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Methods to improve patient compliance with anti-tuberculosis drugs for infection and drug resistance

SM Kadri*,Saleem-ur-Rehman Anil. N.S*****

*Epidemiologist, Division of Epidemiology and Public Health , Kashmir, India,**Director Health Services, Kashmir,
*** Assoc. Prof., Community Medicine.Sri Devaraj Urs Medical College,Tamaka, Kolar - 563 101,India

Corresponding Address: SM Kadri,Epidemiologist, Division of Epidemiology and Public Health , Kashmir, India PO Box 1143, GPO, Srinagar 190001, Kashmir, India

Tuberculosis (TB) is a worldwide, chronic communicable bacterial disease. Caused by a bacterium Mycobacterium tuberculosis. It primarily affects lungs and causes pulmonary tuberculosis. It spreads through air by a person suffering from TB[1].

TB is one of the most ancient diseases. The Egyptian mummies as old as 500 B.C showed the evidence of man suffering from tuberculosis.[2] Tuberculosis is known by many names in India as ' Kshyya Tog', 'Tapedik', whereas in the western world it is known as phthisis, in Romans as tabes and in Greek it was known as consumption. It has also been referred in the Vedas and Ayurvedic Samhitas. World TB day is celebrated on 24th March in commemoration of Mycobacterium tuberculosis discovery by Robert Koch on 24th March in 1882.[1]

In India, the first open air sanatorium for treatment and isolation of TB patients was founded in 1906 in Tiluania, near Ajmer. In 1909, the first non-missionary sanatorium was built near Shimla. Upon the earlier work done by Dr Louis Hart from 1908, the United Mission Tuberculosis Sanatorium (UMTS) was built in 1912 at Madanapalle, South India. Dr Frimodt Moller the first Medical Superintendent played a large role in India's fight against TB through the training of TB workers, conducting TB surveys (1939) and introduction of BCG vaccination (1948). In addition, the first TB dispensary was opened in Bombay in 1917, followed by another in Madras[2].

It usually affects human in productive age group of 15-49 years leading to economic, social and health burden in the community. TB infects one third of the world's population at any given time. In 2008, 9.4 million incident cases of tuberculosis with 11.1 million prevalent cases was reported[3]. 8.8 million people fell ill with TB and 1.4 million died from TB in 2010. Over 95% of TB deaths occur in low and middle-income countries, and it is among the top three causes of death for women aged 15 to 44.[4]
WHO started the stop TB strategy comprising of:[4]

- pursue high-quality DOTS expansion and enhancement
- address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations
- health system strengthening
- engage all care providers
- empower people with TB
- research activities

India accounts for nearly one fifth of global burden of tuberculosis, 2/3 rd of cases in SEAR. Unfortunately the prevalence and incidence rates have remained the same as in 1954-58 and thus with the increase in the country's population, the absolute number of TB cases are expected to increase by many folds[1].
The efforts to control the problem of tuberculosis has been done since 1960s. Based on the findings of the operational studies conducted, a draft recommendation for the District Tuberculosis Programme was prepared in 1961, keeping in mind an average Indian district, its population and health facilities available. The national programme policy as enunciated in the introduction manual of DTP comprised:[2]
Domiciliary treatment
Use of a standard drug regimen of 12-18 months duration
Treatment free of cost
Priority to newly diagnosed patients, over previously treated patients
Treatment organization fully decentralized
Efficient defaulter system/mostly self-administered regimen

Timely follow up
Domiciliary treatment with Isoniazid (INH) and thiacetazone was given for one year to one and half year. In same places short course daily regimen was also introduced.[2]

Chemotherapy of TB underwent revolutionary changes in the seventies owing to the availability of two well-tolerated and highly effective drugs – rifampicin and pyrazinamide. These drugs allowed short course chemotherapy (SCC) and made it possible to simplify treatment and reduce its duration. Discovery of rifampicin in 1967 is considered as one of the greatest achievements in the history of development of anti-TB drugs. After its discovery no new drug of that effectiveness has been found.[2]

The National Tuberculosis Institute had believed in assessment and evaluation as an ongoing process. It welcomed the idea of periodic assessment, especially from experts, on scientific lines as they are vital to the growth and improvement in the programme.[1]

The need for revised strategy: In 1992, the Government of India, together with the World Health Organization (WHO) and Swedish International Development Agency (SIDA), reviewed the national programme and concluded that it suffered from
managerial weakness
inadequate funding
over-reliance on x-ray
non-standard treatment regimens
low rates of treatment completion and
lack of systematic information on treatment outcomes.
As a result, a Revised National Tuberculosis Control Programme (RNTCP) was designed[1].

