# DRUG-RESISTANT TUBERCULOSIS

## INTRODUCTION:

When tuberculous cases are treated, poor drug prescription and poor case management are creating more tuberculous patient excreting resistant tubercle bacilli. The issue of the treatment of those pulmonary tuberculosis patients who remain sputum smear positive following fully supervised WHO retreatment should be considered because these patients constitute an on-going problem for program managers. **(Mendez et al., 1998)**

## DEFINITIONS:

**Drug-resistant tuberculosis:** This is a case of tuberculosis excreting bacilli resistant to one or more of anti-tuberculosis drugs. Basically, drug-resistance can be categorized into initial **(primary)** and acquired **(secondary).** Chronic cases are usually but not always excretors of resistant bacilli. MDR is the most severe form of bacterial resistance essential today as a consequence of inappropriate use of antituberculosis drugs.**(Crofton et al., 1997)**

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

**New:** A patient who has never had treatment for TB or who has taken antituberculosis drugs for less than 1 month.

**Relapse:** A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

**Treatment after failure:** A patient who started a re-treatment regimen after having failed previous treatment.

**Treatment after default:** A patient who returns to treatment, positive bacteriologically, following interruption of treatment for 2 months or more.

**Transfer in:** A patient who has been transferred from another TB register to continue treatment.

**Other:** All cases that do not fit the above definitions. This group includes chronic case, a patient who is sputum-positive at the end of a re-treatment

**Chronic:** A patient with TB who is sputum-positive at the end of a standard retreatment regimen with essential antituberculosis drugs.

**Drug-resistant tuberculosis:** This is a case of tuberculosis (usually pulmonary) excreting bacilli resistant to one or more antituberculosis drugs.

**Failure of retreatment:** The definition of failure of the WHO retreatment regimen is a tuberculosis patient excreting bacilli either after 5 months, or after completion, of the 8-month retreatment regimen, given under direct observation by a health worker.

**Chronic case:** A chronic case is now defined by the failure of the WHO retreatment regimen given under direct observation by a health worker.

**(WHO, 2003)**

## Different resistance patterns:

a. **"Mono-resistance"** is defined as resistance to one of the five first-line drugs (H, R, Z, E or S).
b. **"Poly-resistance"** is resistance to two or more of the first-line drugs.
c. **"Multi-drug-resistance" (MDR-TB)** is a subgroup of poly-resistance, in which there is resistance to at least R and INH, the two most effective drugs against m. tuberculosis.
d. **" Extensive drug resistant" (XDR-TB)** is defined as resistance to:

- At least rifampicin and Isoniazide (MDR-TB).
- A fluoroquinolone
- One or more of the following injectable drugs:

-Kanamycin -Amikacin -Capreomycin

**(NTP, 2007)**

Since its first introduction in 1972 as an anti-tuberculous drug, Rifampicin, along with INH, has formed the backbone of short-course chemotherapy for tuberculosis. **(Kochi et al., 1993)**

The development of resistance to these two drugs means that the efficacy of standard anti-tuberculous treatment is reduced by up to 77%. The emergence of MDR strains of m. tuberculosis poses a serious problem for TB control and underlines the need for the development of rapid, reliable diagnostic methods for drug susceptibility testing in clinical isolates. **(Pozzi et al., 1999)**

## Primary resistance and acquired resistance:

Primary resistance reflects poor treatment in the past, whereas acquired drug resistance indicates current poor treatment. **(Lambregts-van et al., 1998)**

**"Primary resistance"** is that which has not resulted from treatment of the patient with the drug concerned. It includes resistance in wild strains which have never come in contact with the drug **(natural resistance)** and the resistance occurring as a result of exposure of the strain to the drug but in another patient. **Initial resistance** is the resistance in patients who give a history of never having received chemotherapy in the past. It includes primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware. **(Vareldzis et al., 1994)**

