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## Appendix 1.
## WHO-Recommended Treatment Regimens Used in Peru's PNCT

### First Treatment Regimen, "Esquema Uno"

| Drug | Dose during months 1-2 | Dose during months 3-6 |
|---|---|---|
| **Isoniazid** | 300 mg PO QD | 800 mg PO 2x/week |
| **Rifampin** | 600 mg PO QD | 600 mg PO 2x/week |
| **Ethambutol** | 15 mg/kg PO QD | None |
| **Pyrazinamide** | 25 mg/kg PO QD | None |

### Second Treatment Regimen, or "Esquema Dos"

| Drug | Dose during month 1 | Dose during month 2-3 | Dose during months 4-8 |
|---|---|---|---|
| **Isoniazid** | 300 mg PO QD | 300 mg PO QD | 800 mg PO 2x/week |
| **Rifampin** | 600 mg PO QD | 600 mg PO QD | 600 mg PO 2x/week |
| **Ethambutol** | 15 mg/kg PO QD | 15 mg/kg PO QD | 15 mg/kg PO 2x/week |
| **Pyrazinamide** | 25 mg/kg PO QD | 25 mg/kg PO QD | none |
| **Streptomycin** | 1 g/kg IM QD | none | none |

### Retreatment Regimen, or "Esquema Estandarizado"

| Drug | Dose during months 1-3 | Dose during months 4-18 |
|---|---|---|
| **Ethambutol** | 15 mg/kg PO QD | 15 mg/kg PO QD |
| **Pyrazinamide** | 25 mg/kg PO QD | 25 mg/kg PO QD |
| **Kanamycin** | 1 g IM QD | none |
| **Ciprofloxacin** | 1000 mg PO QD | 1000 mg PO QD |
| **Ethionamide** | 750 mg PO QD | 750 mg PO QD |

| Abbreviation Used | Explanation |
|---|---|
| IM | Intramuscular |
| IV | Intravenous |
| PO | By mouth |
| SC | Subcutaneous |
| PRN | As needed |
| QD | Once a day |
| BID | Twice a day |
| TID | Three times a day |
| QHS | At night |
| QOD | Every other day |

## Appendix 2.
## Chemotherapeutic Agents Used in the Treatment of Tuberculosis

| Drug Name | Description | Administration (Adult doses) | Side Effects |
|---|---|---|---|
| Isoniazid | Nicotinic acid hydrazide. Bactericidal. Inhibits mycolic acid synthesis most effectively in dividing cells. Hepatically metabolized. | Regular dose:<br>300 mg or 5 mg/kg PO QD<br><br>High dose:<br>900 mg or 15 mg/kg PO 2x/wk (for strains resistant to low dose INH)<br><br>Administer with pyridoxine 150 –300 mg QD | Incidence of adverse reactions: 5.4%.<br><br>Common:<br>hepatitis (10-20% have elevated in transaminases; INH discontinuation indicated in symptomatic hepatitis; increased risk with alcohol ingestion), peripheral neuropathy (dose-related; increased risk with malnutrition, alcoholism, diabetes, concurrent use of AG or THA)<br><br>Less common:<br>fever, GI upset, gynecomastia, rash (2%)<br><br>Rare:<br>agranulocytosis, anemia, encephalopathy, eosinophilia, hypersensitivity, memory impairment, optic neuritis, positive ANA, psychosis, seizure, thrombocytopenia, vasculitis<br><br>Drug interactions:<br>increases phenytoin levels |
| Rifampin (Rifampicin) | Bactericidal. Produced by *Streptomyces spp*. Inhibits protein synthesis by blocking mRNA transcription and synthesis. Hepatically metabolized. | 600 mg or 10 mg/kg PO QD | Incidence adverse reactions: <4%<br><br>Common:<br>orange-colored bodily secretions; transient transaminitis<br><br>Less common:<br>GI upset (1.5%), hepatitis<br><br>Rare:<br>cholestatic jaundice, drowsiness, fatigue, fever (0.5%), gynecomastia, headache, pruritis, rash (0.8%), renal insufficiency, thrombocytopenia (especially in conjunction with EMB), urticaria<br><br>Drug interactions:<br>decreased reliability of oral contraceptives, protease inhibitor (PI) levels decreased by RIF, decreased activity of drugs metabolized by P450 system (e.g. CPX, corticosteroids, dapsone, diazepam, digitoxin, fluconazole, haloperidol, methadone, oral hypoglycemics, phenytoin, quinidine, theophylline, warfarin) |

