

## DRUGS AVAILABLE FOR STANDARDISED TREATMENT OF MDR TUBERCULOSIS

### First-line drugs

**Pyrazinamide:** Resistance to pyrazinamide is neither easy to acquire nor to prove by susceptibility testing. As pyrazinamide has a bactericidal effect in an acid medium (bacilli inside macrophages), it is advisable to use pyrazinamide in combination with an aminoglycoside (active against bacilli actively multiplying, outside macrophages) to obtain a maximum bactericidal effect against all populations of bacilli.

**Ethambutol:** Ethambutol is used during the continuation phase of the standard first-line retreatment regimen. In South Africa, the rate of acquired resistance to ethambutol is less than 3%, and even in MDR tuberculosis around two thirds of patients carry strains susceptible to ethambutol. Ethambutol is then a valuable bacteriostatic agent for preventing the emergence of resistance to other active drugs, in place of terizidone, which is more expensive and tends to be more poorly tolerated.

### Second-line antituberculosis drugs

**Aminoglycosides:** *Kanamycin* is the least expensive, but also used for indications other than tuberculosis in South Africa. *Amikacin* is as active as kanamycin and better tolerated, but much more expensive. Streptomycin-resistant strains of *M. tuberculosis* usually are susceptible to kanamycin and amikacin. Kanamycin-resistant strains can exhibit resistance to streptomycin and show high cross-resistance with amikacin.

**Thioamides:** *Ethionamide* and *prothionamide* are two different presentations of the same active substance, with bactericidal activity against *M. tuberculosis*. The pharmacokinetics of the two preparations are very similar, but prothionamide may be better tolerated than ethionamide. Prothionamide is not available in South Africa.

**Fluoroquinolones:** *Ofloxacin* and *ciprofloxacin* are two different fluoroquinolones, but with complete cross-resistance inside the group. These drugs have a low bactericidal activity, and are useful in association with other antituberculosis drugs. The pharmacokinetics of ofloxacin are better than the pharmacokinetics of ciprofloxacin but the latter is less expensive. Sparfloxacin should be avoided because of severe cutaneous side effects (photosensitisation). Norfloxacin should not be used because it does not provide adequate serum levels. The toxicity profiles of newer fluoroquinolones (eg. gatifloxacin, moxifloxacin) in long-term chemotherapy have not been established.

**Terizidone/Cycloserine:** Terizidone is a combination of two molecules of cycloserine. *Terizidone and Cycloserine* are bacteriostatic at the recommended dosage. Evidence from South Africa indicates that terizidone has fewer adverse effects (around 1%) than cycloserine (around 11%). It is a valuable companion drug to prevent resistance to other second-line drugs, since it does not share cross-resistance with other active tuberculosis drugs.

## **CROSS-RESISTANCE**

Consideration of cross-resistance is important for selecting drugs acceptable for the treatment of MDR tuberculosis. As usual in the treatment of infectious diseases when a combination of several drugs is required, it is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance.

**Thiomides:** Ethionamide in the group of thioamides induces complete cross-resistance with prothionamide. They should therefore be considered as the same drug.

**Aminoglycosides:** Strains resistant to streptomycin are susceptible to kanamycin and amikacin. Resistance to kanamycin induces complete cross-resistance with amikacin: they should therefore be considered as the same drug. Resistance to kanamycin or amikacin induces also resistance to streptomycin.

**Fluoroquinolones:** Ofloxacin, ciprofloxacin and sparfloxacin induce complete cross-resistance for all fluoroquinolones. There is no cross-resistance with other classes of drugs.

**Terizidone/Cycloserine:** Susceptibility testing of terizidone and cycloserine is unreliable; however, cross-resistance occurs in all probability and they should therefore be considered as the same drug. No cross-resistance with other classes drugs is evident.

