

# HATiP

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# Managing MDR-TB in the community: from presentation to cure or end-of-life care

By Theo Smart

## Reviewers

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Thanks to: Dr Dennis Falzon, Dr Ernesto Jaramillo, WHO; Dr Joan Marston, Dr Liz Gwyther, Dr Kath Defilippi, Hospice Palliative Care Association (HPCA), South Africa; Dr Diana Gibb, UK Medical Research Council Clinical Trials Unit; Dr Simiso Sokhela, MSF Khayelitsha; Dr Graeme Meintjes, GF Jooste Hospital; Dr Sarah Cox, Chelsea & Westminster Hospital, London.

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## Key points

- **Assess, advise, agree, assist, and arrange. Find out about the patient and their life in order to create the best possible conditions for adherence.**
- **Empiric treatment (starting treatment before the results of a drug susceptibility tests are available) should be approached with caution in cases of treatment failure. Only a minority of first-line TB patients who deteriorate have MDR-TB.**
- **Second-line TB treatment should consist of at least four drugs including an injectable agent and two other agents, lasting for at least six months, followed by a further 12-18 months treatment without the injectable drugs.**
- **Moxifloxacin may be a useful drug for MDR-TB treatment, but is very expensive and few clinics have access to it. Greater advocacy is needed to bring down the price and increase access.**
- **Active monitoring of side-effects is important and all clinical staff attending the patient with MDR-TB should be aware of the major side-effects of all second-line drugs. These are nausea, vomiting, diarrhoea and skin reactions.**
- **Gastrointestinal problems are the main reason why patients stop MDR-TB treatment, so they need to be managed.**
- **Hypokalaemia (low potassium levels) leads to cramps, dizziness, numbness and confusion. It is a common side-effect of the injectable drugs, may be**

**life-threatening if severe, and can be treated with potassium and magnesium supplements.**

- **TB and HIV drugs can cause peripheral neuropathy (nerve damage in the limbs). Make sure the patient is taking pyridoxine.**
- **Observe patients carefully for hearing loss, a side-effect of the injectable drug kanamycin.**
- **End-of-life care for patients whose TB does not respond to treatment requires consideration of whether to stop TB treatment, and where individuals should receive end-of-life care.**
- **Dyspnoea (severe breathlessness) is likely to have the greatest impact on quality of life at this time. It can be managed with low-dose opiates.**

## Introduction

This HATIP looks at the sequence of care of a person with, or suspected of having drug-resistant TB, from case detection to cure or, when a cure cannot be achieved, through end-of-life care — an aspect of care which has been overlooked by TB control programmes and clinical research.

It is the fourth in a series of articles looking at the management of multi-drug resistant TB in the community. Previous articles covered the epidemiology and implications of MDR-TB in people with HIV ([HATIP 162](#)); how to improve diagnosis and case detection ([HATIP 164](#)), and models of MDR-TB care delivery in community settings ([HATIP 165](#)).

This HATIP describes the sequence of care, and highlights some of the key messages, challenges and controversies in care as described at recent conferences, discussions with our panel of experts and during site visits in India and Khayelitsha, South Africa.

We hope to underscore the importance of adopting a palliative care approach when working with individuals and families affected by drug-resistant TB, often in the context of HIV.

## Why a palliative care approach to MDR-TB is necessary

"I'm still very much influenced by my background as a doctor and clinician and so want to see we can support countries and governments to care for people, not just cure pieces of lungs that happen to be sick, but to look at the individual. It's difficult to come out with these ideas in an environment where things are so focused on outcomes, how many people cured, how many DOTS programmes are [being created]. But how about all the people, how about those that we are not curing? What are we doing to provide for these people and families and relatives with decent care — and not just delivering pills?" Dr Ernesto Jaramillo of WHO's STOP TB Department told HATIP.

This patient-centred approach — one that considers the physical, emotional, psychosocial, material and spiritual needs individual with M/XDR-TB and his or her family — could improve the health outcomes (and help TB programmes reach their targets) whether the person is managed at a hospital, a clinic, or in their home. But much more importantly, it should reduce suffering and improve the quality of life for the affected family, regardless of the outcome.

A palliative care patient-centred approach should be incorporated into each step of care, from presentation through to end of life care. To support the palliative care needs of people with M/XDR-TB, a number of resources are in development, for instance,

the Hospice Palliative Care Association (HPCA) is in the process of finalising guidelines for the provision of palliative care to patients with drug-resistant TB.

We should first start however by pointing out that the guidelines for M/XDR-TB care are addressed by a number of WHO documents: the 2008 edition of the Guidelines for Programmatic Management of Drug-Resistant TB (PMDT), and its accompanying [Field Guide on the Management of MDR-TB](#) which are both soon to be updated. In addition, the 2010 Treatment of Tuberculosis Guidelines contains some of key updates (such as a shift in emphasis towards universal access to diagnosis and care).

As this HATIP goes to press, the best published resource on the topic that we can identify is the Field Guide, authored by Dr Kwonjune Seung and Dr Hind Satti of Partners in Health Lesotho.

This article relies heavily on their guide, which follows the format of the Integrated Management of Adolescent and Adult Illness (IMAI) module, describes how to provide care and treatment at the primary care level. It recommends that healthcare workers use the general principles of good chronic care with their client:

1. Develop a treatment partnership with your patient
2. Focus on your patient's concerns and priorities
3. Use the 5 A's—Assess, Advise, Agree, Assist, Arrange (see section on adherence below for example)
4. Support the patient's education and self-management
5. Organize proactive follow-up
6. Involve 'expert patients', peer educators and support staff at your health facility
7. Link the patient to community-based resources and support
8. Use written information—registers, treatment plans, the patient calendars, treatment cards—to document, monitor, and remind
9. Work as a clinical team (and hold team meetings)
10. Assure continuity of care

We would urge you to download this version of the field guide. Another version is in the works, which we understand will contain more information than is currently in the Guidelines for Programmatic Management of Drug-Resistant TB (PMDT), which will no doubt be useful. However, the simplicity of the field guide makes it very handy for nurses and other mid-level cadre health workers to use.

## First contact, triage, and baseline assessments

The first contact with the patient will differ somewhat depending upon how their case was identified and the type of facility that initiates TB treatment. If only certain TB facilities are managing MDR-TB cases, the patient will have to be traced and contacted in order to be admitted into the programme, while programmes that have integrated MDR-TB management into existing primary TB care clinics — such as in Khayelitsha — will already have the client in care. Upon enrolment, some programmes assign the patient to a nurse or community health worker, who becomes responsible for contact, initial assessments and follow-up.