## Appendix 2. Continued
## Chemotherapeutic Agents Used in the Treatment of Tuberculosis

| Drug Name | Description | Administration (Adult doses) | Side Effects |
|---|---|---|---|
| Ethambutol | Bacteriostatic at conventional dosing (15mg/kg). Inhibits lipid and cell wall metabolism. Renally excreted. | 15-25 mg/kg PO QD<br><br>Adjust for renal insufficiency | Incidence adverse reactions: <2%<br><br>Less common:<br>arthralgia, GI upset, headache, malaise<br><br>Rare:<br>disorientation, dizziness, fever (0.3%), hallucination, peripheral neuropathy, pleuritis, rash (0.5%), retrobulbar neuritis (0.8%, dose-related and reversible, increased risk with renal insufficiency)<br><br>Drug interactions:<br>none reported |
| Pyrazinamide | Nicotinamide derivative. Bactericidal. Mechanism unknown. Effective in acid milieu (e.g. cavitary disease, intracellular organisms). Hepatically metabolized, renally excreted. | 15-35 mg/kg PO QD | Common:<br>arthropathy, hepatotoxicity, hyperuricemia<br><br>Less common:<br>GI upset, impaired diabetic control, rash<br><br>Rare:<br>dysuria, fever, hypersensitivity reactions, malaise<br><br>Drug interactions:<br>none reported |
| Aminoglycosides<br><br>Streptomycin<br>Kanamycin<br>Amikacin | Bactericidal. Inhibits protein synthesis through disruption of ribosomal function. Less effective in acid, intracellular environment. Renally excreted.<br><br>SM least nephrotoxic. AMK has been shown to be highly mycobactericidal compared to other aminoglycosides in vitro. Cross-resistance rare between SM and other aminoglycosides. Frequent cross-resistance between KM and AMK | Streptomycin:<br>1 g or 15 mg/kg IM QD<br><br>Adjust for renal insufficiency<br><br>QOD or biweekly dosing not recommended<br><br>Kanamycin:<br>1 g IM/IV QD<br><br>Amikacin:<br>1 g or 15 mg/kg IM/IV QD | Incidence adverse reactions: 8.2%<br><br>Common:<br>pain at injection site<br><br>Less common:<br>cochlear ototoxicity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), facial paresthesia, nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), peripheral neuropathy, rash, vestibular toxicity (nausea, vomiting, and vertigo)<br><br>Rare:<br>anaphylaxis, hemolytic anemia, neuromuscular blockade, pancytopenia<br><br>Drug interactions:<br>ototoxicity potentiated by certain diuretics |

## Appendix 2. Continued
## Chemotherapeutic Agents Used in the Treatment of Tuberculosis

| Drug Name | Description | Administration (Adult doses) | Side Effects |
|---|---|---|---|
| Capreomycin | Polypeptide isolated from *Streptomyces capreolus*. Renally excreted. Varying degrees of cross-resistance reported between KM and CM; no cross-resistance reported between SM and CM; frequent cross-resistance between viomycin and CM. | 1 g IM QD<br>Adjust for renal insufficiency<br>QOD or biweekly dosing not recommended | Common:<br>pain at injection site<br>Less common:<br>ototoxocity and nephrotoxicity (dose-related both to cumulative and peak concentrations, increased risk with renal insufficiency)<br>Rarely:<br>electrolyte abnormalities, eosinophilia, hypersensitivity, neuromuscular blockade<br>Drug interactions:<br>enhanced risk of neuromuscular blockade with ether anesthesia |
| Fluoroquinolones<br>Ciprofloxacin<br>Levofloxacin<br>Ofloxacin<br>Sparfloxacin<br>Moxifloxacin<br>Gatifloxacin | Likely bactericidal. DNA-gyrase inhibitor. Not FDA-approved for use during pregnancy – associated with arthropathies in studies with immature animals. Renally excreted. Levofloxacin active moiety and thus possibly the drug of choice. Cross-resistance among first-generation fluoroquinolones thought to be near complete. | Ciprofloxacin:<br>750 mg PO BID<br>Levofloxacin:<br>500mg PO QD<br>Adjust doses for creatinine clearance < 50 ml/min<br>Ofloxacin:<br>400mg PO BID<br>Sparfloxacin:<br>200mg PO BID | Well tolerated, well absorbed<br>Less common:<br>diarrhea, dizziness, GI upset, headache, insomnia, photosensitivity (8% occurrence with SPX), rash, vaginitis<br>Rare:<br>arthralgia, interstitial nephritis, palpitations, psychosis, seizure, transaminitis (CNS effects seen almost exclusively in elderly)<br>Drug interactions:<br>CPX, OFX prolong half-life of theophylline with increased risk of toxicity; $CaSO_4$ or $FeSO_4$ and antacids with Al, Mg may inhibit GI absorption of fluoroquinolones; altered phenytoin levels (increased and decreased); exacerbated hypoglycemic effect of glyburide; increased coumadin levels reported with CPX, OFX; probenacid increases CPX, OFX levels; use of SPX contraindicated in persons receiving any drug that prolongs the Q-T interval |