RNTCP-Revised national tuberculosis control program.
Objectives:

- Emphasis on the cure of infectious and seriously ill patients of tuberculosis, through administration of supervised short course chemotherapy, to achieve a cure rate of at least 85%.
- Augmentation of the case finding activities to detect 70% of estimated cases, only after having achieved the desired cure rate[1].

Revised strategy:

- Augmentation of organizational support at central and state levels for meaningful coordination.
- Increased budgetary outlay.
- Use of sputum testing as the primary method of diagnosis among self reporting patients.
- Standardized treatment regimens.
- Augmentation of the peripheral level supervision through the creation of a subdistrict supervisory unity.
- Ensuring a regular uninterrupted supply of drugs up to the most peripheral level.
- Emphasis on training, IEC, operational research and NGO involvement in the program.

All patients are provided short course chemotherapy free of charge. During the intensive phase of chemotherapy all the drugs are administered under direct supervision called Direct Observed Therapy Short term (DOTS). DOTS is a community based tuberculosis treatment and care strategy which combines the benefits of supervised treatment and the benefits of community based care and support.

5 components:

- Political commitment
- Good quality sputum microscopy
- Directly observed treatment
- Uninterrupted supply of good quality drugs
- Accountability.

The Revised National Tuberculosis Control Programme (RNTCP), based on the DOTS strategy, began as a pilot in 1993 and was launched as a national programme in 1997. Rapid RNTCP expansion began in late 1998. By the end of 2000, 30%of the country's population was covered and the entire country was covered under DOTS by 24th March 2006.

Every day in India, under the RNTCP,

More than 15,000 suspects are being examined for TB, free of charge.

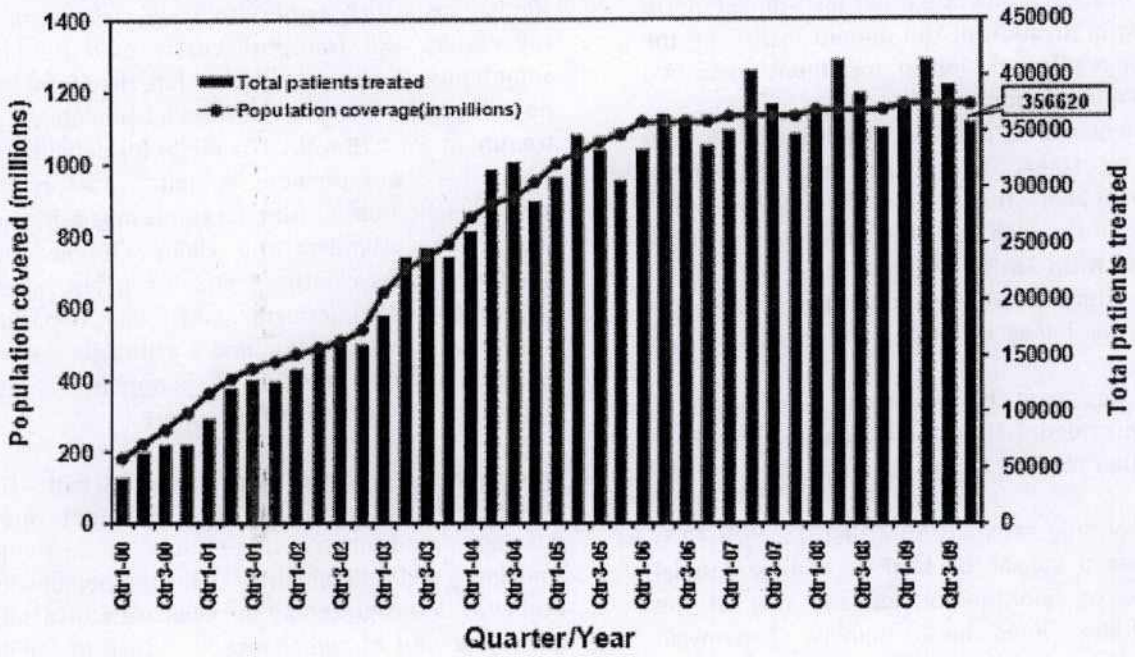
The diagnosis of these patients and the follow-up of patients on treatment is achieved through the examination of more than 50,000 laboratory specimens.