**SECOND-LINE ANTITUBERCULOSIS DRUGS USED IN THE STANDARDISED REGIMEN:  
DOSAGE AND ADVERSE EFFECTS**

**Kanamycin and Amikacin: Preparation and dose:** Kanamycin (Novo) is available in injection formulation containing 1g/3ml vial. Amikacin (B-H Squibb) is available as an injection containing 1 g/ml or as injection formulations. The drug should be dissolved (Intramed) at concentrations 100 mg/2ml, 250 mg/2ml and 500 mg/2ml respectively. The optimal dose for both kanamycin and amikacin is 15 mg/kg bodyweight, usually 750 mg to 1g given daily or five days per week, by deep intramuscular injection. Rotation of injection sites reduces local discomfort. The duration of daily therapy is four months. **Adverse effects:** These are similar to the adverse effects associated with streptomycin. Ototoxicity, deafness or vertigo may occur, as well as reversible nephrotoxicity. **Precautions:** In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during use. Kanamycin and amikacin should not be used in pregnant women except as a last resort.

**Ethionamide: Presentation and dose:** Ethionamide (Healthcare Generica) is provided in 250 mg tablet formulation. The maximum optimum daily dose is 15-20 mg/kg or 1g. The usual dose is 500 mg to 1g daily, depending upon body weight and tolerance. Few persons can take more than 750 mg daily. Patients may find the drug more acceptable if it is administered with orange juice or milk, or at bedtime to avoid nausea. Among patients on directly observed treatment, a daily dose of 750 mg can be given as 250 mg and 500 mg administered 10-12 hours later. **Adverse effects:** The main problems are epigastric discomfort, anorexia, nausea, metallic taste and sulphurous belching. Vomiting and excessive salivation can occur. Tolerance varies in different populations: the drug is usually well tolerated in Asia and in Africa. Psychotic reactions including hallucinations and depression may occur. Hypoglycaemia is a rare but dangerous occurrence, obviously particularly important in diabetic patients. Hepatitis may occur in about 10% of cases, but is rarely serious. When major liver damage occurs, jaundice and highly symptomatic disease is created, with prolonged elevation of transaminases (6-8 weeks). Drug administration should be interrupted during this period. Other rare adverse effects have included gynaecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy. **Precautions:** Ethionamide is teratogenic in animals and should not be given in pregnancy. It should be very carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

**Ofloxacin and Ciprofloxacin: Presentation and dose:** Ofloxacin (Tarivid, Noristan) is supplied in 200 mg and 400 mg tablet formulation, while ciprofloxacin (Ciprobay, Bayer Healthcare) is available in 250 mg, 500 mg and 750 mg tablet formulation as ciprofloxacin during the initial phase. If the dose of 800 mg ofloxacin is poorly tolerated, the daily dose can

be reduced to 400 mg during the continuation phase. Either can be given in single daily dose (especially applicable in directly observed treatment) or the daily dose can be divided into 12-hour intervals. **Adverse effects:** Adverse effects are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous symptoms (dizziness, headache, mood changes and, rarely, convulsions). **Precautions:** Ofloxacin and ciprofloxacin should not be used in pregnant women or growing children because they may impair growth and produce injury to growing cartilage. **Because of adverse interaction, the following drugs should be avoided during fluoroquinolone therapy: antacids, iron, zinc, sucralfate.**

**Terizidone/Cycloserine: Presentation and dose:** Terizidone (Aventis) and Cycloserine (Eli Lilly) is supplied in 250 mg capsule formulation. The maximum daily dose is 15-20 mg/kg, the maximum dose being 750 mg. The daily dose can be divided into 250 mg in the morning and 500 mg in the evening. **Adverse effects:** These include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most serious risk is suicide and mood changes should be carefully watched. Very rarely there may be hepatitis or general hypersensitivity. **Precautions:** In view of the above adverse effects monitoring for central nervous system reactions is essential. Minor adverse effects such as insomnia can be managed by small doses of an appropriate tranquiliser. Pyridoxine may decrease central nervous system effects and 150 mg pyridoxine should be prescribed to all patients receiving terizidone or cycloserine. Health care staff and family members of patients receiving terizidone or cycloserine should be educated to report undue depression or personality changes immediately, since depression-related suicide is a definite risk. Terizidone and cycloserine should be avoided in patients with a history of epilepsy, alcoholism and mental illness especially depression. It should be used very cautiously in patients with renal failure.