If the patient first comes in to a clinic for care, the Field Guide recommends triage basics. After receiving the client and retrieving their records, health staff should make certain that smear-positive cases are instructed in cough hygiene, and to first attend to new smear-positive MDR-TB cases (who are likely to be infectious since they are not yet on effective treatment). The field guide recommends that the facility should follow good infection control practice in the waiting areas — isolating people with HIV away from

smear-positive TB cases, and isolating smear-positive MDR-TB cases from other TB cases.

It is notable that the approach to separating clients due to HIV status and infectiousness is different in some facilities, however. Since the most infectious TB cases and most susceptible HIV patients are usually undiagnosed when they arrive at the facility, some clinics have everyone wait in highly ventilated or outdoor waiting areas — and to make certain that everyone wears surgical masks and practices cough hygiene (as is done in the Ubuntu Clinic in Khayelitsha).

Furthermore, having everyone wear a surgical mask may also be less stigmatising for the person suspected of having drug-resistant TB. These waiting rooms are public places, and different isolation policies for different individuals could mark them in the community or potentially disclose their HIV status.

During the first meeting with someone who has been newly diagnosed with drug-resistant TB, education and adherence preparation are essential; baseline clinical and laboratory work should be performed; and there should be an assessment of the family status and the patient's other psychosocial and socioeconomic circumstances.

## Education and preparing for adherence

"Addressing adherence is the key to success," said Dr Hind Satti at the 40th Union World Conference on Lung Health in Cancun. This is an understatement — and adherence preparation is even more essential in a person with drug-resistant TB, particularly for those who acquired drug resistance due to poor adherence. The Field Guide suggests using the Five A's, which we have abbreviated as follows:

### Assessing

the patient's level of understanding about TB, its treatment and drug resistance is the first step in the education and adherence preparation process. Finding out whether the patient knows his or her HIV status, and assessing their treatment history, ability to keep appointments, and to adhere to other medications are also recommended.

It may be useful to have the attending nurse fill out a questionnaire regarding the psychosocial and socioeconomic circumstances of the patient as it can provide insight for the community staff regarding what to expect when visiting the patient and their family in the home.<sup>1</sup>

### Advise:

The health care worker should explain key educational messages about drug-resistant TB, such as how it evolves, how it is transmitted, and how people with HIV are more susceptible. The patient should be told that he or she may be infectious, particularly while smear-positive, and that he or she needs to be conscious of infection control in the home and other areas (for instance, they should wear a surgical mask when using, or avoid, public transport).

DR-TB treatment and its duration need to be explained — including the fact that there is no other treatment. In addition, the patient (and their treatment supporter at subsequent visits) should be told about the side-effects of second-line TB treatment that can be managed, if the patient and their treatment supporter communicate problems with the DR clinical team.

### Agree:

The treatment partnership requires that the patients agree to take the full course of treatment and to attend scheduled clinic visits. If care is clinic or community-based, one of the first things to do is discuss with the patient and agree with the patient on a treatment supporter (the health staff should be prepared to offer a list of possible candidates who are willing and who live nearby).

#### Assist:

The patient can be given advice to facilitate adherence. They can also be put in contact with support groups and assisted with accessing social grants, food or nutritional or transportation support if needed and available. Those who live in especially remote areas may need assistance relocating closer to the clinic.

#### Arrange:

If the patient is receiving injections at home, these should be arranged. Arrangements should also be made to educate the treatment supporter, family, and to conduct contact screening and assess infection control in the home.

A similar process could be used during subsequent visits to monitor adherence, to determine if there is a problem and assess the reasons for non-adherence. Is it due to side-effects or forgetfulness? Are there problems with the treatment supporter? Are there financial, transport problems or a lack of food? Are there problems at work? Is the patient seldom at home and disorganised? Are there other medical problems or substance use issues? Is the patient depressed? Key messages about treatment and adherence can be reinforced as needed.

Staff should also assist the client with aids or skills to improve adherence, and try to make sure that the patient has adequate support by obtaining help from family and friends, working with the treatment supporter to find solutions or referring them to a support group. Referrals can also be made for members of the clinical team for medical or psychological care, or arrangements made with a social worker or local NGO's to help the patient get needed socio-economic support.

### Adherence support at TRC in India is individualised - and based on getting to know the patient

"MDR-TB patients are a difficult lot to deal with. We find many of them just give up, are angry, feel hopeless. So we try to find what it is that challenges them. But one thing which we try to contribute a lot is motivation," Dr Beena Thomas of the Tuberculosis Research Centre (TRC) in Chennai, India, told HATIP.

The TRC runs many important TB clinical trials and maintains a very high rate of adherence despite what are sometimes challenging protocols for the patients. Part of this is due to careful patient selection, but Dr Thomas explained that they spend time getting to know the patient. Then they use what they have learned to work through whatever the barriers to adherence might be.

She explained that TRC is conducting a DOTS-plus MDR-TB study. Upon diagnosis, treatment is begun almost immediately but the Centre encourages the patients to be admitted to the hospital for two months, or "at least for 15 days until they feel that the client is okay with coming to take their injections," she said.

Dr Thomas described one case where a patient was threatening to quit the study (and treatment). Quitting the study she said was one thing but to quit treatment was another problem altogether.

"I had to sit with him for about an hour. His problem was [the requirement] to take 24 months of treatment — that and his family.

His whole family has written him off as a diseased person. Because of the twenty-four months of treatment [when they knew it normally took six months to treat TB], they said 'what's *wrong* with you!' On one hand, they are trying to be over-indulgent but at the same time they are making the patient feel like he is the most useless human being on earth. Everyone is telling him what to do. And his wife is getting upset."

So Dr Thomas had to call various family members and speak to the wife. "Then I explained to him everything about his lab results, which is another thing which is hardly done — how many people take time to explain to the patient their investigations, and the research?"

"And I had to keep saying: 'Forget you say you are hopeless, you don't want treatment, you've reached the end of your tether. You are responsible for this lady here. So it's not about you alone. You have to look after yourself, get well, to look after her,' — and they are married for hardly two years. — 'you need to start a family. Why do you make yourself feel like as if you've got some terminal illness where you don't — just because you have to take 24 months? Just get on with it! And with some support of your wife, you are going to really respond and then you know.'