As a result of these examinations, each day, about 3,500 patients are started on treatment, stopping the spread of TB in the community.

In order to achieve this, more than 600,000 health care workers have been trained and

More than 11,500 designated laboratory Microscopy Centres have been upgraded and supplied with binocular microscopes since the inception of the RNTCP[1].

Population in India covered under DOTS and Total TB Patients put on treatment each quarter[5]



RNTCP Phase II:

The RNTCP phase II of the world band project has been approved for a period of 5 years from Oct 2006 to Sep 2011[6]. Phase II of the RNTCP is a step towards achieving the TB related MDG targets. The goal of the TB control programme is to decrease the mortality and morbidity due to TB and cut transmission of TB. Some of the salient features are DOTS remain the core strategy.

Network of RNTCP accredited quality assured state level intermediate reference laboratories (IRL), providing culture and drug sensitivity testing services.

DOTS plus sites for the case management of Multi drug resistant TB patients.

Multi drug resistant tuberculosis (MDRTB): MDRTB refers to strains of the bacterium which are proven in a laboratory to be resistant to the two most active anti-TB drugs, isoniazid and rifampicin[7].

Regimens for treatment of MDR TB are tailor made and depend on the sensitivity pattern of the bacilli. Second line of drugs are: Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin, sparfloxacin, pefloxacin), kanamycin, amikacin, capreomycin, ethionamide, cycloserine etc[1].

DOTS Plus: DOTS programme that add components for MDR TB diagnosis, management and treatment. 5 components[6,1]:

- Sustained government commitment.

- Accurate timely diagnosis
- Appropriate treatment utilizing second line drugs
- Uninterrupted supply of quality assured anti TB drugs
- Standardised recording and reporting systems.

Patient of MDR TB is managed according to following principles[1]:

Detailed appraisal of the treatment history of the patient regarding the drugs used, period and dosage.

Review of chest X rays and other tests done before.

Intensive motivation of the patient explaining the need for regular and longer treatment up to two years or more as advised.

The patient needs to be reviewed after at least 6 weeks by smear microscopy and radiological assessment apart from symptomatic improvement.

Because do the high risk of relapse the treatment in case of MDR TB is continued for at least 18-24 months after culture has converted to negative with regular follow up at approximately 6 weeks intervals.

Some cases may be assessed for resectional surgery provided the disease is localized and there are no other adverse factors for surgery.

Extensively drug resistant TB(XDR-TB)[1].: XDR TB is defined as a subset of MDRTB with additional resistance to fluoroquinolones and one of the second line injectables namely Kanamycin capreomycin and amikacin.

Treatment of MDRTB is extremely expensive, toxic, arduous and often unsuccessful. Merging drug-resistance strains would make it even more difficult to limit the spread of the infection. DOTS have been proven to prevent the emergence of MDRTB, and also to reverse the incidence of MDRTB where it has emerged. MDRTB is a tragedy for individual patients and a symptom of poor TB management. The best way to confront this challenge is to improve TB treatment and implement DOTS. But for the implementation of DOTS patient adherence is required.

Adherence is a complex and dynamic phenomenon. Financial burden: 'Cycle of poverty'[8]. Difficulty in obtaining sick leave for treatment; fear of asking for money to purchase TB drugs and fear of losing work or dismissal. Many didn't feel the treatment as a 'choice' for good health but rather a conflict between attending for clinic-based treatment and the need to earn a living. Patients also expressed guilt over the impact that the disease had on their family livelihoods[9].

Hidden costs such as hospital stays, reviews of X-ray results and transport costs could be high sometimes. But some patients felt that from the doctors point of view it is always a completely free treatment. Past TB was a risk factor for default only when there was previous default.[10] Factors like lower weight, poor nutritional status might prevent them from attending the clinic. Chronic liver diseases and psychiatric illnesses can also affect adherence[10]. Side-effects such as hepatitis, dyspepsia, exanthema and arthralgia were responsible for termination of therapy in majority of patients during the intensive phase.[12]

Second-line drugs for multidrug-resistant TB, during which as many as 86% of patents may develop medication side-effects[12]. Currently smoking and Psychiatric illnesses/personality problems unrecognized by the clinic staff adversely affect the rate of compliance.[10, 13] Lack of family support and fear of catching the disease was a factor in household members' with negative reactions to care of the TB patient[14].

