# HIV & TUBERCULOSIS

# TREATMENT, PREVENTION AND CONTROL

# Important differences in Treatment of patients with TB when coinfected with HIV

Treatment of TB in presence of HIV infection is essentially the same as in patients without HIV infection with the following exceptions:

- Once weekly INH-RIF in continuation phase should not be used in any HIV infected patient.
- Twice weekly INH-RIF or Rifabutin should not be used when CD4 count < 100/mm3
- Paradoxical reactions are more common.
- Potential for drug interactions between rifamycins and antiretrovirals.

# TB DRUG INTERACTION AND ABSORPTION

- Coadministration of rifabutin with ritonavir, hard-gel squinavir or delavirdine is contraindicated.

- Use of Rifampicin is contraindicated with Protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

- Rifampicin can be used with PIs & NNRTIs in only three situations when the regimen includes
  - Efavirenz + 2 NRTIs
  - Ritonavir + one or more NRTIs
  - Two protease inhibitors (Ritonavir + Saquinavir – hard gel or soft gel)

- Start PIs or NNRTIs atleast 2 weeks after the date of last dose of RIF.

MMWR, Vol.49, No.9, pp185, 2000

# TB DRUG INTERACTION AND ABSORPTION

- Rifabutin is less potent inducer than RIF. It can be used concurrently with PIs and NNRTIs with dose adjustments.

- Rifamycins have drug interactions with other medications used by HIV patients such as hormonal contraceptives, ketoconazole, corticosteroids, anticoagulants, etc.

- Malabsorption of Anti-TB drugs reported in HIV infection results in TB Treatment failures and drug resistant TB.

- INH, EMB, PZA & SM can be used with Antiretroviral therapy without dose modification.

MMWR, Vol.47, RR-20, 1998

# Recommended doses of Rifabutin & ARV drugs in combined therapy

| ARV Regimen | Rifabutin Dose | ARV Dose adjustment |
|---|---|---|
| ***Protease Inhibitor regimens:*** | | |
| Nelfinavir, Indinavir or amprenavir (+2 nucleosides) | RIB 150 mg (daily) 300 mg (Intermittent) | Nelfinavir 1250 mg 12 hourly Indinavir 1000 mg 8 hrly |
| Saquinavir (+2 nucleosides) | RIB 300 mg daily or intermittent | 1600 mg 8 hrly |
| Ritonavir (+2 nucleosides, other PIs, and or NNRTIs) | RIB 150 mg twice weekly | None |
| Lopinavir / ritonavir (+2NRTIs/ an NNRTI) | RIB 150 mg twice weekly | None |

AJRCCM,. Vol 164, pp 7-12, 2001

# Treatment recommendations for patients coinfected with HIV & TB in low resource settings

| Situation | Recommended Treatment |
|---|---|
| Pulmonary TB &<br>CD4 count < 50/mm3 or<br>Extrapulmonary TB | One of following regime started as soon as tolerated: ZDV/3TC/EFZ<br>ZDV/3TC/SQV/r<br>ZDV/3TC/NVP |
| Pulmonary TB &<br>CD4 count 50-200/mm3 or<br>Extrapulmonary TB | One of following regimens started after 2 months of anti TB treatment:<br>ZDV/3TC/EFZ<br>ZDV/3TC/SQV/r<br>ZDV/3TC/NVP |
| Pulmonary TB &<br>CD4 count > 500/mm3 or<br>total lymphocyte count > 1200/mm3 | TB is treated as per the DOTS strategy. CD4 counts monitored. |