The term **"acquired resistance"** has often been used with the implication that resistance has developed due to exposure of the strain to anti-tuberculous drugs and the consequent selecting out of resistant mutant bacilli. However, some of the drug-resistant isolates in previously treated patients may actually represent primary resistance among patients who remain uncured. In the strict sense, the term "acquired resistance" can be used to refer to strains proven to have drug resistance in a reliable laboratory, which were subsequently isolated from a patient in whom initial susceptibility testing was done to document the presence of a drug-susceptible strain earlier. If initial drug susceptibility testing has not been done, the term "resistance among previously treated patients" would be a more appropriate term than "acquired drug resistance". **(Frieden and khatri, 2002)**

There should be a strong suspicion of drug resistance, including MDR-TB, in persons with a history of prior treatment or in treatment failure cases. **(Ormerod, 2005)**

## Magnitude of the problem:

The global magnitude of the problem is not well known, there are two groups of bacteriological positive tuberculosis patients:

New cases: patients who have never received anti-tuberculosis drugs during one or more courses of chemotherapy. The rate of primary resistance in new cases is lower than the rate of acquired resistance, primary resistance is less severe than acquired resistance , primary resistance is more often to one drug than to two drugs or more. The level of resistance is lower in primary than in acquired resistance in patients previously treated. The retreatment regimen combining five drugs during the initial phase of treatment is necessary to overcome the risk of failure due to resistance to Isoniazide or Isoniazide and streptomycin. MDR arises in setting where anti-tuberculosis chemotherapy has been applied inappropriately for several years. Susceptibility testing should be used in representative samples of all new cases as a tool for monitoring bacterial resistance. **(Crofton et al., 1997)**

The DOTS strategy of which two of the main elements are directly observed therapy (DOT) and short course chemotherapy (SCC), and which is endorsed by the (WHO) as the current standard for tuberculosis treatment, has been adopted for use by TB treatment control programme in 148 countries. **(WHO, 2002)**

The efficacy of DOTS in the treatment and control of TB is widely recognized. Knowledge of prevalent drug resistant (DR) patterns and effective treatment strategies targeting drug resistance strains are needed. Treatment regimens may need to include second line drugs, which, compared to (SCC) Drugs, are often less effective, more expensive and more toxic and must be administrated for up to four times as long. **(Mukherjee et al., 2004)**

Second line drugs may be provided by (WHO) sponsored DOTS-PLUS programme, and are administered either in individualized treatment regimens (ITR), tailored to the resistance profile of the infecting strain, or in empiric standardized treatment regimens (STR). ITR can be highly effective , with a cure rate of 83% observed on one population of chronic TB patients who had previously failed multiple treatments. **(Mitnick at al., 2003)**

However, ITR based strategies require resource intensive capabilities and special laboratories facilities for drug susceptibility testing (DST), which are currently difficult or unfeasible to implement in resource-limited settings .STR for MDR-TB can also be highly effective, particularly in populations with little previous exposure to the drugs included in the regimen. **(Weyer , 2003)**

However in setting of high-grade resistance, i.e. resistance to more than INH and RMP, Cure rate for STR regimens may be less than 50 % . **(Espinal, 2003)**

knowledge of the prevalence of DR pattern in these populations may enable the development of more effective treatment regimens. Worldwide, there are more than 8 million new cases of TB each year, of which tens to hundreds of thousands may be infected with geographic location. **(Timperi et al., 2004)**

## Status of drug resistance in the world:

Reliable information about the global incidence of drug-resistant tuberculosis is difficult to obtain, because sputum culture and drug susceptibility testing are not routinely performed in impoverished areas where the disease is particularly common. Despite these limitations, large surveys of worldwide drug-resistance have indicated that drug-resistant tuberculosis is a large and increasing problem. **(WHO/IUATLD,2008)**

With treatment approaches that rely on standardized rather than tailored regimens, treatment outcomes are substantially worse in the presence of initial drug resistance. In a study including data from 103 countries where standardized treatment regimens are used, failure and relapse rates were significantly higher if the initial multidrug resistance prevalence was 3 percent or higher. In these countries, more than 20 percent of patients treated required retreatment. **(Mak et al .,2008)**

The World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease surveyed 62,746 M. tuberculosis isolates from 81 countries between 2002 and 2006 and found that multidrug-resistant tuberculosis (MDR-TB) represented 5.3 percent of all new and previously treated TB cases worldwide. It is estimated that approximately 490,000 cases of TB emerged in 2006 and that the global proportion of any drug resistance was 4.8 percent.

