate immunological reconstitution, and decrease AIDS-defining illness and mortality. This benefit is seen across different ranges of CD4 counts			

**The use of the standard 600mg/day dose of EFV is recommended for patients receiving EFV and Rifampicin.*
**In women of child-bearing age, the use of contraceptives should be ascertained because of drug reaction, as and when NNRTIs and Rifampicin are being used*
**Special Attention to be paid for monitoring hepatotoxicity*

Immune reconstitution inflammatory syndrome (IRIS)may occur in up to one-third of patients who have been diagnosed with TB and who have started ART. It typically presents within three months of the initiation of ART but can occur as early as five days. Patients with TB-associated IRIS most commonly present with fever and worsening of pre-existing lymphadenopathy or respiratory disease. The symptoms are similar to the paradoxical reactions seen in immuno-competent patients on ATT, but occur more frequently. Most cases resolve without any intervention and ART can be safely continued. Serious reactions, such as tracheal compression caused by massive adenopathy or respiratory difficulty, may occur. Therapy may require the use of corticosteroids.

First Line ART for HIV-TB

TENOFOVIR 300mg + LAMIVUDINE 300 mg + EFAVIRENZ 600 mg (FDC)		
Regimen	Tenofovir + Lamivudine + Efavirenz	All new co-infected patients should be initiated on FDC of TLE single pill based regimen irrespective of HB level/ CD4 count. Those patients who are already on ART on ZLN regimen at the time of TB diagnosis need to be changed to regimen ZL+E at the initiation of ATT due to interaction of ATT & NVP. Such patients will not be changed from EVF to NVP after ATT is completed and will continue on ZLE regimen. There is no change of regimen for patients who are already on ZLE at the time of TB diagnosis & treatment

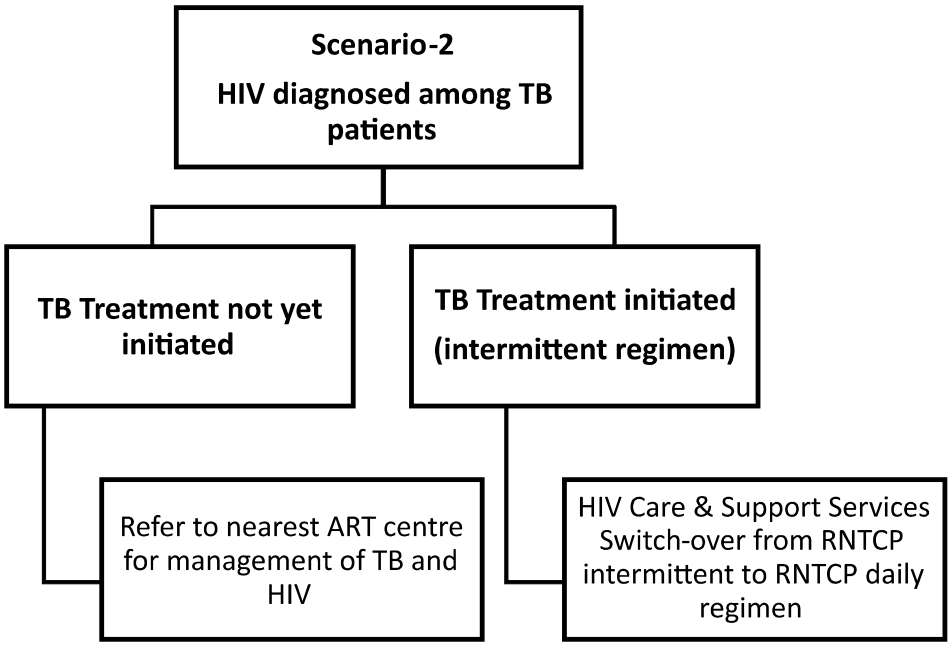
Second Line ART for HIV-TB:
The following regimens are available under the National Programme currently for second line ART:
Tenofovir + Lamivudine + PI (Atazanavir / ritonavir or Lopinavir / Ritonavir)
Zidovudine + Lamivuidne+ PI (Atazanavir / ritonavir or Lopinavir / Ritonavir)
Stavudine+ Lamivudine + PI (Atazanavir / ritonavir or Lopinavir / Ritonavir)
Abacavir+ Lamivudine+ PI (Atazanavir / ritonavir or Lopinavir / Ritonavir)
Rifampicin alters the metabolism of Protease Inhibitors, including Atazanavir and Ritonavir and reduces their effectiveness in standard doses