PATIENT NAME

DOTS-Plus NUMBER

				/				
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TREATMENT EPISODE NUMBER

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**DOTS-Plus FOR MULTIDRUG-RESISTANT TUBERCULOSIS  
PATIENTS IN SOUTH AFRICA**

**Systematic evaluation of a standardised treatment regimen applied under  
tuberculosis control programme conditions**

**CASE RECORD FORM**

**January 2004**

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
PATIENT INFORMATION SHEET**

Hello,

You have been found to have a type of TB called “multidrug-resistant (MDR)” TB, which cannot be treated with the usual TB drugs. Instead, you will have to be treated at the MDR Centre where you will receive special drugs. These drugs are very expensive and are not available outside the MDR Centre. You will have to take them for a long period (up to 22 months) and it is very important that you do not stop at any time. These drugs are provided free of charge to you by the Department of Health and the Doctor in charge at the MDR Centre will explain to you how your MDR-TB will affect your life and what needs to be done to try to get you well.

The Medical Research Council (MRC) is evaluating the treatment of MDR-TB in South Africa in a research project and the MDR Centre where you will be treated is taking part in the research. We are interested to see how well the MDR-TB drugs are working. To do this, we would need to use the medical information that will be collected at the MDR Centre as part of your treatment and we would like to ask your permission to do this. All your information will be kept strictly confidential by the researchers and will not in any way affect your care at the MDR Centre. Also, your name will not be made known if the research results are published.

You are free to choose not to make your medical information available to the MRC. This will not in any way affect your medical care at the MDR Centre. If you do decide to let the MRC use your information and change your mind later, you only have to tell the Doctor in charge and s/he will let us know immediately. Also, if you have any questions, the Doctor in charge at your MDR Centre will discuss them with you. You are welcome to phone Dr Karin Weyer of the Medical Research Council in Pretoria, at telephone number (012) 339-8550.

If you are happy to let the MRC use your medical information for the research study, please read and sign the attached consent form.

Thank you

Dr Karin Weyer  
Medical Research Council, Pretoria

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
PATIENT CONSENT FORM**

DOTS-Plus NUMBER 

					/				
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FULL NAME \_\_\_\_\_

AGE 

--	--

RACE 

1	2	3	4	9
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GENDER 

M	F
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Physician/Nurse \_\_\_\_\_ Centre \_\_\_\_\_

Dr/Mr/Ms \_\_\_\_\_ has explained my disease to me, and has explained the nature and commitment it requires from me for the next 16 to 22 months. S/he has also told me that the Medical Research Council (MRC) is evaluating the treatment of MDR tuberculosis as part of a research study and that the MRC would want to use my medical results to do this.

Dr/Mr/Ms \_\_\_\_\_ has assured me that all medical information will be kept in the strictest confidence and that I will not be identified by name when the results are published. S/he has also assured me that, if I choose not to make my medical information available to the MRC, it will not affect my medical care.

I understand everything that was explained to me and agree to have the MRC use my medical information for the research study.

Signature of patient \_\_\_\_\_ Date \_\_\_\_\_

Signature of physician/nurse \_\_\_\_\_ Date \_\_\_\_\_

Signature of witness \_\_\_\_\_ Date \_\_\_\_\_

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
PATIENT RECORD**

Patient Personal Details

Title

First name(s)

Surname

Gender   Race

Nationality

If other, specify

ID Number

Date of Birth (ddmmyy)   /   /

Age   yrs

Address

Postal Code

Tel: Code  Number

Fax: Code  Number

Study Information

DOTS-Plus Study

DOTS-Plus Number     /

MDR Centre

DOTS-Plus Registration Date (ddmmyy)   /   /

Location Information

Clinic  Town

District  Province

Region

Patient Contact Details

Contact Person

Tel: Code  Number

Other Information

Completed by

Signature

Date (ddmmyy)