## Appendix 2. Continued
## Chemotherapeutic Agents Used in the Treatment of Tuberculosis

| Drug Name | Description | Administration (Adult doses) | Side Effects |
|---|---|---|---|
| Ethionamide<br><br>Prothionamide | Derivative of isonicotinic acid. Bacteriostatic. Partial cross-resistance with thiacetazone. Hepatically metabolized, renally excreted. Efficacy profiles similar; prothionamide may cause fewer side effects | Ethionamide:<br>500-1000 mg PO QD<br><br>Prothionamide:<br>500-1000 mg PO QD<br><br>Increase gradually to maximum dose<br><br>Administer with pyridoxine 150–300 mg QD | Common:<br>GI upset (nausea, vomiting, abdominal pain, loss of appetite), metallic taste, hypothyroidism (esp. when taken with PAS)<br><br>Less common:<br>arthralgia, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity<br><br>Rarely:<br>optic neuritis, psychosis, seizure (increased risk of CNS effects with concurrent use of ethanol, INH, CS, or other centrally acting medications)<br><br>Drug interactions:<br>transiently increased INH levels |
| Cycloserine | Alanine analogue. Bacteriostatic. Interferes with cell-wall proteoglycan synthesis. Renally excreted. Recommended for TB of CNS given ready penetration into CNS. | 500-1000 mg PO QD<br><br>Administer with pyridoxine 150-300 mg QD<br><br>Increase gradually to maximum dose | Common:<br>neurologic and psychiatric disturbances including headaches, irritability, tremors<br><br>Less common:<br>hypersensitivity, psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, INH, THA, or other centrally acting medications)<br><br>neurologic adverse effects may be lessened by pyridoxine coadministration<br><br>Drug interactions:<br>interacts with phenytoin |
| Para-aminosalicylic acid | Bacteriostatic. Hepatic acetylation, renally excreted. | 4 g PO BID or TID<br><br>Delayed-release granules should be administered with acidic food or drink | Incidence adverse reactions: 10%<br><br>Common:<br>GI upset (nausea, vomiting, diarrhea), hypersensitivity (5-10%), hypothyroidism (especially when taken with ethionamide)<br><br>Less common:<br>hepatitis, electrolyte abnormalities<br><br>Drug interactions:<br>decreased INH acetylation, decreased RIF absorption in non-granular preparation, decreased B12 uptake |

## Appendix 2. Continued
## Chemotherapeutic Agents Used in the Treatment of Tuberculosis

| Drug Name | Description | Administration (Adult doses) | Side Effects |
|---|---|---|---|
| Clofazimine | Substituted iminophenazine bright-red dye. Bacteriostatic. Transcription inhibition by binding guanine residues of mycobacterial DNA. | 200-300 mg PO QD<br>Initiate dose at 300 mg; decrease dose to 200 mg when skin bronzes | Common:<br>discoloration of skin and eyes, GI upset<br>Less common:<br>photosensitivity, malabsorption, severe abdominal distress due to crystal deposition<br>Drug interactions:<br>none reported |
| Amoxicillin-clavulanic acid | Beta-lactam antibiotic with a beta-lactamase inhibitor. Bactericidal effect demonstrated *in vitro* | 500 mg PO TID<br>Administer with food | Common:<br>GI upset<br>Less common:<br>hypersensitivity<br>Drug interactions:<br>none reported |
| Clarithromycin | Semisynthetic erythromycin derivative. Demonstrated efficacy against *M. avium* complex; *in vitro* bactericidal effect on susceptible strains of *M. tuberculosis.* | 500 mg PO BID | Well tolerated<br>Less common:<br>GI side effects (abdominal pain, diarrhea, metallic taste)<br>Rare:<br>ototoxicity<br>Drug interactions:<br>increased theophylline and carbamazepine levels; use of terfenadine is contraindicated |
| Rifabutin<br>Rifapentine | Bactericidal. Rifamycin spiropiperidyl derivative. Cross-resistance with rifampin >70%. | Rifabutin: 150-300 mg PO QD<br>Rifapentine: 600 mg PO 2x/wk | Similar or lesser side effect profile and drug interactions compared to RIF, including reduced activity of drugs metabolized by P450 system<br>Drug interactions:<br>RFB interacts less with PI levels than does RIF; RFB & RFP decrease PI levels; RFB levels increased by PIs |
| Thiacetazone | Weakly bactericidal. Inhibition of mycolic acid synthesis. | 150 mg PO TID | Common:<br>GI upset (nausea, vomiting), hypersensitivity<br>Rare:<br>cutaneous reactions (including Stevens-Johnson syndrome, increased risk in HIV-infected patients), jaundice, reversible bone-marrow suppression<br>Drug interactions:<br>may potentiate ototoxicity of aminoglycosides. |