Initiating ART (Anti-Retroviral Therapy) in patients with DR- TB

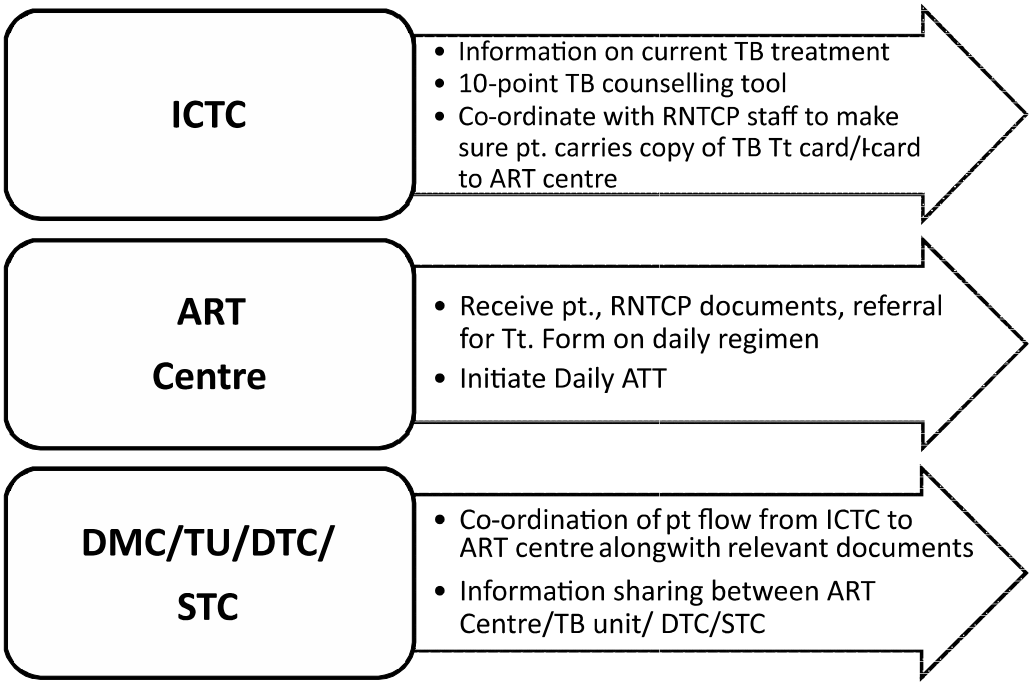
- The use of ART in HIV infected patients with TB improves survival for both drug resistant and susceptible disease. However HIV infected MDR patients without the benefit of ART may experience mortality rates exceeding 90%. The likelihood of adverse effects could compromise the treatment of HIV or MDR TB if both treatments are started simultaneously. On the other hand undue delay in starting ART could result in significant risk of HIV related death amongst MDR patients.
- For patients who are already on ART at the time of DR-TB diagnosis be continued on ART when MDR-TB therapy is initiated. Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs or radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medication (IRIS Syndrome).

Timing of referral to ART Centre

The following algorithm can be followed.



switch over from intermittent to daily regimen steps



- Patients who are not yet on ART should be provided with a referral to the ART centre immediately on identification as an HIV-infected TB patient. However, these patients (especially microbiologically confirmed pulmonary TB) should be counselled to attend the ART centre after at-least 2 weeks of anti-TB treatment have been completed, so that the risk of TB transmission to others is lessened.