"It was a 'love-marriage' [as opposed to an arranged marriage] so I worked on that. I said, 'What's this romance about? Unless you get well, you can throw romance out of the door and I said, 'What about your sex life?' So we talked about that. So I said: 'Hospitalised all the time? This is not fair to her. She left her family, she had a tough time - all for you - and this is what you give her?'

"It took at least a couple of hours over a couple of visits with them. But today that guy comes so regularly, and he is doing so, so well."

Dr Thomas clearly takes a somewhat aggressive approach to adherence support, and it may not work for everyone or in every culture. But the main point is that she gets to know the person and the family first before she decides on an individualised intervention. And it is hard to argue with her results — TRC studies have a very low rate of drop-outs and loss to follow-up.

### Peer-delivered adherence support in Khayelitsha

**Someone with personal experience taking a second-line regimen may best be suited to follow-up on difficult patients. Busisiwe Beko is a former MDR-TB patient, who supports adherence of people with MDR-TB in Khayelitsha. A video shown at the 2<sup>nd</sup> South African TB Conference, followed Ms Beko around on the job. After leaving the clinic, she spends most afternoons walking the backstreets of Khayelitsha looking for defaulters, to stress the dangers of not going back to treatment.**

**The video showed her approaching one woman who has become a regular on her rounds.**

**"You KNOW the risks, Umtumiseko!" said Ms Beko.**

**"Do you want to kill everybody here in Khayelitsha?"**

**The lady gestured 'No.'**

**"So what do you want to do? Nothing? You are not going for the treatment?" said Ms Beko. "These drugs, if you are going to take them `on and off, on and off` you are going to get resistance. And then from there you will**



**get extremely drug-resistant TB. So we have to stop the treatment until you decide that you want to take the drugs. Please don't do this."**

**However, at the conference, an audience member noted that this sort of work can take a toll on peer adherence supporters, who may need special psychosocial support and training in order to keep working with sometimes very challenging cases.**

## Clinical and laboratory assessments

At the first visit, the patient's medical history should be reviewed, particularly their history of past TB treatments. At each visit, the patient should be asked about their general health, whether they have recently needed urgent medical care, and about TB symptoms and whether they have improved.

Once a person with MDR-TB has started treatment, they should be asked carefully about side-effects such as nausea/vomiting, fatigue, skin rash, tingling in hands or feet, deafness or ringing of ears, headache, seizures or loss of consciousness, and whether they've had feelings of anxiety, sadness or depression. Routine clinical assessments for weight loss, anaemia, jaundice and thrush should also be performed.

Many programmes developed standardised checklists to make certain that the patient is asked about each important symptom at every follow-up visit. But it is particularly important to know whether the patient is pregnant, has a liver problem, diabetes, heart or kidney disease before starting a second-line TB regimen (pregnancy is not a contraindication for MDR-TB treatment, but ethionamide and injectable TB drugs should probably be avoided in pregnant women).

The Field Guide recommends that before starting on second-line TB treatment, the patient should have a complete blood count (CBC), and their aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, creatinine, and potassium levels checked the first few months, while thyroid-stimulating hormone levels should be checked at month two and intermittently thereafter. Women should have a pregnancy test. Provider-initiated HIV testing and counselling should be offered to all patients whose HIV status is unknown. Those who are HIV-positive, should have a CD4 cell count, and haemoglobin levels should be checked for any patient who is beginning an AZT-containing ART regimen.

## Schedule of lab work for people with MDR-TB (adapted from the Field Guide on the Management of MDR-TB)

Month	Clinical consult	Smear	Culture	DST	AST, ALT, bili†	CR, K†	TSH
1	Every 2 weeks	√			√	√	
2		√			√	√	√*
3		√	√		√	√	
4	Monthly	√					
5		√					
6		√	√	√			√
7		√					
8		√					

9		√	√				
10		√					
11		√					
12		√	√	√			√
Until completion	Monthly	Every three months	Every six months				

† Liver function and renal function tests may be done at any time when clinically indicated.

\* TSH in month two is recommended in settings with early onset of hypothyroidism.

## Assessment of the family situation and infection control in the home

As already noted, the patient should be asked about their family (including pregnancy status in women, who should practice contraception while on MDR-TB treatment). Immediately after admission into a community-based or clinic-based programme, community workers/outreach staff should visit the home and screen all the household contacts for HIV and TB.<sup>2</sup> The visit also offers an opportunity to educate the family to support the person with MDR-TB, and to assess and make recommendations for improving infection control in the home.

"An individual infection control plan is devised for each patient. Those who are believed to be highly infectious are relocated to PIHL rental homes until they are sputum culture-negative (thus avoiding hospital admission)," according to a poster at the 2<sup>nd</sup> South African TB conference (2<sup>nd</sup> SATB).<sup>3</sup>

## MSF's approach to infection control in the home and community

"Most transmission probably occurs before diagnosis and treatment initiation, and improving case detection and getting more patients onto treatment earlier is key to reducing transmission," Dr Helen Cox of MSF in Khayelitsha said at the 2<sup>nd</sup> SATB conference earlier this year. "We have more than 60% rate of culture conversion by two months of treatment in our programme, and although we don't really have a measure for infectiousness, in light of Dr Ed Nardell's research (see previous HATIP), clearly infectiousness will have dropped rapidly considering how quickly people are culture converting. So given the relative proportion of patients who are undetected and undiagnosed, the risk of infection is really there."

"Consistently, however, there are around 10% of patients who have not culture converted by six months of treatment, and these are very important patients, because they will still be infectious and they will still be in their homes. So I think it emphasises the importance of proper monitoring and monthly cultures and actually identifying these patients so that we take extra measures such as changing their treatment, hospitalising them or taking extra infection control measures in the home," she said.

To assess and improve infection control in the home, a counsellor visits each household, to educate the patient and family members, to talk about TB transmission, what is this disease, how does the treatment work, etc. But included in the visit is an assessment of the vulnerability of that particular household when it comes to TB transmission risk — how overcrowded is the home, does it contain people who are HIV-positive, are there very young children, are there concomitant illnesses?

From this visit, a risk reduction plan is formulated specifically for that household. Dr Cox said that a “major part of it is education about TB transmission and cough hygiene — together with separate sleeping arrangements. The patient is also encouraged to wear a paper mask in overcrowded and closed conditions, and the caregiver is provided with N95 respirators. We also provide follow-up and support.”