Indian J Tuberc 2004; 51; 5-16

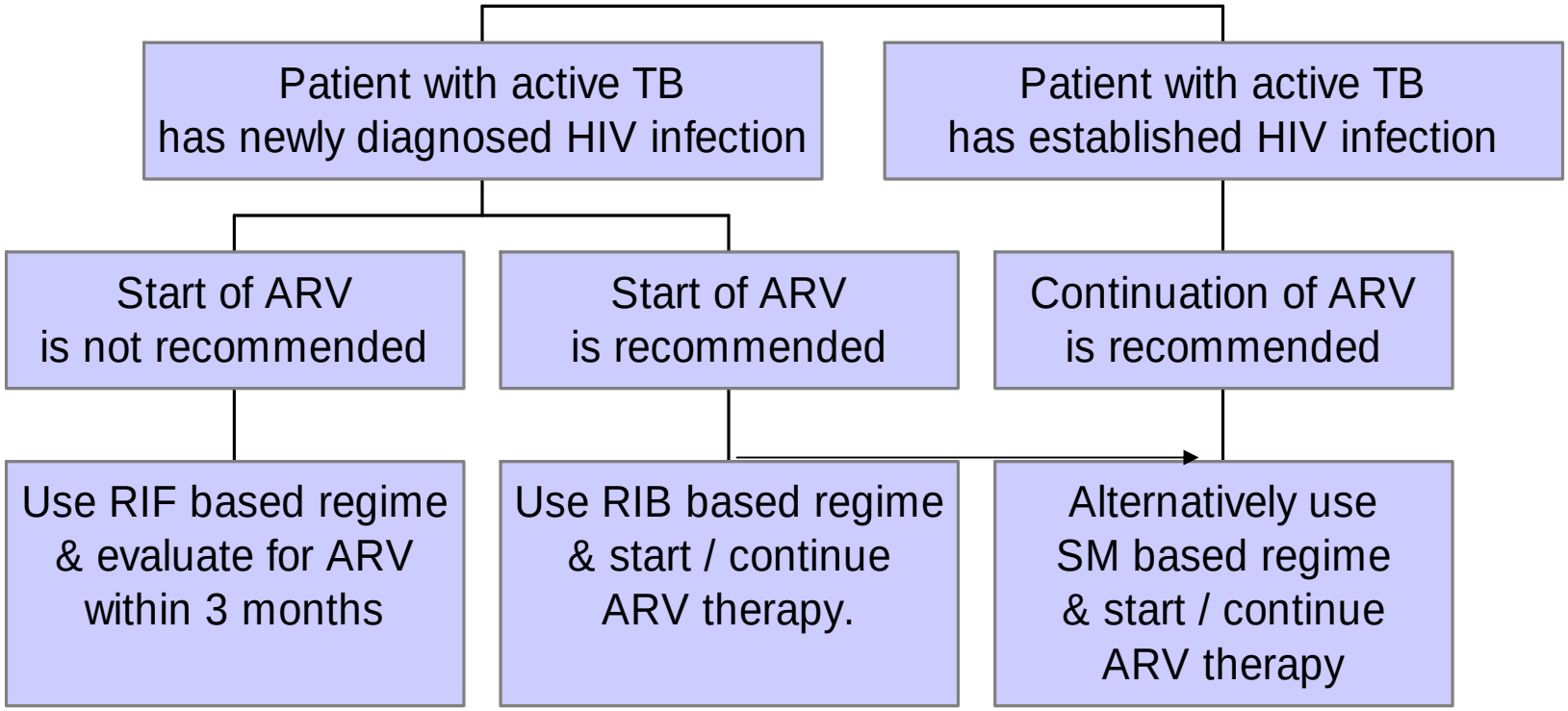
# Guidelines for starting antiretroviral treatment in patients with HIV infection in resource limited settings

- If CD4 testing available
  - WHO Stage IV disease irrespective of CD4 count
  - WHO Stage I, II, III with CD4 count < 200/mm3.
- If CD4 testing unavailable
  - WHO Stage IV disease irrespective of Total Lymphocyte count.
  - WHO Stage II or III disease with a Total Lymphocyte count < 1200/mm3.

In the absence of CD4 testing, asymptomatic HIV infected patients (WHO Stage I) should not be treated with ARV therapy.

Indian J Tuberc 2004; 51; 5-16

# Management of HIV infected patients with active TB




Indian J Tuberc 2004; 51; 5-16

# Treatment options for HIV infected patients with drug susceptible TB

- DOTS should be used for all patients with HIV related TB.

- For patients on PIs / NNRTIs, initial phase of 6 month regime consists of INH, RFB, PZA, EMB for 2 months. Second phase consists of INH & RFB for 4 months.

- When Rifamycins are contraindicated, 9 month non-rifamycin regime is given.
    - INH, SM, PZA, EMB for 2 months followed by
    - INH, SM, PZA for 7 months.

MMWR, Vol.47, RR-20, 1998.

# Treatment options for HIV infected patients with drug susceptible TB

- For patients in whom ARV is not recommended, 6 month regime consisting of INH, RIF, PZA, EMB is given.
- Pyridoxine (Vitamin B6) – 25-50 mg daily should be administered to all HIV infected patients undergoing treatment with INH to prevent the side effects on central and peripheral nervous system.
- Stopping protease inhibitors to allow the use of Rifampicin is not recommended.

MMWR, Vol.47, RR-20, 1998.