**The following findings were also noted:**

- In a survey of resistance in new cases from 72 countries, primary resistance to at least one drug ranged from zero percent in some European countries (e.g., Iceland, Andorra) to 56 percent in Baku, Azerbaijan. The proportion of new cases due to MDR-TB ranged from zero percent in eight countries to 22 percent in Baku, Azerbaijan and 19 percent in the Republic of Moldova.
- Among previously treated cases surveyed in 66 countries, resistance to at least one drug ranged from zero percent in three European countries to 86 percent in Tashkent, Uzbekistan. The highest proportions of MDR-TB were from Tashkent, Uzbekistan (60 percent) and Baku, Azerbaijan (56 percent).
- China, India, and the Russian Federation, are estimated to carry the highest number of MDR-TB cases. China and India have approximately 50 percent of the global burden of MDR-TB cases, while the Russian Federation has 7 percent.
- The rates of MDR-TB are increasing in Peru, the Republic of Korea, and some parts of the Russian Federation (Orel and Tomsk).
- Only six countries in Africa (Cote d'Ivoire, Ethiopia, Madagascar, Rwanda, Senegal, and the United Republic of Tanzania) provided data for this survey. Rates of MDR-TB ranged from 0.7 percent in Madagascar to 3.9 percent in Rwanda.

**(WHO/IUATLD,2008)**

Globally the problem of Tuberculosis (TB) and its control has been exacerbated by two Major factors. One is the HIV pandemic; the other is

the emergence of resistance to the drugs used to treat TB. Drug resistance has developed in Mycobacterium Tuberculosis (TB) strains and potentially poses a major threat to international TB Control efforts. Drug-Resistant TB was first observed in 1948 and MDR TB now occurs in most countries. Since the mid-eighties cases of MDR-TB have been diagnosed in all Provinces of South Africa. Various forms of drug resistance have developed and have recently been more widely reported as the threat of the emerging epidemic is appreciated. The threat of antimicrobial resistance in general is growing nationally and internationally we are now beginning to pay the price for our neglect of tuberculosis. At the dawn of a new millennium, we are faced with a new crisis; a former curable killer, such as TB, is now covered in increasingly impenetrable armor of antimicrobial resistance. **(WHO, 2000)**

MDR-TB patients often live for several years before succumbing to the disease. **(Migliori et al., 2004)**

Prevalence of MDR-TB may therefore be three times greater than its incidence, suggesting that the true number of MDR-TB cases in the world today may approach or exceed one million. **(Blower and Chou, 2004)**

In 1994, the global project on drug-resistance surveillance was initiated to monitor the trends of resistance. The first report published in 1997, contained data from 35 geographical settings for the period 1994-1996. The report showed that drug resistance was present globally, and that MDR-TB ranged from 0% to 14% in new cases (median: 1.4%) and 0% to 54% in previously treated cases (median: 13%). **(Pablos et al., 1998)**

A second report for the period 1996-1999, followed in 2000 and included surveillance data from 58 geographical sites. This report

confirmed that drug resistant TB was a sufficient problem since MDR-TB ranged from 0-16% (median: 1%) among new cases and from 0% to 48% (median: 9%) in previously treated cases. In the first global report, the term “hot spot” was used to refer to areas with a high prevalence of MDR-TB among new cases. Also this report introduced a reference point of 3% prevalence of MDR-TB among new cases, as an indication of high MDR prevalence. Over time, a 3% prevalence of MDR among new cases became the customary threshold to define a “hot spot”. **(Espinal, 2003)**

## Magnitude of the DR-TB problem in Egypt:

Many studies done in Egypt about the MDR-TB and drug resistance.

The primary and the secondary resistance among 200 patients with pulmonary tuberculosis was studied and showed that the majority of cases in primary resistance were with moderately advanced lesion while the majority of cases in secondary resistance were with far advanced lesions.