  /   /

# DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA TREATMENT EPISODE RECORD

Date Treatment Started (ddmmyy)   /   /

Treatment Episode No

Folder Number

Resistant to

<input type="checkbox"/>	Isoniazid
<input type="checkbox"/>	Rifampicin
<input type="checkbox"/>	Ethambutol
<input type="checkbox"/>	Other drugs

Transfer In From

MDR Centre	<input type="text"/>
Province	<input type="text"/>
Contact Person	<input type="text"/>
Contact Details	<input type="text"/>

Site of Disease 

<input type="checkbox"/> Pulmonary	<input type="checkbox"/> Extra-pulmonary	<input type="checkbox"/> Both
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Patient Classification 

<input type="checkbox"/>	New MDR, Never Treated Before
<input type="checkbox"/>	MDR, Treated For TB Before
<input type="checkbox"/>	MDR, Treated For MDR Before

Date MDR Diagnosis Confirmed   /   /

Clinical Details

Medical History (ddmmyy)

## DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA TREATMENT AND BACTERIOLOGY RECORD

Month	Weight (kg)	Height (cm)	BACTERIOLOGY				TREATMENT								Treatment adjustment (specify reasons)	
			MRC Lab No	Date Sputum Taken	Smear Result	Culture Result	Date	Ka/Am	Z	Et	Of/Ci	E	Te/Cy	Other (specify)		
Pre-Rx																
1																
2																
3																
4																Change to continuation phase
5																
6																
7																
8																
9																Assess drug susceptibility if culture is still positive
10																
11																
12																
13																
14																
15																
16																
17																
18																
19																
20																
21																
22																
23																
24																

Ka = Kanamycin    Am = Amikacin    Z = Pyrazinamide    Et = Ethionamide    Of = Ofloxacin    Ci = Ciprofloxacin    E = Ethambutol    Te = Terizidone    Cy = Cycloserine







## DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA TREATMENT ADHERENCE SUMMARY

Month	No of Days Rx Prescribed	Adherence			Supervision*						Interruption Record and Source					
		✓	X	—	H	C	CV	E	S	O	Patient	No of Doses Missed	Doctor	No of Doses Missed	Total	Cumulative Total
1																
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
13																
14																
15																
16																
17																
18																
19																
20																
21																
22																
23																
24																

\* Supervision: H – Hospital    C – Clinic    CV – Community Volunteer    E – Employer    S – Self    O – Other, list \_\_\_\_\_





**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
SERIOUS ADVERSE DRUG EFFECT (ADE) REPORT**

Repeat this page as necessary

Serious ADE = Any untoward medical occurrence that at any drug dose results in death, is life-threatening, requires patient hospitalisation or prolonging of existing hospitalisation or results in persistent or significant disability/incapacity

Patient Name \_\_\_\_\_

MDR Centre \_\_\_\_\_

DOTS-Plus Registration Date   /   /

DOTS-Plus Number     /

Date of ADE Onset (ddmmyy)   /   /

Duration   :   hours:minutes

Drug(s) Implicated:  Kanamycin/ Amikacin  Ethionamide  Ofloxacin/ Ciprofloxacin  Cycloserine/Terizidone  
 Ethambutol  Pyrazinamide  Other, list \_\_\_\_\_

Action Taken:  Drug(s) Withdrawn  Drug Sensitisation  
 Hospitalisation / Prolonged Hospitalisation  Other: \_\_\_\_\_

Outcome of Event:  Complete Recovery  Death  
 Ongoing Condition / Sequelae  Unknown