But Dr Cox didn't place that much emphasis on ventilation. “It's very hard to keep windows open, there are security issues and it's cold — so it is something that, in practical terms, is not that easy to do,” she said. She added that although they haven't performed a formal evaluation, they have observed that among 80 houses visited, about 67 were able to make arrangements for the patient to sleep alone. Some additional shacks have been provided, and there have been some cases where they decided that they needed to admit patients for infection control-related reasons.

## Treatment: empiric treatment and optimising regimens

Once adherence preparation has been completed, it is important to get someone on an effective regimen as quickly as possible. But knowledge of what regimen to use — or even who to treat — is limited by lab capacity.

HATIP 164 described how most countries do not yet have access to rapid drug sensitivity testing, and as a site visit to Khayelitsha demonstrated, even when the new tests are being rolled out, it takes a while to use them to their full potential in the clinic (at present rapid DST is only being conducted on cultures). In other words, it can take at least one month to confirm drug-resistant TB in suspected cases, and the process takes longer when rapid drug susceptibility testing is only performed after documented treatment failures.

In the meantime, clinical decisions need to be made about how to treat people at risk of resistance — keeping in mind that people with HIV in particular, may not survive long on ineffective first-line treatment. In some cases, empiric treatment for drug-resistant TB may be warranted — but there are few clinical data, and opinions vary widely on the subject.

In Lesotho (and in the Field Guide), the following protocol is recommended for empiric treatment.

Whenever anyone is categorised as being at medium or high risk of DR-TB (based upon their treatment and contact history), two sputums are sent out for culture and DST.

The initial treatment while waiting for the DST results depends upon categorisation by risk of resistance. Migrants and health workers with TB are categorised as being at risk for DR-TB but are placed upon a first-line regimen until DST results come back indicating the need for second line treatment.

Previously treated patients who have defaulted or relapsed are placed upon what was once called the ‘category II regimen’ or now, the retreatment regimen (a slightly prolonged and beefed up version of the standard regimen with streptomycin thrown in). WHO wants to move away from the retreatment regimen as rapid DST becomes more widely available, because it is not effective against drug-resistant TB and it is unnecessary for drug-susceptible TB.

People with active TB who are household contacts of a person with M/XDR-TB are placed upon the same second-line TB treatment that their contact is taking. For anyone with a history of treatment with second-line drugs, a specialist is consulted to help construct an individualised regimen (avoiding previously used drugs if possible). Probable treatment failures, including anyone who is smear-positive

in the fifth month of the first-line or re-treatment regimen, or people with HIV who worsen on treatment, start with a standardised second-line treatment regimen. But, the Field Guide notes: “there are many reasons for clinical worsening in HIV-positive patients besides treatment failure. Consult specialist for advice.”

Dr Hind Satti insisted that, in Lesotho at least, “We find empiric treatment of MDR-TB suspects is very helpful in decreasing early mortality of these patients and this is why we worked out the protocol for medium and high-risk patients.”

In other settings, though, clinicians are likely to wait for more laboratory or clinical confirmation of failure on first-line treatment. During a visit to the Ubuntu clinic in Khayelitsha, we learnt that if a household contact of a person with M/XDR-TB develops active disease, the care team doesn't immediately put the person on the same treatment as the index case, because they have found that in most of the cases, the person will have drug-susceptible TB (which is really ubiquitous in this setting). However, they will send out for a rapid DST and switch treatment if necessary based upon those results. And according to Dr Simiso Sokhela, a clinical officer at the site, they still commonly use the retreatment regimen.

“The few cases that have had empiric TB treatment, it will be discussed and started on by specialists. We can't do it on a clinic basis. We have to refer to somebody else to make the decision to start on empiric MDR-TB treatment. But the best that we can do is the retreatment regimen, which is just adding one drug to a failing regimen,” she said.

“We do have to be careful about starting patients on empiric treatment for failure,” Dr Helen Cox said. “Because in Dr Graeme Meintjes and Dominique Pepper's study on deterioration on TB treatment, drug-resistant TB is only a small fraction of that. There are all of these other reasons for failure.”

Indeed, in the study by Pepper et al in people with HIV and TB on dual treatment, only 10% of the clinical deterioration that occurred was due to drug-resistant TB, while 72% was due to other illness, most commonly other AIDS-defining events. TB Immune Reconstitution Inflammatory Syndrome was a greater cause of illness than MDR-TB (18%).<sup>4</sup>

Dr Graeme Meintjes of GF Jooste Hospital explained his view on the matter to HATIP.

“Regarding the decision to start empiric MDR treatment in a patient suspected of having MDR TB before lab confirmation, there is no clinical data on this that I am aware of. My view is that this should only be done in exceptional circumstances given the toxicities, duration, cost and poorer efficacy of MDR-TB treatment. The latter consideration is important because starting a patient with susceptible TB on MDR treatment is doing them a major disservice. My approach is to only consider MDR-TB treatment empirically in the following circumstance:

- The patient is hospitalised
- The original diagnosis of TB is proven by smear or culture
- Other causes for deterioration have been excluded
- The patient is deteriorating with features of TB despite adherence to TB treatment
- If this patient had MDR-TB and I don't start MDR-TB treatment they are likely to die within the next 2-3 weeks (respiratory distress, severe wasting syndrome, neuroTB, etc)
- That several clinical specimens have been sent for culture and DST
- Then start 3 MDR-TB drugs in addition to *Rifapir* while awaiting the DST result
- Follow up clinical and lab results closely”

Only a minority of patients who deteriorate have MDR. This is relevant to the decision.”

The starting second-line regimen can vary from place to place — in Nepal for instance, the standardised regimen has been selected upon the basis of resistance surveillance studies of the population — and according to the recent paper by Malla et al, this was simpler for supply logistics and for providing standardised training to health personnel.<sup>5</sup> In other settings, programmes use a broad standardised regimen with the goal of having several active drugs, which might be modified based on treatment or contact history, and then modified again on the basis of DST results once they become available.