# Treatment regimens for HIV related TB

## 9 months SM based therapy ( may be prolonged to 12 months)

| Induction Phase | | Continuation Phase | |
|---|---|---|---|
| Drugs | Interval & Duration | Drugs | Interval & Duration |
| INH<br>SM<br>PZA<br>EMB | Daily for 2 months<br>(8 weeks) | INH<br>SM<br>PZA | 2-3 times/week<br>for 7 months (30 weeks) |
| OR | | OR | |
| INH<br>SM<br>PZA<br>EMB | Daily for 2 weeks & then 2 times/week for 6 weeks | INH<br>SM<br>PZA | 2-3 times/week for<br>7 months (30 weeks) |

For patients with delayed response to treatment, duration prolonged from 9 months to 12 months or to 6 months after culture conversion is documented.

MMWR, Vol.47, RR-20, 1998

# Treatment regimens for HIV related TB

## 6 months RFB based therapy ( may be prolonged to 9 months)

| Induction Phase | | Continuation Phase | |
|---|---|---|---|
| Drugs | Interval & Duration | Drugs | Interval & Duration |
| INH<br>RFB<br>PZA<br>EMB | Daily for 2 months<br>(8 weeks) | INH<br>RFB | Daily or 2 times/week<br>for 4 months (18 weeks) |
| *OR* | | *OR* | |
| INH<br>RFB<br>PZA<br>EMB | Daily for 2 weeks *&*<br>then 2 times/week<br>for 6 weeks | INH<br>RFB | 2 times/week for<br>4 months (18 weeks) |

For patients with delayed response to treatment, duration prolonged from 6 months to 9 months or to 4 months after culture conversion is documented.

MMWR, Vol.47, RR-20, 1998

# Treatment regimens for HIV related TB

## 6 months RIF based therapy ( may be prolonged to 9 months)

| Induction Phase | | Continuation Phase | |
|---|---|---|---|
| Drugs | Interval & Duration | Drugs | Interval & Duration |
| INH<br>RIF<br>PZA<br>EMB (or SM) | Daily for 2 months<br>(8 weeks) | INH<br>RIF | Daily or 2-3 times/week<br>for 4 months (18 weeks) |
| *OR* | | *OR* | |
| INH<br>RIF<br>PZA<br>EMB (or SM) | Daily for 2 weeks & then<br>2 times/week for 6 weeks | INH<br>RFB | 2 times/week for<br>4 months (18 weeks) |
| *OR* | | *OR* | |
| INH<br>RIF<br>PZA<br>EMB (or SM) | 3 times/week for<br>2 months (8 weeks) | INH<br>RIF<br>PZA<br>EMB (or SM) | 3 times/week for<br>4 months (18 weeks) |

MMWR, Vol.47, RR-20, 1998

# Paradoxical Reactions

- Immune restoration syndromes that occur within days to weeks of starting Anti Retroviral therapy.
- Manifestations include fever, increasing adenopathy, worsening pulmonary infiltrates, serositis, cutaneous lesions, expanding CNS mass lesion.
- Associated with low CD4 cell count.

AJRCCM, Vol.164, p 7-12, 2001.

# Paradoxical Reactions

- Should be differentiated from TB treatment failures, drug hypersensitivity and other opportunistic infections in HIV.
- It is a diagnosis of exclusion.
- Mild to Moderate reactions

  Reassurance + NSAIDs
- Severe reactions (e.g. airway compromise)

  Short course steroids 1 mg/kg; tapered after 1-2 weeks.

AJRCCM, Vol. 164, pp 7-12, 2001.

# Regimens for management of patients with Drug resistant Pulmonary TB in HIV infected patients

| Drug resistance | Regimen | Duration of Treatment |
|---|---|---|
| INH | RIF, PZA, EMB | 6-9 months (4 months after culture conversion) |
| RIF | INH, SM, PZA, EMB 2 months INH, SM, PZA 7 months | 9 months |
| INH + RIF (MDR TB) | SM, FQ, EMB, PZA | 24 months after culture conversion |

AJRCCM, Vol.167, 2003, pp. 603-662

# Treatment of TB in HIV infected Pregnant women

- If Pyrazinamide is not used, then minimum duration is 9 months
- Standard regimen including INH, RIF, PZA & EMB should be followed.
- Pyridoxine 25 mg/day should be given with INH.

AJRCCM, Vol.167, 2003, pp. 651

# Treatment of TB in HIV infected Pregnant women

- Patients suspected of having Tuberculosis or having positive cultures for Mycobacterium Tuberculosis should be treated without delay.
- Use of Aminoglycosides is contraindicated.
- Use of Pyrazinamide in pregnant women is recommended for routine use by WHO & IUATLD in developing countries as its benefits outweigh potential hazards to fetus.