Adverse Effect:  Abdominal pain  Fatigue  Rash  
 Constipation  Fever  Skin colourisation  
 Decreased hearing  Headache  Tinnitus  
 Depression  Joint pain  Tremors  
 Diarrhoea  Nausea  Vision changes  
 Dizziness  Psychosis  Vomiting  
 Other: list \_\_\_\_\_

Please prepare a comprehensive report on the serious ADE and its management and submit this to the National Coordinator **within five calendar days.**

Physician's Name \_\_\_\_\_

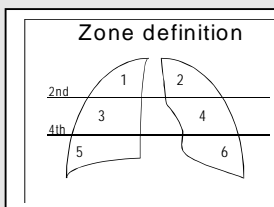
Signature \_\_\_\_\_

Date   /   /      
(ddmmyy)

# DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA

## CHEST X-RAY EVALUATION

Page 1



<input type="checkbox"/>	Bilateral
<input type="checkbox"/>	Effusion
<input type="checkbox"/>	Glands
<input type="checkbox"/>	Unilateral

**DIAGNOSIS:**                      **Date**      /   /      **(ddmmyy)**

<i>Disease (a)</i>	<i>Symbol</i>	<i>Score</i>
No disease	: Leave blank	0
< 50% of area affected	: <	1
≥ 50% of area affected	: >	2
<i>Cavitation (b)</i>	<i>Symbol</i>	<i>Score</i>
No cavitation	: Leave blank	0
Single cavity, <2cm diameter	: 1a	0.25
Single cavity, 2-4cm diameter	: 1b	0.50
Single cavity, >4cm diameter	: 1c	1.00
Multiple cavities, largest <2cm diameter	: 2a	0.50
Multiple cavities, largest 2-4cm diameter	: 2b	1.00
Multiple cavities, largest >4cm	: 2c	2.00

Zones affected	1	2	3	4	5	6
Disease						
Score (a)						
Cavitation						
Score (b)						
Total score (a) + (b)						
↓						
Composite score (all zones)		.				

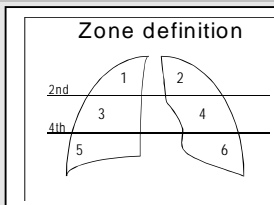
**END OF INTENSIVE PHASE:**                      **Date**      /   /      **(ddmmyy)**

<i>Disease (a)</i>	<i>Symbol</i>	<i>Score</i>
No disease	: Leave blank	0
< 50% of area affected	: <	1
≥ 50% of area affected	: >	2
<i>Cavitation (b)</i>	<i>Symbol</i>	<i>Score</i>
No cavitation	: Leave blank	0
Single cavity, <2cm diameter	: 1a	0.25
Single cavity, 2-4cm diameter	: 1b	0.50
Single cavity, >4cm diameter	: 1c	1.00
Multiple cavities, largest <2cm diameter	: 2a	0.50
Multiple cavities, largest 2-4cm diameter	: 2b	1.00
Multiple cavities, largest >4cm	: 2c	2.00

Zones affected	1	2	3	4	5	6
Disease						
Score (a)						
Cavitation						
Score (b)						
Total score (a) + (b)						
↓						
Composite score (all zones)		.				

## DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA CHEST X-RAY EVALUATION

Page 2



<input type="checkbox"/>	Bilateral
<input type="checkbox"/>	Effusion
<input type="checkbox"/>	Glands
<input type="checkbox"/>	Unilateral

**AFTER 9 MONTHS:**      Date   /   /   (ddmmyy)

<i>Disease (a)</i>	<i>Symbol</i>	<i>Score</i>
No disease	: Leave blank	0
< 50% of area affected	: <	1
≥ 50% of area affected	: >	2
<i>Cavitation (b)</i>	<i>Symbol</i>	<i>Score</i>
No cavitation	: Leave blank	0
Single cavity, <2cm diameter	: 1a	0.25
Single cavity, 2-4cm diameter	: 1b	0.50
Single cavity, >4cm diameter	: 1c	1.00
Multiple cavities, largest <2cm diameter	: 2a	0.50
Multiple cavities, largest 2-4cm diameter	: 2b	1.00
Multiple cavities, largest >4cm	: 2c	2.00

Zones affected	1	2	3	4	5	6
Disease						
Score (a)						
Cavitation						
Score (b)						
Total score (a) + (b)						
↓						
Composite score (all zones)		.				