WHO's recent TB Treatment Guidelines lists five groups of drugs to treat M/XDR-TB:

Group 1: First line oral agents: pyrazinamide (Z), ethambutol (E), rifabutin (Rfb)

Group 2: Injectable agents: kanamycin (KM), amikacin (AM), capreomycin (CM), streptomycin (S)

Group 3: Fluoroquinolones: levofloxacin (Lfx), moxifloxacin (Mfx), ofloxacin (Ofx)

Group 4: Oral bacteriostatic second-line agents: para-aminosalicylic acid (PAS), cycloserine (Cs), terizidone (Trd), ethionamide (Eto), prothionamide (Pto)

Group 5: Agents with unclear role in treatment of drug-resistant TB: clofazimine (Cfz), linezolid (Lzd), amoxicillin/clavulanate (Amx/Clv), thioacetazone (Thz), imipenem/cilastatin (Ipm/Clv), high-dose isoniazid (high dose H), clarithromycin (Clr).

The TB Treatment Guidelines state that treatment regimens should consist of at least four drugs with either certain, or almost certain, effectiveness, including whatever first-line drugs to which the individual may still be susceptible to. If the effectiveness of a certain drug is not clear (and for some drugs, this may be because DST results are less reliable), the drug may be used, but it should not be depended upon as one of the four drugs. Group 5 drugs are generally reserved for XDR-TB regimens (and to some extent, are only used because it is difficult to come up with any other options). More detailed information on each drug, including adverse effects, contraindications, monitoring, and dosing based on weight bands is available in the annexes of the Treatment of Tuberculosis Guidelines (4<sup>th</sup> Edition).

Treatment is generally given in an intense phase (with more drugs) for at least six months (Nepal treats intensely for eight months) followed by a less intense phase of 12-18 months (usually without the injectable drugs).

### Optimising the regimen in Khayelitsha

“We need a regimen that requires minimal adjustment once we have DST available, because otherwise, we risk losing the drugs that we are using at that point of time,” Dr Helen Cox said during yet another presentation at the 2<sup>nd</sup> SATB Conference titled “One chance of cure and the need for a strengthened starting regimen in South Africa.”

At present, South Africa's standard starting regimen is kanamycin, ofloxacin, ethambutol, pyrazinamide, ethionamide and terizidone (which has only recently been added). But Dr Cox walked the audience through a case study to illustrate some of the common problems with this regimen.

In the case study rapid DST results have shown that the patient is resistant to isoniazid and rifampicin. When the culture DST results come back, they indicate that the person is resistant to ethambutol and ofloxacin. Unfortunately, DST isn't reliable when it comes to

pyrazinamide or ethionamide, so “we have got two drugs in the regimen that may be working for this particular patient. While we have a lower risk of developing XDR-TB [than when terizidone wasn't in the regimen], I'm sure most of you who are treating DR-TB would not rely on just two drugs in the regimen - it's not going to be effective at all,” Dr Cox said.

At MSF, they have decided to replace ofloxacin with moxifloxacin, which data seem to suggest may be effective against some ofloxacin resistant strains. “[And when the DST results come in] we can also add further drugs like PAS at this point, because we not actually adding a drug to a failing regimen. Hopefully, at this point we've had three drugs on board that are working and it's not going to fail. So we have a much lower risk of XDR-TB developing,” said Dr Cox.

But there is a problem with this approach. MSF is currently supplying the drug on a pilot basis in Khayelitsha — no one else can afford it. “Moxifloxacin is currently incredibly expensive and very few national programmes - including South Africa - can afford to purchase this drug at this current point of time. And it's certainly not something that we would expect until the price comes down. So we need much more advocacy to reduce the price and increase access to moxifloxacin. And certainly MSF internationally is working on this because we feel that this is a key drug for DR-TB, that people who have DR-TB should have access to,” she said.

In the meantime, South Africa is considering replacing ofloxacin with high dose levofloxacin, which may also retain some activity against ofloxacin-resistant TB.

In fact, in a review of the second-line drugs given at the Union World Conference on Lung Health in Cancun last year, Dr Salmaan Keshavjee, or Harvard University and the Green Light Committee noted “there may be things about these fluoroquinolones and the way that they're working that we're not fully knowledgeable on yet.”

### MDR-TB palliative care in children

A couple years ago, HATIP published a clinical review series on TB in children. One of the cases cited in the series concerned a child with XDR-TB that failed to respond to any treatment. But as Dr Diana Gibb, of the UK's Medical Research Council Clinical Trials Unit pointed out to HATIP, the diagnosis, care and management of children suspected of having MDR-TB, XDR-TB is extremely difficult.

“Diagnosis of children with MDR or XDR TB is very difficult as we know,” she said. “For instance, it is very difficult to get a sputum specimen from a child - and without sputum, it is difficult to get culture or DST. Thus detecting resistance has to be done almost by proxy - in other words, if a household adult has MDR or XDR. And then what about treatment? It's going very slowly for kids.”

Commonly, children with TB who are household contacts of a person with M/XDR-TB are treated with the same drugs as are used in their parents. However, Dr Tony Moll, describing contact tracing in the community at the Union World Conference on Lung Health in Paris in 2008, noted that most of the child household contacts of XDR-TB patients that they identified appeared to have drug-susceptible disease, or to at least respond to standard treatment.

In Khayelitsha, however, some children are being managed as though they have drug-resistant TB. According to Dr Cox, they consult with a specialist, who “looks at how close the index case is to the child and the age of the child, and makes an assessment on that. Obviously, the risk of drug resistance is high, if the child is being breastfed by the index case, who's smear-positive drug-resistant TB.

"The decision on what to use for treatment is based upon the proximity of the contact," said Dr Sokhela, "but we've had a few children who've had no TB contact in the house at all. So we do know they have contacts elsewhere. But at the same time, just because there's an active M/XDR-TB case in the house, doesn't mean they might not have another contact elsewhere with drug-susceptible TB."

Dr Joan Marston of the Hospice Palliative Care Association of South Africa told HATIP that these children have special palliative care needs: "What we are seeing in children's palliative care is that children are admitted with drug-resistant TB, often for periods of up to two years, and need to have special schooling in hospital, where this is available."

"Often for financial reasons, families cannot visit regularly and the contact between the child and family is broken. I have seen children suffering from depression due to the separation and families eventually abandoning the child. Children's hospices may then admit children who are smear-negative for completion of treatment and are then faced with the problem of re-integrating children into their families or finding alternative care. Children need intensive support through this period and after they leave hospital after they are reintegrated."