Poor initial adherence[15] and not being on the first course of TB medications were and lack of public transport contributed to poor adherence.[11] Lack of community support and exclusion from social interactions and relationships along with poor knowledge about TB treatment contributed for poor adherence.[14]

Even trivial beliefs might have a big impact. Patients may question the efficacy of the pills or think that only injections are "medicine". Because of the stigma they would want to hide the disease

and not seek the treatment altogether or they might deny. Patients could be nonadherent if they were taking other western or traditional medicines and perceived there to be negative consequences if these were taken concurrently with TB medication.[9] Fearing of catching the disease and family members might distance themselves from the patients, lead to hiding the disease from the family and others.[14] In some cultures, females diagnosed with TB were at risk of divorce, and their husband taking a second wife, or of being sent to their natal homes. Sometimes a patient's role and responsibilities in the family could motivate them to adhere to treatment in order to recover and resume to their duties.[9]

A poorly functioning health system may undermine adherence.[9] In most public health systems, patients are unable to schedule appointments.[8] Distance from the hospital[11] and health gap resulting in accessing health care facilities better in urban than rural areas. Inconvenient opening hours, Lack of privacy, Provider absenteeism, Poor follow up by providers, Maltreatment by the providers: scolding a patient for missing appointments and No flexibility- 'doing jail time' indirectly contributed for nonadherence.[9]

Painful injections, lengthy treatment[9] and afraid of the side effects along with insufficient time with health care workers to address adherence issues, and to see different providers at every consultation, all of which undermine adherence behavior.[8] Improvements in the functioning of the health system are "necessary but not sufficient" to improve adherence[8], because in the end it's the patient who has to comply with the treatment. So much rests upon his/her decisions.

Many patients with tuberculosis suffer from a wide range of social problems, which include: homelessness, poverty and psychological disorders. A successful programme must take into consideration these difficulties and appropriate measures like incentives should be included as part of a comprehensive programme. Local factors should be considered in detail in formulating the content of the damage control measures. Default rate is a crude approach to adherence monitoring, since it does not really reveal why the patient interrupted treatment for two or more consecutive months.[12] So the reasons should be sought and relevant measures should be taken.

Incentives: Based on behavioural theories of reward for "good"behavior, an incentive can be provided. This might be able to break the cycle of poverty. Care should be taken that it shouldn't result in 'perverse incentives' for people to remain ill and continue receiving them[8].

Flexibility: In a number of studies conducted with patients being directly observed adherence to treatment was facilitated by flexibility and patient choice[9].

Reconsideration of DOTS: Resource implications for such a policy i.e. DOTS are substantial, particularly in low-income and middle-income countries where the case load is high; and it may make adherence worse if it is rigidly applied in an authoritarian setting or where people are expected to travel considerable distances to have their treatment supervised[16].

The use of DOTS or the introduction of newer, better tolerated regimens in the last years didn't improve the alarming rate of patients defaulting TB treatment in a study conducted in Africa[7]. And also the perceived advantages of DOTS might be because of simultaneous administration of several other factors, like a health worker constantly motivating the intake along with directly observing the treatment compliance.[16]

Change of attitude among health personnel- Those who are not adherent to treatment will be branded sometimes as 'difficult cases''[9,13] . Nonadherent patients were judged to lack interest, to be lazy and not care, or to want to remain sick to qualify for financial support[9]. We the health personnel should never underestimate the decision making capacity or the intelligence of the patients. We should provide uniform respect and care to all.

Motivation: Caution should be exercised when attributing adherence solely to"personal motivation", because not only can important influences be ignored, but this factor is difficult to modify or even operationalise[9]. Counselling patients on possible side-effects of treatment and also providing the facilities for managing the side effects in case they happen[12]. Increase the visibility of TB programmes in the community, which may increase knowledge and improve attitudes towards TB Provide more information about the disease and treatment to patients and communities Increase support from family, peers, and social networks
Provide more information about the effects of medication to reduce the risk of patients becoming nonadherent when experiencing treatment side effects.[9]

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