## Appendix 3.
## DOTS-Plus Organization at the Community Level

| Health Workers | Proposed Worker: Patient Ratio | Responsibilities | Training |
| --- | --- | --- | --- |
| MDR TB Health Workers | 1:10-15 | Clinical surveillance, including daily and emergency visits. Maintenance of data and patient records. Coordination of clinical care with other health professionals. Active screening and outreach, patient/family education. Supervision of community health promoter, including vigilance of directly observed therapy (DOT). | Knowledge of antituberculous drugs, principles of MDR TB therapy, emergency and side effect management. Drug administration, including IM and IV medications. Knowledge of principles of TB transmission, nutritional surveillance, and TB symptoms. Background in providing educational and psychosocial patient support. |
| Community Health Workers | 1:2-3 | DOT administration of all doses received outside of health establishments. Communication of all routine and emergency clinical issues to MDR TB health promoters and health professionals. | Drug administration, including IM medications. Familiarity with MDR TB drugs, side effect and emergency protocols. Knowledge of TB transmission principles, nutritional surveillance, TB symptoms. Training in the provision of educational and psychosocial patient support. |

## Appendix 4.
## Guidelines on Health Worker Safety

Health workers are at increased risk of occupational exposure to TB, and MDR TB is no exception. While the risk of exposure and infection may be minimized, it cannot be eliminated altogether. Countries with a wealth of medical resources can follow state-of-the-art recommendations, including strict isolation of infectious patients in negative-pressure airflow rooms, the use of ultraviolet light, and the use of new, individually fitted masks for providers exposed to patients with pulmonary TB. The efficacy of control measures to prevent nosocomial spread has been widely acknowledged. Yet these measures are available in almost none of the settings in which we work. While lack of resources and technology impede the implementation of such precautions, other measures may nonetheless minimize risk:

1. Smear-positive patients should receive their therapy in their homes until smear conversion in order to minimize risk of nosocomial spread.
2. Areas in health centers where DOT is administered should be well-ventilated and well-lit. Ultraviolet lights are recommended if available.
3. Home visits for DOT or clinical evaluations of smear-positive patients should be brief with precautions of ventilation and distance from patient whenever possible.
4. Patients should be educated on means of minimizing transmission, such as covering the mouth, directing one's cough away from nearby people, and avoiding close contact when possible.
5. Health workers who work extensively with TB patients should receive a chest x-ray and PPD before beginning such work, with intermittent follow-up.
6. BCG vaccination should be administered to health-care workers in close contact with patients with MDR TB since there are no established and effective regimens for chemoprophylaxis. In a study conducted among the close contacts of MDR-TB patients in urban Brazil, a history of BCG vaccination appeared to be protective against the development of TB. For further review of BCG administration, see Kritski, Ozorio-Marques, Rabahi, et al. 1996.

Another issue that should be addressed with health workers– especially those who will be administering parenteral medications– is how to safely use and dispose of needles and injection equipment. All health workers administering parenteral medications should have received the full series of hepatitis B vaccinations as well as a recent (within the last 5 years) tetanus vaccination. If possible, baseline HIV testing should be done as well, although concern should be given to the privacy of the health worker as regards HIV status.

Training in the safe use of needles should include the following:

1. Methods for capping and uncapping needles to minimize the risk of needlestick.
2. Safe disposal of needles and other "sharps".
3. What should be done if a health worker experiences a needlestick.

The exact policies for these areas will differ from place to place, and we suggest consulting local health authorities for the protocols followed in specific hospitals and health centers.

For further review of health-care worker safety in resource-rich countries, see Centers for Disease Control and Prevention 1992a; Passannante, Gallagher, Reichman 1994; Stevens, Daniel 1996.

## Appendix 5.
## Position on INH Prophylaxis in MDR TB Contacts

INH prophylaxis has proven effective in areas where MDR TB is not highly endemic. In PPD-positive individuals whose TB contact history includes patients with MDR TB, the use of INH may reasonably be questioned. INH prophylaxis for close contacts only of patients with MDR TB is unlikely to be effective, may induce toxicity, and may enhance the risk of increased resistance. Alternative prophylaxis treatments have been suggested. These include PZA and CPX, or a single drug, such as PZA or EMB, in areas where resistance to these drugs is rare.

To date, the only prophylactic treatment with agreed-upon efficacy has been the prevention of exposure, i.e. the prompt treatment of MDR TB in infected individuals. For these reasons, the International Working Group on MDR TB recommends no prophylactic treatment of MDR TB contacts, unless future studies demonstrate efficacy of a given prophylactic regimen. Instead, measures which should be taken to prevent MDR TB disease include the following:

1. Timely diagnosis and appropriate treatment of active MDR TB cases.
2. Nutritional support to families of MDR TB patients.
3. Vigilance of MDR TB contacts with routine screening and prompt diagnosis of active cases.
4. Further research into effective and nontoxic prophylaxis in areas of high MDR TB prevalence.
5. Consideration of BCG vaccination for close contacts of MDR TB patients.