## HIV care in people with MDR-TB

A number of studies appear to indicate improved outcomes even of XDR-TB in people who are on antiretroviral therapy; and it is WHO policy to initiate ART treatment as soon as feasible in people who are coinfecting with TB and HIV. Likewise, cotrimoxazole prophylaxis should be given to all TB patients with HIV. However, as in TB programmes in general, this will require very strong linkages between DR-TB care delivery sites or complete 'one-stop' service integration to get people with drug-resistant TB onto ART in a timely fashion. Clinicians should be on the alert for TB-IRIS however.

### Manage common clinical problems

Palliative care looks beyond simply treating the pathogen, but strives to relieve the symptoms and suffering associated with the illness. The following section is abbreviated from the *Field Guide*.

- **Cough or difficult breathing:** TB causes cough that may take several months to resolve despite effective TB treatment, and in some cases scarring of the lungs can lead to worsening wheezing. In addition, secondary bronchitis or pneumonia can occur. In people with HIV, *Pneumocystis jirovecii* pneumonia (PCP) may need to be considered. In people who have recently started ART, a worsening cough may be a sign of TB IRIS. If difficulty breathing is associated with nausea and abdominal pain in someone taking d4T, it may be a sign of lactic acidosis. A beta-agonist inhaler may relieve coughing and wheezing. When there is severe shortness of breath, a short course of prednisone (10-20 mg) daily for seven days may be considered.
- **Haemoptysis (coughing up blood):** Chronic haemoptysis with small amounts of blood is common and may take months to resolve on effective TB treatment, but can be dangerous and life-threatening if there is a large volume of blood. Call a specialist.
- **Persistent fever:** TB-related fever may take months to resolve. Other fevers could be due to other common causes or TB IRIS. Supportive care includes increased fluid intake to prevent dehydration, moderate doses of paracetamol, and sponging with tepid water if the patient wishes.

- **Persistent nausea or vomiting:**

A number of the second-line TB drugs can cause persistent nausea or vomiting, usually ethionamide (more immediate) or PAS (more delayed). The effect is dose-related but reducing the dose may lead to treatment failure, so consult for advice. Antiretroviral drugs such as AZT can cause transient nausea; if associated with d4T and shortness of breath it may be a sign of lactic acidosis.

- **Supportive care:**

It is important to encourage the patient to keep taking treatment – gastrointestinal side-effects are a leading cause of treatment discontinuation, and are worse at the start of treatment. Staggering the doses so the patient does not have to take all drugs at once and giving soft porridge before taking the doses may reduce nausea. Increase fluid intake to prevent dehydration, with non-caffeinated, non-alcoholic drinks. Give metoclopramide (10 mg every eight hours, or 30-60 minutes before doses).

- **Persistent diarrhoea:**

Persistent diarrhoea may be caused by PAS but in people with HIV, there may be an infectious cause that should be treated empirically. Supportive care includes increasing the patient's fluid intake to prevent dehydration. Give oral rehydration salts if there is a large volume of diarrhoea. If the diarrhoea is drug-related, consider a constipating drug unless there is blood in the stool or fever is present or if the patient is elderly. Advise the patient on care for their rectal area and a supportive diet.

- **Peripheral neuropathy:**

Many TB and HIV drugs can cause peripheral neuropathy that can result in permanent nerve damage. If d4T is causing neuropathy, switch to tenofovir or AZT. If cycloserine/terizidone or an injectable is causing neuropathy, discuss the risks and benefits of decreasing the dose or stopping these drugs – one of the risks is treatment failure. Supportive care: make sure the patient is taking pyridoxine. See [HATIP 133 on peripheral neuropathy](#).

- **Depression, anxiety or psychosis:**

Depression and anxiety can be caused by many things in people with drug resistant TB, including socioeconomic problems. In people with HIV, it is sometimes associated with efavirenz. However, terizidone or cycloserine can cause severe depression, anxiety or psychosis and can even lead to coma. Symptoms usually improve when the dose of cycloserine is decreased. Stop cycloserine immediately if the patient is suicidal or psychotic.

- **Hypokalaemia (low potassium):**

Low potassium levels are common in severely ill patients and may be caused by a variety of things including vomiting, diarrhoea, drugs and other reasons. It may present with symptoms such as fatigue, cramps, numbness, paraesthesias, leg weakness, palpitations, somnolence, and confusion. The injectable drugs, particularly capreomycin, can cause hypokalaemia due to its effects on the kidney. Potassium should be checked on a regular basis whenever beginning to use an injectable. Management: give the patient oral potassium and magnesium supplements, and check the potassium in a few days. In severe cases, intravenous replacement is needed. Call for advice.

## Managing the side-effects of drugs

A table in the Field Guide provides a good overview of the side-effects of second-line TB medications. At recent meetings the extremely high rate of adverse events seen with these drugs has



also been discussed extensively. According to Dr Satti, the rates appear higher in southern Africa.

“For inpatients we usually admit very sick patients *mostly co-infected*, they are bedridden and severely wasted with severe opportunistic infections or patients who develop severe side-effects, among them liver toxicity [severe hypokalemia] and acute renal failure,” she said. “We’ve tried to compare what side-effects that we are seeing in our patients with those happening in the rest of the countries. And it was very interesting to see a big, huge difference between the percentage of side-effects that we are observing among our patients and what the community is reporting from other countries. Is it related to HIV-infection? Or is it related to severe malnutrition that we are observing among our patients?”

At the 2<sup>nd</sup> SATB Conference, Karen Shean of the Lung Infection and Immunology Unit of the University of Cape Town reported similar findings in South Africa.

“We know that drugs are poorly tolerated but we have few data, especially in low-income countries, about severity of side-effects and tolerability of drugs, specifically second-line drugs,” she said.

“We do know however that from a study done on defaulters on patient-related reasons as to why they interrupted treatment, the highest cause was side-effects. So we know we have a problem. But what is the effect of HIV infection on treatment and adverse side-effects? How does it affect tolerability and severity?”

Ms Shean, who is a nurse, conducted a retrospective review of 115 XDR-TB cases from Upington, Cape Town and Johannesburg looking at how XDR-TB regimens were tolerated, whether people with HIV had more severe side-effects and how the adverse events affected outcomes. Sixty-seven of the 115 (58%) reported adverse events.