AJRCCM, Vol.167, 2003, pp. 651

# Treatment of TB in HIV infected children

- HIV infected children suspected of having TB should be treated without delay.
- If drug susceptibility results are not available, four drug regimen (HRZE) for 2 months followed by intermittent administration of INH & RIF for 4 months should be given.
- EMB 15 mg/kg should be included, even in those children who are too young to be evaluated for visual acuity and color perception.
- American Academy of Pediatrics recommends initial therapy with at least 3 drugs (HRZ) for first 2 months and total duration of therapy for at least 9 months.

AJRCCM, Vol.167, 2003, pp. 603-662

# Treatment of TB in HIV infected patients with Extra-pulmonary TB

- Extra-pulmonary forms of TB are more common with advanced stage HIV disease.
- Recommendations and duration are same as that for Pulmonary TB in adults & children.
- For meningioma, bone & joint TB, using a rifamycin based regimen for at least 9 months is recommended.

Indian J Tuberc 2004; 51; pp 5-16

# Treatment of latent TB infection in HIV infected persons

## *Candidates for TB preventive therapy among HIV infected persons*

- Patients with Tuberculin Skin Test > 5mm with no history of Anti-TB therapy should receive TB preventive therapy, regardless of their age.

- Patients who had recent contact with infectious TB patient, should receive TB preventive therapy regardless of their age, results of TST or history of previous TB preventive treatment.

MMWR, Vol.47, RR-20, 1998

# Treatment of latent TB infection in HIV infected persons

## *Candidates for TB preventive therapy among HIV infected persons*

- Patients with history of prior untreated or inadequately treated past TB that healed and no history of adequate treatment for TB, should receive TB preventive therapy, regardless of age or TST results.

- Primary prophylaxis for TST negative, HIV infected persons with high risk of exposure to Mycobacterium Tuberculosis should be considered. (e.g. residents of prisons, jails or homeless shelters in which prevalence of TB is high)

MMWR, Vol.47, RR-20, 1998

# TB preventive therapy regimens for adults with HIV infection

| Rating | Drug | Interval & Duration | Indications |
|---|---|---|---|
| A II | INH | Daily for 9 months | HIV infected persons who are candidates for TB preventive therapy. |
| B I | INH | 2 times/week for 9 months | DOPT used when twice weekly dosing is used. |
| A I | RIF + PZA | Daily for 2 months | HIV infected persons who are candidates for TB preventive therapy |
| B III | RFB + PZA | Daily for 2 months | HIV infected persons who are contacts of patients with INH resistant TB. |

MMWR, Vol.47, RR-20, 1998

# Treatment of latent TB infection in special situations

- DOPT should always be used with intermittent dosing regimen.
- For strains resistant to INH & RIF, use combination of at least two anti-TB drugs that the strain is believed to be susceptible to.

  (e.g. EMB + PZA / Levofloxacin + EMB)
- For HIV infected pregnant women, use INH daily or twice weekly for 9 months.
- For HIV infected children, use of INH daily for 12 months is recommended by American Academy of Pediatrics.

MMWR, Vol.167, RR-20, 1998

# Safety & tolerability of Anti-TB drugs in HIV infected persons

- 20% of patients with HIV require alteration of TB regime due to side effects.
- RIF is the drug implicated most commonly.
- Rash is the most frequent symptom.
- Use of Thiacetazone is not recommended in patients with HIV infection due to 20 times increased incidence of Stevens Johnson syndrome.

AJRCCM, Vol. 167, 2003, pp. 642-645

# Safety & tolerability of Anti-TB drugs in HIV infected persons

- Risk of hepatotoxicity due to anti-TB therapy is increased in patients with both HIV & HCV infection.
- All HIV infected patients should be screened for HCV infection.
- First Line Anti-TB drugs (INH & RIF) should not be stopped permanently without strong evidence that anti-TB drug was the cause of reaction.

AJRCCM, Vol. 167, 2003, pp. 642-645

# Overlapping side effect profile of first line Anti-TB drugs and Anti-retroviral drugs

| Side effect | Anti-TB drugs | Anti-retroviral drugs |
|---|---|---|
| Skin rash | PZA, RIF, RFB, INH | Nevirapine, Delavirdine, Efavirenz, Abacavir |
| Nausea, vomiting | PZA, RIF, RFB, INH | Zidovudine, Ritonavir, Amprenavir, Indinavir |
| Hepatitis | PZA, RIF, RFB, INH | Nevirapine, Protease Inhibitors |
| Leukopenia, Anemia | RFB, RIF | Zidovudine |

AJRCCM, Vol.164, pp 8, 2001

# TB therapy outcomes among patients with HIV-related TB

- The clinical, radiological and microbiological response to short course chemotherapy in HIV positive & HIV negative patients are similar.