The resistance to each individual drug was as the following:

Table (6):

| Drug | Primary Resistance | Secondary Resistance |
|---|---|---|
| SM | 32.2% | 48.5% |
| INH | 29% | 55.4% |
| PAS | 8% | 19% |
| EMB | 17.7% | 38.9% |
| REF | 8% | 31.2% |
| ETH | 35.5% | 58.3% |

The highest incidence of resistance to two drug combination was with INH+ ETH (19.3%) and the lowest incidence was with INH+RIF (6.25%). In secondary group the resistance decreased as the number of drugs in combination increased. So, any program of TB therapy should include four drugs to overcome the very high resistance in our country. **(Esmat et al., 1988)**

The incidence of primary drug resistance among newly diagnosed cases of pulmonary tuberculosis who were admitted to Masr El-Gidida Chest Army Hospital during the period from 1/7/1985 to 1/6/1986 was studied. The study was conducted on 53 patients with smear-positive for AFB newly diagnosed and without any previous history of anti-tuberculosis therapy. Primary cultures for all patients were done 2 cultures were contaminated, one culture was negative and so had positive culture to which subsequent sensitivity tests was performed to the tested drugs (Streptomycin, Isoniazide, Thiacetazone, Ethambutol, Rifampicin and Ethionimide) using an indirect method. The results obtained showed that out of 50 positive cultures 29 (58%) were fully sensitive to the 6 drugs tested while the other 12 (24%) were resistant to one or more drugs. The incidence of primary resistance among positive cultures was as follow; To one drug (24%), to two drugs (16%), to three drugs 0%, to four drugs (0%) and to five drugs (2%). And no resistance was detected with 6 drugs. Among 50 positive cultures, the primary resistance was as follow: resistance to streptomycin (30%), to Isoniazide (24%), to Thiacetazone (4%), to Rifampicin (2%), (6%) to Ethionimide and no resistance to Ethambutol was detected. The highest incidence of resistance to two drug combinations was with INH + SM (14%) and the lowest incidence was with

RIF + EMB and RIF + INH (0%) and (2%) respectively. Among patients with cavitary lesions drug resistance was (54.2%) while among non cavity lesions it was (30.8%) with non-significant difference. The study concluded that the primary resistance is still very high in our community. The drug resistance decreased as the number of drugs in combination is increased. So any program of TB therapy should include three drugs or more to overcome this high resistance. **(Oaf et al., (1989)**

A study on 50 patients with smear positive sputum newly diagnosed and without any previous history of anti-tuberculosis therapy, primary cultures for all patients were done and all of them had positive culture to subsequent tested drugs (Streptomycin, Isoniazide, Ethambutol and Rifampicin) using an indirect method that out of 50 positive cultures 17 were fully sensitive to the 4 drugs tested while other 33 were resistant to one or more drugs. They found that the incidence of initial resistance among positive culture to one drug was 18 (36%) to 2 drugs was 13 (26%) to 3 drugs was 2 (4%) and no resistance was detected with 4 drugs. **(Masoud et al., 1989)**

A study on 21 cases of active pulmonary tuberculosis that had been treated regularly with Rifampicin and 25 cases that had been treated irregularly. They found that, the secondary drug resistance among regular cases appeared in the 5th month while it appeared earlier in the 2nd month among the irregular cases. It is evident from this study that drug resistance to Rifampicin is increasing in developing countries. **(Osman et al., 1993)**