Drugs used in regimens (n=115) and the severity of the events	
Drug	Number of events (% of severe events)
Ethambutol	19 (41%)
Pyrazinamide	24 (30%)
Amoxicillin-clavulanate	19 (29%)
Dapsone	9 (25%)
Capreomycin	26 (25%)
Clarithromycin	23 (23%)
Terizidone	25 (24%)
Ethionamide	21 (24%)
PAS	24 (24%)
Ofloxacin	6 (21%)
INH	5 (13%)

20% of the cases, or one in five, had a severe side-effect — severe enough for the drug to be stopped, to be life threatening or even cause death (which occurred in 6 patients or 3.7%).

The most common side effects (n=161)		
Side-effect	HIV-positive	HIV-negative

nausea and/or vomiting	17 (46%)	20 (54%)
diarrhoea	8 (36%)	14 (64%)
other GI symptoms	5 (25%)	15 (75%)
dizziness	5 (33%)	10 (67%)
hearing loss	2 (20%)	8 (80%)
renal failure	6 (60%)	4 (40%)
body aches/cramps	5 (50%)	5 (50%)
headache	4 (50%)	4 (50%)
skin reaction	4 (57%)	3 (43%)
hypokalemia	5 (71%)	2 (29%)

Women were significantly more likely to experience severe ADRs ( $p=0.014$ ) as were people with HIV ( $p=0.045$ ). In addition those with severe ADRs have poorer treatment related outcomes, with a lower sputum culture conversion rate and a higher mortality rate.

“Early detection and monitoring of ADRs is crucial. All levels of healthcare workers need to know the side-effects of their drugs, and I’m afraid we fall down very badly on that. Unless we have early ‘picking-up’ or monitoring and finding of these side-effects and early management of these side-effects, we are losing patients. Not only to interruption but also to very severe side-effects,” Shean said.

### Peer support

There was considerable discussion of how to manage these side effects at the 2<sup>nd</sup> South African TB Conference. One member of the audience asked whether people were really experiencing the symptoms or whether they had simply heard and were afraid of the symptoms — pre-emptively complaining.

“The patients have a very good idea about which drug is causing their side-effect. And sometimes when you see a doctor stopping 3 or 4 drugs and then reintroducing and stopping this and starting that, you often wonder why they don’t ask the patient, because the patients know very well. Even children can identify which tablet is causing the problem,” she said.

“But the downside of that, is that they tell each other. Often they spread that perception around and you find in one ward that a whole lot of patients will be refusing treatment. I think these kind of things really need to be explored. Is he now stopping it because he knows it’s causing him gastric problems? Or is it because the mate next door to him has said, ‘I’m not taking it! I wouldn’t take it if I were you.’”

Dr Helen Cox pointed out that they had observed this in Khayelitsha. “What we found in Khayelitsha is we have these support groups in all of the clinics that meet once a week; and they are structured and there’s a counsellor there. And the patients themselves will talk about their side-effects with the counsellor there who knows all about them. So you can remove these sort of negative impacts of patients talking to each other with some proper advice there. And then they can help each other to get through the side-effects and stay on treatment. I think having peer support is a very important thing for that,” she said.

### Hearing loss

Others wondered how to manage hearing loss associated with some second-line drugs when it starts occurring.

"It is actually very difficult to know what to do, when you do see hearing loss during treatment," said Dr Cox.

"I think the approach is to be very individualised — so if a patient is starting to develop hearing loss, and maybe they've been on treatment for 4 or 5 months and they are doing well otherwise, then you could perhaps stop the injectable drug at that point. But if it's very early on in treatment, in the first month when you start to see this hearing loss, it's very difficult to know what to do because the injectable, as we know, is one of the key drugs for DR-TB treatment. And there's no evidence that reducing down to three times a week actually makes much difference. Although some people are doing this. We really need much more data to be able to identify patients who might be liable to have hearing loss during treatment. And we're starting to do a study to follow this much more closely."

"I think we have all heard the expression - and it's a very brutal one - 'deaf or dead?' And basically a lot of the time it comes down to that," said Ms Shean, adding that this was frequently a source of tension between the audiologist and the doctor, who would insist 'we need the aminoglycoside.'

But especially if they are out-patients, *watch your patients*: How are they looking at you? Are they turning their head sideways? Are they complaining about noise in their ears? How are your patients communicating? How deaf are they? I'm not saying that you shouldn't stop, and let everyone go deaf because that's not good. But there are things we can do, not just to stop immediately when the audiograms say stop. I think we have to have a balance of what we do with patients - we need the aminoglycosides."

"There's an NGO which is selling secondhand hearing aids and providing very good support services in terms of counselling but then also provision of hearing aids. And so we are trying to link up with them so that patients who do have hearing loss can actually access hearing aids," said Dr Gilles Van Cutsem during HATIP's site visit at the Ubuntu clinic. [The NGO in question is Deaf Community of Cape Town — and anyone in the area who is interested in the service should contact HATIP.]

Aside from hearing loss, Dr Sokhela told HATIP she gets the most complaints about "GI symptoms, nausea, gastric pain. I think they complain more about it because they're more uncomfortable. I'm not even sure whether it's the one that they suffer from the most but it's the one that they present with. Because it makes you very uncomfortable."

"I think this is the one that probably has the most impact on adherence," said Dr Cox.

"Because if you're feeling nausea you won't really take drugs," said Dr Sokhela. "But half the patients don't know their kidneys are failing so they will still come and get drugs. Which is why they have to monitor them closely, do the bloods, the creatinine more often, potassium if they are on capreomycin. But they *will* present with GI symptoms and if you don't sort them out, they stop taking the drugs."

"So we use the adjunctive medicines to manage that. Sometimes you have to change drugs or alter doses, split the ethionamide because the patient doesn't want to take [any] drugs no more. But half the time they do well with just drugs to manage that," she said.

Improving side-effect management is high on the list of things to strengthen in the next version of WHO's PMDT guidelines, according to Dr Dennis Falzon.

"One of the questions we will look at is the toxicity of drugs for MDR-TB among HIV infected patients," he told HATIP. "We want to focus on the surveillance of side-effects of TB drugs, particularly in patients with DR-TB or HIV/TB or both. Better information will give us a handle on what is the contribution of drug toxicity to poor

adherence or other unfavourable outcomes. The wider availability of drugs (possibly free-of-charge to the patient) to provide symptomatic relief will be one thing to lobby for."

The surveillance of side-effects of drugs is done both routinely as well as actively. The intention is to establish minimum requirements for pharmacovigilance (PV) for all countries submitting proposals for TB funds to the GF. We are currently working on a handbook not very different from the one already established for ARVs," he told HATIP.