- Among the patients who complete short course chemotherapy, recurrence rate is similar in HIV positive & HIV negative patients.

- Prolonging duration of treatment from 6 to 9 months in patients with delayed clinical & bacteriologic response, reduces the frequency of relapse.

www.nchstp/tb; RNTCP, 2002

# TB therapy outcomes among patients with HIV-related TB

- Relapse is more common in self administered treatment as compared to DOTS
- Relapse rate is higher with treatment regimen that uses EMB & INH during the continuation phase.
- Failure to use DOTS in the face of HIV can lead to explosive spread of TB with cases tripling and drug resistance increasing rapidly.

RNTCP, 2002.

# Case fatality rates in TB / HIV coinfection

- Case fatality of TB/HIV patients, one year after starting TB treatment is 30%.
- 25% of those who complete treatment, die during next 12 months.
- Mortality rate in HIV infected persons with TB is 4 times greater than in HIV – negative persons.
- Death after induction phase of anti-TB therapy is usually attributed to complications of HIV other than TB.

RNTCP. 2002

# Case fatality rates in TB / HIV coinfection

- In HIV infected persons, active TB is associated with increased risk of opportunistic infections and deaths.
- Mortality shows bimodal distribution peaking within first 3 months of Anti-TB therapy and then again after one year.
- Pulmonary TB acts as a potent stimulus for cellular level replication of HIV.
- HIV infected smear negative Pulmonary TB patients have a worse prognosis than HIV positive patients with smear positive pulmonary TB.

MMWR, Vol 47, No. RR 20, 1998

# Control of HIV related Tuberculosis

- All patients with active and latent TB should be offered voluntary HIV testing and counseling.
- TB treatment card should never mention the HIV status of person.
- Initiate prompt and effective DOTS for all patients with HIV related tuberculosis.
- Prompt Anti Retroviral therapy should be offered for patients with tuberculosis & HIV infection.

RNTCP, 2002

MMWR, Vol.47, No. RR-20, 1998.

# Control of HIV related Tuberculosis

- Early recognition and implementation of effective treatment for drug resistant tuberculosis.
- WHO & UNICEF recommend BCG vaccination as per immunization policies for asymptomatic HIV infected children.
- BCG should be withheld in a child having symptomatic HIV infection as it may lead to disseminated BCG disease.

RNTCP, 2002

# Impact of HIV on TB control

- Over diagnosis of sputum smear negative Pulmonary TB.
- Under diagnosis of sputum smear positive Pulmonary TB.
- Inadequate supervision of anti-TB chemotherapy.
- Low cure rates (< 85% of sputum smear positive cases- Global target for TB control).

# Impact of HIV on TB control

- High case fatality rates during treatment.
- High default rates due to adverse drug reactions.
- High rates of TB recurrence.
- Increased emergence of drug resistance.

# Response of National TB Programs to TB / HIV epidemic

- Strengthening of NTP (structures & activities) and decentralization of Treatment activities.
- Strengthening of co-ordination & collaboration between NTPs, HIV / AIDS / STD services and general health services.
- Reinforcing diagnostic criteria for pulmonary & extrapulmonary Tuberculosis.
- Searching for local solutions in certain settings where there has been the biggest increase in TB burden, e.g. large cities.
- Co-ordinated care of TB patients.

RNTCP, 2002

# Recommended collaborative TB/HIV activities

***Establish the mechanisms for collaboration***

- Set up a coordinating body for TB/HIV activities effective at all levels
- Conduct surveillance of HIV prevalence among tuberculosis patients
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation

www.who.ch/gtb, WHO/HTM/TB/2004.330

# Recommended collaborative TB/HIV activities

***Decrease the burden of tuberculosis in people living with HIV/AIDS***

- Establish intensified tuberculosis case-finding
- Introduce isoniazid preventive therapy
- Ensure tuberculosis infection control in health care and congregate settings

www.who.ch/gtb, WHO/HTM/TB/2004.330

# Recommended collaborative TB/HIV activities

***Decrease the burden of HIV in tuberculosis patients***

- Provide HIV testing and counseling
- Introduce HIV prevention methods
- Introduce co-trimoxazole preventive therapy
- Ensure HIV/AIDS care and support
- Introduce antiretroviral therapy

www.who.ch/gtb, WHO/HTM/TB/2004.330

# Counseling of HIV / TB patients

- What is Tuberculosis?
- Modes of spread of Tuberculosis
- Treatment of Tuberculosis.
- Necessity of doing sputum smear examinations.
- Necessity of taking treatment until completion.
- Contact screening.
- Sputum disposal
- Contact Medical officer if side effects develop.

# All the best..