**END OF TREATMENT:**      Date   /   /   (ddmmyy)

<i>Disease (a)</i>	<i>Symbol</i>	<i>Score</i>
No disease	: Leave blank	0
< 50% of area affected	: <	1
≥ 50% of area affected	: >	2
<i>Cavitation (b)</i>	<i>Symbol</i>	<i>Score</i>
No cavitation	: Leave blank	0
Single cavity, <2cm diameter	: 1a	0.25
Single cavity, 2-4cm diameter	: 1b	0.50
Single cavity, >4cm diameter	: 1c	1.00
Multiple cavities, largest <2cm diameter	: 2a	0.50
Multiple cavities, largest 2-4cm diameter	: 2b	1.00
Multiple cavities, largest >4cm	: 2c	2.00

Zones affected	1	2	3	4	5	6
Disease						
Score (a)						
Cavitation						
Score (b)						
Total score (a) + (b)						
↓						
Composite score (all zones)		.				

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
HIV HISTORY**

**HIV History**

**HIV Test Period**

- Diagnosis
- End of Treatment
- End of Follow-up
- Other

**Date of HIV Test  
(ddmmyy)**

		/			/				
		/			/				
		/			/				
		/			/				

**Test Results**

Pos	Neg
Pos	Neg
Pos	Neg
Pos	Neg

**HIV-Associated Illnesses/Conditions**

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA  
PATIENT STATUS AND FINAL OUTCOME**

**Discharge**

**Reason**

- Culture Conversion Achieved
- End of Intensive Phase
- Further Treatment Refused
- Treatment Terminated due to SDAEs
- Social Problems
- Disciplinary
- Other, list \_\_\_\_\_

**Sputum Status**

- Smear Pos/Culture Pos
- Smear Neg/Culture Pos
- Smear Pos/Culture Neg
- Smear Neg/Culture Neg
- Unknown

**Discharge Documentation Completed**

- Patient Treatment Card
- Patient Clinic Card
- Patient Referral Form

Discharged to

Date (ddmmyy)  /  /

Acknowledgement of Transfer  Yes  No

**Final Treatment Outcome**

- Cured
- Treatment Completed
- Treatment Failure
- Defaulted
- Died
- Transferred
  
- Lost to Follow-up

**Reasons for Not Treated**

- Died Before Treatment
- Untreatable Resistance Pattern: \_\_\_\_\_
- Disease Too Advanced
- Drug Intolerance
- Patient Refusal
- No Access to Care
- Drugs Not Available
- Not MDR-TB
- Other, list \_\_\_\_\_

Date (ddmmyy)  /  /

Completed by

Signature

**Follow-up Appointment Schedule Arranged**  Yes  No

Annexure 4

**DOTS-PLUS FOR MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA**  
**PATIENT REFERRAL FORM**

Transferred To  From

Address   
  
 Address

Tel: Code  Number  Tel: Code  Number

DOTS-Plus Registration Date  /  /   
(ddmmyy)

DOTS-Plus Number  /

First Name  Surname

Gender  M  F Race  1  2  3  4  9

Nationality  RSA  Other If Other, Specify

ID Number

Date of Birth  /  /  (ddmmyy) Age  yrs

Current MDR TB Treatment Status  Intensive Phase  
 Continuation Phase

Month of Treatment

Bacteriological Status  Smear Positive  Culture Positive  
 Smear Negative  Culture Negative  
 Unknown  Unknown

Comments

**ACKNOWLEDGEMENT OF TRANSFER**

Patient First Name  Surname

DOTS-Plus Number  /

Presented at Clinic Name  on Date  /  /

Seen by Name  Signature