For a review of the literature on this topic, see Centers for Disease Control and Prevention 1992a; Kritski, Ozorio-Marques, Rabahi, et al. 1996; Passannante, Gallagher, Reichman 1994; Kirkland 1996; Livengood, Sigler, Foster, et al. 1985.

## Appendix 6.
## MDR TB in Pediatrics and Obstetrics

Little literature exists on the treatment of pediatric cases of MDR TB. Nonetheless, given the paucity of drugs available to treat MDR TB, careful consideration of risks and benefits of each drug should be made before deciding on a regimen. Potential parents should be informed of these risks and benefits as well. In general, drugs should be dosed according to weight.

| Drugs[1] | Dosage Forms | Daily Dose mg/kg/day | Frequency | Maximum Daily Dose |
|---|---|---|---|---|
| **Kanamycin** | Vials:37.5, 250, 333, 500mg/ml | 15-30 | QD | 1g |
| **Amikacin** | Vials: 50, 250mg/ml | 15-22.5 | QD | 1g |
| **Capreomycin** | Vials: 1g/ml | 15-30 | QD | 1g |
| **Ciprofoxacin** | Tabs: 100, 250, 500, 750mg<br>Oral Suspension: 250mg, 500mg/5ml | 20-40 | BID | 2g |
| **Ethionamide** | Tabs: 250mg | 15-20 | BID | 1g |
| **Cycloserine** | Capsules: 250mg | 15 | QD or BID | 1 g |
| **PAS** | Paser 4g packets | 150 | BID or TID | 12g |
| **Clofazimine** | Tabs: 50mg | 3-5 | BID | 300mg |
| **Amoxicillin-clauvulanic acid** | Tabs: 500/125mg | 25-45(bassed on the amoxicillin component) | BID | 2g |

While teratogenicity has been demonstrated in few of the drugs used to treat MDR TB, most have not been approved for use in pregnancy– in large part because there has been little experience treating pregnant women with MDR TB. Our view is that pregnancy is not a contraindication to the treatment of active MDR TB, since active, untreated TB and MDR TB are far greater risks to the life of the mother and fetus than is drug toxicity. Nonetheless, all patients of child-bearing age should be tested for pregnancy upon initial evaluation; birth control should be strongly recommended to all women receiving MDR TB therapy. Of note, oral contraceptives may have decreased efficacy given drug interactions with MDR TB drugs and we thus recommend the use of depo-provera for pregnancy prevention.

Gravid patients should be carefully evaluated, taking into consideration gestational age and severity of MDR TB. In the case of those with severe symptoms, risks and benefits of MDR TB treatment should be considered carefully with a primary goal being to render the mother smear-negative in order to protect her health and the health of the child, both before and after birth. If symptoms are life-threatening– massive hemoptysis, for example– and the decision is made to initiate MDR TB treatment, drugs should be chosen to reflect the degree of severity of the patient's symptoms as well as the gestational age of the fetus. Since the majority of teratogenic effects occur in the first trimester, therapy during that time should be avoided, if possible– especially the use of aminoglycosides and less well-studied drugs, such as fluoroquinolones. Patients in the third trimester have reduced risk of teratogenicity, although aminoglycosides may still damage the fetal ear. One strategy is to begin treatment in the third trimester with three or four drugs known to be safe and with demonstrated efficacy against the infecting strain, and then to reinforce the regimen with an injectable and other drugs immediately post-partum.

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For a review of MDR TB in pediatrics see Swanson, Starke 1995; DeVincenzo, Berning, Peloquin, et al. 1999; Schaaf, Vermeulen, Gie, et al. 1999. For a review of treatment of MDR TB in obstetrics, see Miller, Miller 1996; Hamadeh, Glassroth 1992; Vallejo, Starke 1992.

[1] Table from Samson DS, Starke JR, Drug resitant tuberculosis in Pediatrics. Pediatric Clinics of North America. (95)0031-3955 and Siberry GK, Iannone R, Eds. The Harriet Land Handbook, Fifteenth Edition. Mosby, Baltimore 2000, pp 599-892.

## Appendix 7.
## Guidelines for Collection and Transport of Biomaterials

### I. SAMPLE COLLECTION:

When possible, samples should be collected the same day they are to be plated for culture. If this is not feasible (due to delays in shipping, proximity of the patient to lab, etc.), samples should be collected as close to that date as possible. If the delay is more than two days and resources permit, two samples should be collected, and one should be cultured immediately at a local laboratory. If positive, the culture can then be sent at a later date for susceptibility testing.