## Failing on treatment: options, clinical and palliative

But putting up with poorly tolerated drugs is one thing is a cure is likely or possible. However, as researchers from St Luke's Hospice pointed out in a poster at the 2<sup>nd</sup> SATB Conference, in many XDR-TB cases or cases where there are terminal comorbid conditions, the patient may not be curable. A major issue is that health care workers find it difficult to declare TB treatment futile because of the infectious risk to society and because it is perceived as giving up on the patient.

But it is important to not shy away from the fact that M/XDR-TB is often a fatal disease. There may be some natural reluctance to deal with this aspect of the clinical care of people with MDR-TB because the media has so hyped M/XDR-TB as a 'killer' disease — and people may need to be convinced that a cure is possible, in order to encourage them to adhere to treatment.

But an unfortunate consequence for some people is that their clinicians may keep force-feeding the patient drugs that are doing nothing but increasing morbidity. There has been little to no research on how to relieve suffering when TB has become a terminal condition, and one which can take a long time to kill some individuals.

In addition, programmes are often at a loss of where to send those deemed to be untreatable.

"It is an extremely complex problem," said Dr Van Cutsem in Khayelitsha. "Because at the moment there is this protocol that they need to be discharged to their home with a lot of interventions to minimise the risk of transmission at home. But the reality is that they're under-resourced so it doesn't really happen in the way it is put in the protocol and patients just sometimes [don't bother to wear their masks]. And they are not always so sick and can live for a few years with highly infectious XDR-TB. So at the moment we support the home - we try - with the existing capacity. But we've also realised the limitations of that strategy, or the risks of that strategy."

In other rare cases, programmes are being confronted with difficult ethical decisions of whether to discontinue treatment in people who repeatedly default on treatment.

"We have these hardcore group of people.... that are very difficult to manage," said Dr Keertan Dheda at the 2<sup>nd</sup> SATB Conference. "And in the Western Cape we have a Review Committee that looks at these recurrent defaulters. And we look at each case on its merits but there have been several cases now where the Review Committee has taken a decision and actually withdrawn further treatment. Because we felt that these patients were going to default again and there was a high risk of amplifying resistance in these patients."

"And there's this whole discussion on incarceration versus confinement and there are these hardcore patients who simply will not take their medications, will repeatedly come into hospital for short periods of time and then default. How do we deal with this problem? Should we go back to the old-style sanatoria? Should we

have some incarceration facility, should we have community treatment facilities?... Currently our XDR-TB beds in many of the provinces are full. In fact in the Western Cape, we are now discharging failed XDR treatment cases back into the community. Fair enough, we do an assessment of the household, but it starts becoming very questionable when you start to discharge patients into communities like this,” he said.

So now the Western Cape, which in other contexts, is decentralising drug-resistant TB care to bring it closer to where people live, plans to ship people who have failed XDR-TB care to a facility in Nelspoort, a remote part of the province. This may simply be a matter of convenience for the province, because the facility is available. But even so, it's a six or seven hour drive away from where most of their families live.

Again, responding to end-of-life issues seems to be a blind spot in TB programmes, according to Dr Jaramillo of WHO.

“The issue of palliative care in TB has been quite painful to me for a long time, and I've felt quite lonely in that. Many people in TB simply didn't care, or even felt that paying attention to palliative care could be a distraction from delivering treatment... We are using this figure, mostly for advocacy purposes, that 1.8 million people are dying of TB. This is awful, but what are we doing to provide these people with a decent, dignified death?”

Indeed, although people with HIV have been reported to die quite quickly from XDR-TB, it is not the case for many HIV-negative people. We may also find that people on antiretrovirals may have prolonged slow deaths from XDR-TB.

They will need compassionate end-of-life care, but because this is a place where TB experts have refused to look, there has been very little research on the subject. Dr Jaramillo told HATIP that symptomatic relief for end-stage TB might be similar to that for chronic obstructive pulmonary disorder (COPD). Palliative care for COPD is also relatively neglected compared to, say, palliative care for lung cancer, the few palliative care experts working with COPD patients are using respiratory-specific quality of life symptom scales to assess their clients' needs.

In assessments of people with COPD, the symptom everyone said most impacted their quality of life was dyspnoea — severe breathlessness (upon minor exertion or even while trying to rest/sleep), and perhaps the anxiety associated with it.

The literature suggests a number of supportive care interventions, including:

- bronchodilators, especially long acting ones;
- opioids to treat dyspnoea — starting at lower doses than used for pain control (1.25 or 2.5 mg orally every 4 hours, intermediate release methadone) and titrating up until symptomatic improvement is obtained. (And it should of course be given with a laxative);
- benzodiazepines to reduce anxiety that can accompany dyspnoea, and also to further reduce dyspnoea (midazolam);
- potentially, oxygen therapy in settings where this is available.

Dr Jaramillo and WHO plan to hold a consultation looking at palliative care for drug-resistant TB in the near future. He told HATIP that some consensus may be needed for such questions as when to give up on curative treatment (although many people present late and die quickly, others can take a long time either to recover or pass). What is reasonable? Worsening disease? Failure to achieve

culture conversion by 10 months? And what should be done to alleviate symptoms and provide end-of-life care for people with M/XDR-TB — in way that is safe for the family and the healthcare providers? Programmes and healthcare workers clearly need guidance on these issues, he said.

In the meantime, other models should be explored for providing high quality end-of-life care.

“I think there is a capacity for some of these patients to be at home, but I don't think we've yet got a model, I think it requires much more intensive counselling and support than even MSF have been providing to date, in terms of home patients,” Dr Cox told HATIP. “So I think we need options for these patients, some sort of facility - you know - within the community. I think we need a mix of models. But I also think we have to caution against having one model for everyone. Because everyone is different. Some people will have enough household support and the family will be very supportive. Others not and so you need something different for those ones, and you need inpatient [certainly] right at the end for some people.”

For instance, there are beds for end-of-life care reserved in the small inpatient clinic in Khayelitsha, and some hospices may be able to provide a similar service that is closer to the community — and close to the emotional and spiritual support that families can provide. However, if palliative care teams are to become involved, to support families, palliative care organisations need to be trained in infection control measures, both for hospices and homes. And finally, Dr Jaramillo pointed out to HATIP, “we also need to remember that caregivers of people dying with or from TB also need to be given psychosocial support.”

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