A study of the pattern of drug resistance among newly diagnosed and retreatment patients who were admitted to Abbassia Chest Hospital as well as patients registered in Chest Clinics in Cairo in 2004. 138 male and female patients with sputum smear positive for AFB using Ziel-Neelsen's stain were included in this study. The study revealed that the resistance to one drug or different drug combinations including multi-drug resistance (MDR-TB) was higher in retreatment patient than in newly diagnosed patients. Both groups of patients had higher figures of resistance than in previous studies. It was also found that the overall resistance (resistance to one or more drug in newly diagnosed patient was 34%). It is concluded that mono-resistance in newly diagnosed group was 14% and in retreated group was 50%. In the newly diagnosed group the resistance to INH was 6%, resistance to the RIF was 4%, to EMB was 2% and to the SM was 2%. While in retreated group the resistance to INH was 17%, to the RIF was 17%, to EMB was 5.6% and to SM was 10.2%. The overall poly-resistance (combined drug resistance not including RIF+ INH together) in newly diagnosed group was 10% while in retreated group was 25%. Resistance to drug combination of 2 drugs in newly diagnosed group (INH + SM ) was 2% while in retreated group was 5.6% in addition to this resistance to (RIF + EMB) was 2% in newly diagnosed group, while in retreated group the resistance to (RIF + EMB) was 3.4% while to (RIF + SM) the resistance was 2% in newly diagnosed. In retreated group the resistance was 5.6%.As regards any kind of resistance, the resistance to INH was 20%, the resistance to RIF was 20%, the resistance to EMB was 12% and the resistance to SM was 18%.While in retreated patients resistance to INH was 54.5%, the resistance of RIF was 52.2%, to EMB was 28.4%, and to SM was 40.9%.As regards multi-drug resistance, the overall resistance in newly

diagnosed patient was 10% while in retreated group was 23.9%.The resistance to INH + RIF was 2% in newly diagnosed patients while in retreated group was 9%. Also the resistance to (INH + RIF+SM) was 4% in newly diagnosed group while the resistance in retreated patients was 5.6%. In addition, the resistance to (INH + RIF + SM+ EMB) was 4% in newly diagnosed group, while in retreated group the resistance was 5.6%. Also resistance to (INH + RIF+ EMB) was 0% in newly diagnosed group while the resistance in retreated group was 3.4%. **(Mona et al.,2005)**

A study found overall resistance rate was 55.6% and the resistant rate for INH was 26.4% for RIF 26.4% and for both 12.5% the resistant rate among newly diagnosed cases was 39.9% with 16.7 to INH and 8.3% to RIF, MDR was 2.8%, while in previously treated cases the resistance rate was 22.2%, with 22.2% to each INH and RIF. **( Mohamed et al., 2002)**

The overall resistance rate was 39% and the resistance rate for INH was 15.2% for RIF 13% and for both 10.8% .the resistance rate among newly diagnosed cases was 28.6% with 14.3% to INH and 10.7% to RIF, MDR was 3.6% while in previous treated cases the resistance rate was 55.6% with 16.75 to each INH and RIF, MDR was 22.2%. So they concluded that the mycobacterial resistance to INH and RIF is high, whether among recently diagnosed or previously treated cases. **( Hussein et al.,2000)**

The overall resistant rate of 50.2% with 34.2% INH, 17% of RIF And 51.2% to both drugs. However, these studies did not relate the resistance to previous history of chemotherapy and their result were variable according to patient groups and used techniques for assessing the sensitivity pattern of patient. **(EL-Gazzar et al, 1998)**

The study included 116 patients admitted to Abbassia chest Hospital. The patients were resistant to at least rifampicin and INH. It was done in the period between July 2006 to June 2008.Resistance to isoniazid and rifampicin were 100%, resistance to streptomycin was 91.1%, resistance to ethambutol was 79.6%. **(Mohamed A et al .,2009)**.

According to WHO TB profile for Egypt in 2004, the prevalence rate of new cases of multi-drug-resistant tuberculosis was 2.2%, while that of previously treated tuberculous cases, which was discovered to be multidrug-resistant, was 38%. **(WHO, 2004a)**

## Morbidity and mortality

Multi-drug-resistant TB (MDR-TB), associated with high death rates of 50% to 80%, spans a relatively short time (4-16 weeks) from diagnosis to death. **(Dooley et al., 1992)**

Drug resistance is a threat to TB control programs worldwide. Patients infected with multiple-drug resistant strains are less likely to become cured. **(Goble et al., 1993)**

Particularly if they are infected by HIV or suffer from another immune disease. The treatment is much more toxic and much more expensive (about 700 times) than the one of patients with sensitive organisms. **(Mahmoudi and Iseman, 1993)**