#### A. Sputum

Specimen container:

- Orange-top plastic containers

Collection:

- If the patient produces scanty sputum, he/she should drink copious water the night prior to collection.
- Specimen should be the first sputum expectorated in the morning.
- If a person assists in sputum collection, exposure to the coughing patient should be minimized. Collector should stand behind the patient, or the patient should leave the room to cough and produce a sample.
- Chest physical therapy (e.g., vigorous cupping) may be performed at the time of collection.
- Specimen container should be handled with gloves to minimize the risk of contamination.
- The exterior of the container should be wiped with alcohol and maintained clean and dry.
- Specimen container should immediately be placed in a sealed plastic bag to prevent contamination.
- Specimens collected from patients with hemoptysis should consist of as much sputum as possible, with minimum amounts of blood. Samples consisting predominantly of blood have a lower bacillary yield.

#### B. Urine

Specimen containers:

- Orange-top plastic specimen containers.

Collection:

- Sample should be the first urine of the morning.
- Sample should be of a generous quantity, as bacillary concentration in urine is low.
- Specimen container should be handled with gloves to minimize the risk of contamination.
- The exterior of the container should be wiped with alcohol and maintained clean and dry.
- Specimen container should immediately be placed in a sealed plastic bag to prevent contamination.

## Appendix 7. Continued
## Guidelines for Collection and Transport of Biomaterials

### C. Bronchial lavage, tissue biopsy

Specimen containers:

- Orange-top plastic specimen containers.

Collection:

- As per hospital protocol.
- An additional specimen should be simultaneously sent to a local laboratory for culture which can sent for susceptibility testing at a later date.

### D. Cultures:

Specimen containers:

- Glass culture tubes (2 cm diameter, 10 cm length) with plastic screw cap.

### 2. PACKAGING OF SAMPLES:

- All samples should be clearly labeled with permanent ink on the specimen container. Data should include the full name of patient and date of specimen collection.
- Each sample must be tightly sealed.
- Each sample container should be placed in a sealed plastic bag.
- This unit must then be placed in a metal tube canister that must be tightly screwed closed.
- Each metal tube canister must then be placed in a sealed biohazard plastic bag.
- An identification card must then be completed and placed in the outer compartment of the biohazard bag. Cards must be filled out in legible print or type. The minimum information necessary to process the specimen is the following:
  1. Full name of patient (last name first)
  2. Type of sample
  3. Date of sample collection
  4. Referring physician
  5. Address or location of patient

### 3. TRANSPORT:

- Samples should be stored and transported at cool temperatures.
- Samples should not be exposed to light, during collection, packaging or transport.
- Samples should be delivered to the receiving laboratory as soon as possible.

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For more in-depth guidelines, see Collins, Grange, Yates 1997.

## Appendix 8.
## Susceptibility Testing Methods

Susceptibility testing aims to determine the drugs to which a patient's isolate is susceptible in order to design appropriate therapy. An essential part of any MDR TB treatment program, susceptibility testing should be carried out in an experienced laboratory and performed on wide panel of drugs. There are several methods of drug-susceptibility testing, but similar principles underpin the various methods. Typically, the patient's isolate is incubated in media impregnated with a given antituberculous drug. Growth is then compared with that of controls known to be susceptible. Given the slow growth of *Mycobacterium tuberculosis* in culture, there is often a long wait before results become available. Conventional methods include the absolute-concentration, proportion, resistance-ratio, and disc diffusion methods. In addition to methods using conventional media, radiometric methods are also used.

**The absolute-concentration method.** This method determines the minimum inhibitory concentration (MIC)– the lowest drug concentration required to inhibit mycobacterial growth– by preparing culture media with serial drug concentrations. The plates are then inoculated with the patient's isolate and monitored for growth. The MIC is the drug concentration that allows the growth of no more than 2 to 3 colonies. This method is also performed using microplates and broth containing serial drug concentrations. The broth is assayed for turbidity.

**The proportion method.** This method cultures the patient's isolate in drug-free media and in media containing serial drug concentrations. The number of colonies grown on the drug-free plates is compared with those on the plates containing drugs. The isolate is considered resistant to a given drug if the number of colonies growing on the plate containing the drug is 1% or more of the colonies growing on the drug-free plate.

**The resistance-ratio method.** This method compares the MIC for the patient's strain with the modal average of several control strains. The isolate and controls are grown on drug-free and drug-containing media. The MIC for each strain is determined. The resistance-ratio is the ratio of the patient's MIC to the mean control MIC. Strains with a resistance-ratio of 1 or 2 are considered susceptible.

**The disc method.** In this method, paper discs impregnated with each drug are placed on culture-media plates containing the patient's isolate and on plates containing control isolates. Growth around the disc is then assessed for both controls and patient isolates.

**Radiometric method (BACTEC).** This method uses radioisotopes to measure metabolic activity of the mycobacteria, thus providing results more rapidly than conventional methods discussed above. Radio-labeled liquid media (usually containing Carbon-14) are inoculated with the patient and control isolates. Both drug-containing and drug-free bottles of liquid media are used. The difference in metabolic activity on consecutive days is measured and calculated as a daily growth index. If the strain's growth index in a drug-containing solution is less than the growth in a 1:100 dilution of the control strain, the patient's isolate is deemed susceptible to that drug.

For a more in-depth discussion of testing methods, see Collins, Grange, Yates 1997; Heifets, Cynamon 1991; Laszlo 1996.

## Appendix 9:
## Recommendations for Treatment of HIV-TB Coinfected Patients

### Exam:

Complete history including history of previous opportunistic infections, as well as history of previous TB that was treated and cured. Exam should be directed toward evidence of immune suppression, such as candida, chronic diarrhea, and evidence of extrapulmonary disease. The most important additional laboratory test in patients with HIV and TB is a CD4 count at start of therapy, with follow-up every three to six months.

### Treatment:

**Group 1:** Patients with CD4 greater than 200, without evidence of relapse or extrapulmonary disease

*Treat tuberculosis with standard algorithm*

**Group 2:** Patients with CD4 less than 200, or relapse after cure, or previous opportunistic infection, or extrapulmonary disease

*Consider antiretroviral therapy (ART) two to four months after starting TB treatment*

**Group 3:** Patients on ART

*Continue ART and start TB treatment*

*Caution of drug interactions, mainly rifampin*

### Antibiotic prophylaxis:

Because patients with HIV are susceptible to other infections, those with a CD4 count of less than 200 should be started with trimethoprim+sulfamethoxazole (cotrimoxazole)

- One single-strength tablet per day
- Cotrimoxazole should be started one month before or one month after initiation of MDR TB treatment, to minimize confusion between side effects of cotrimoxazole and MDR TB drugs

### Documentation needed for follow-up:

Date diagnosed with HIV

Presentation at diagnosis

Presumed mode of transmission

Initial CD4

Lowest CD4

Previous HIV treatment regimens (include dates, degree of regularity, reasons for any changes)

Previous opportunistic infections (date of diagnosis, outcome)

Current ART, if taking

Reasons if not taking ART

Prophylaxis, if taking

Most recent CD4 and viral load

Site of HIV care and physician

## Appendix 10: Proposed Treatment Outcome Definitions for Multidrug-resistant Tuberculosis[1]

The definitions described in this appendix were created by a committee of the DOTS-Plus Working Group for the Treatment of MDR TB. They are meant to serve as guidelines for performing program analyses and not necessarily as clinical parameters.

### Case definition[2]

*A case of MDR TB:* A patient with laboratory-confirmed in vitro resistance to at least isoniazid and rifampin.

### Category of patient for MDR TB registration

As the specific characteristics of previous treatment experience are likely to affect outcomes, three categories of previous treatment history were established:

*New, never treated MDR TB patients:* MDR TB patients who have never received TB treatment prior to this episode.

*MDR TB patients previously treated with first-line drugs:* MDR TB patients who, during a previous TB episode, were treated for one month or more with first-line anti-TB drugs.

*MDR TB patients previously treated with second-line drugs:* MDR TB patients who, during a previous TB episode, were treated for 1 month or more with any second-line anti-TB drug.

### Interim Outcome Definitions for MDR TB Patients

Given the long duration of MDR TB regimens, an interim outcome indicator, based upon sputum bacteriologic results, was designed as a marker of patient progress early in the treatment regimen. For optimal measure of patient progress, sputum cultures should be performed monthly (or, at a minimum, once every three months) during therapy. Due to their low sensitivity, sputum smears should only be used in the absence of culture.[3] All patients will have had a positive culture at some point prior to therapy for MDR TB. Many patients, however, will not have evidence of a positive culture at treatment initiation.

*Culture/smear converted:* After treatment initiation, an MDR TB patient who has two negative consecutive cultures (or smears in the absence of culture), taken at least one month apart will be considered to have converted. For those patients with positive cultures at initiation of MDR TB therapy, treatment efficacy may be more accurately measured using the following culture conversion definition: an MDR TB patient who is culture-positive at the initiation of treatment, and who has two negative consecutive cultures taken at least one month apart.

*Time interval to culture/smear conversion:* Time to conversion is calculated as the interval between the date of MDR TB treatment initiation and the date of the first of two negative consecutive cultures/ smears,[4] taken at least one month (30 days) apart. This interval should be recorded separately for culture and smear conversion.

[1] Excerpt reprinted with permission of Laserson, Thorpe, Leimane, et al. 2002 (June). Manuscript in preparation; final published version may differ.

[2] In order to apply these definitions in the evaluation of treatment outcomes, the authors have recommended the collection of core data. Please see Laserson, Thorpe, Leimane, et al. 2002.

[3] World Health Organization 1998b.

[4] The date sputum specimens are collected should be used.

## Treatment Outcome Definitions for MDR TB Patients

Due to the lack of a universal standard MDR TB treatment regimen, the following mutually exclusive MDR TB outcome definitions have been designed to fit the wide range of country-specific regimens and treatment durations currently in use. These definitions rely on the use of culture; smears should only be used in the absence of culture.

*Cure:* A patient who has completed MDR TB treatment, is culture-negative in the last month of treatment, and has been culture-negative during the preceding 11 months of treatment. A minimum of five cultures must be performed within the last 12 months of treatment. To allow for the possibility of contamination, a patient may still be considered cured if one positive culture is reported during that time. However, in order to meet the criteria for cure, a positive culture must be followed by a minimum of three consecutive negative cultures.[5]

*Treatment Completed:* A patient who has completed MDR TB treatment but does not meet the definition for cure or failure due to lack of bacteriologic results.

*Death:* A patient who dies for any reason during the course of MDR TB treatment.

*Treatment default:*[6] A patient whose MDR TB treatment was interrupted for two or more consecutive months. Patients who are removed from treatment by clinicians due to persistent interruptions should also receive a default outcome.

*Treatment failure:*[7] A patient with more than one positive culture[8] in the last 12 months of treatment, with a minimum of five cultures performed during the last 12 months. A patient will also be considered a treatment failure if one of the last three cultures taken during treatment is positive, or if he/she is persistently culture-positive and a clinical decision has been made to terminate treatment early. Patients permanently removed from treatment due to drug intolerance will also receive a treatment failure outcome.

*Transfer out:* A patient who has been officially transferred to another reporting and recording unit which has a documented MDR TB treatment program and for whom the treatment outcome is unknown.

*Still on treatment:*[9] A patient who is still on MDR TB treatment at the end of a designated cohort period.

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[5] In patients with a late positive culture, programs are encouraged to extend treatment.

[6] The following algorithm should be followed for patients returning after default:

1. If the individual has taken more than one month of MDR TB treatment, and upon return is smear-positive, then he/she will receive a final outcome of default and will need to be re-registered and reinitiated on a new MDR TB treatment regimen;
2. If the individual has taken more than one month of MDR TB treatment, and upon return is smear-negative, then MDR TB treatment will continue, and a culture will be performed;
    a. If the culture returns positive, then he/she will receive a final outcome of default and will need to be reinitiated on a new MDR TB treatment regimen
    b. If the culture returns negative, then the patient will not be given a default outcome and will continue treatment. The MDR TB regimen may be extended to make-up for the period of default. This patient can receive cure as his/her final outcome if the cure criteria are met.

[7] This is a programmatic definition for cohort analysis; thus after a patient "fails treatment," countries are still encouraged to perform susceptibility testing of second-line drugs in order to find a successful treatment option for the patient or may continue treatment after a programmatic outcome has been assigned.

[8] A positive culture requires >10 colonies; two consecutive positive cultures must be obtained if <10 colonies are in the first culture; if second culture is also <10 colonies, the culture should be interpreted as positive.

[9] This is a provisional outcome until a final outcome is available. One year after the cohort period ends, patients still on treatment should be programmatically classified as treatment failure, although treatment may continue on a case-by-case basis.

## MDR TB Cohort Definitions

*MDR TB Cohort Analysis:* Analysis of treatment outcomes for all MDR TB patients treated with second-line anti-TB drugs during a defined time period. Patients in each category (new, retreatment with first-line, retreatment with second-line) should be analyzed in separate cohorts. Sub-analysis of different cohorts (e.g., according to HIV status) may also be useful.

National TB Programs with DOTS-Plus strategies are encouraged to provide MDR TB treatment for all diagnosed MDR TB patients. If any MDR TB patients are left untreated, the reasons for not receiving an MDR TB treatment regimen should be explicitly delineated. The following sub-categories may apply:

a) Died before treatment initiated;

b) Untreatable due to drug resistance pattern (exact resistance pattern should be recorded);

c) Disease too advanced;

d) Drug intolerance;

e) Patient unwilling to be treated;

f) Patient unable to be treated due to limited health facility access (geographical distance to health center, etc);

g) Drug supply shortage;

h) Others (should include all clinically and/or socially related reasons).

*Time frame of MDR TB Cohort Analysis:*[10] During a specific time frame (e.g., one calendar year), all MDR TB patients are included in the cohort analysis based on the date of MDR TB treatment initiation. To account for the long duration of MDR TB treatment regimens, cohort analysis should be performed 36 months after last patient enrollment.

[10] Some patients may be registered twice during one cohort period (failure or default patients who are re-registered); therefore, the cohort analysis should identify the total number of patients as well as the total number of cases. Stratifying cohort analyses by category of patient (new, retreatment) will minimize the frequency with which a patient is counted twice in the same cohort.