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Chapter

Loss to Follow-Up (LTFU) during Tuberculosis Treatment

Kyaw San Lin

Abstract

Loss to follow-up (LTFU) is a serious issue in the field of tuberculosis (TB) since it can lead to TB outbreaks and drug resistance. The proportion of LTFU patients differs among different countries, regions, year, and institutions. In some countries, the number of patients that were LTFU nearly reaches half of the total patients. Underlying factors such as age, gender, education, residence, financial factors, migration, and social stigma are discussed in this chapter. These factors should always be taken into consideration whenever a treatment program is designed. Suggestions have been made regarding some interventions that could potentially solve the problem of LTFU. With these points in mind, an ambitious approach should be taken to reduce the number of LTFU patients up to zero.

Keywords: tuberculosis, TB, loss to follow-up, LTFU, default

1. Introduction

Tuberculosis (TB) is a disease, which requires more than just biomedical treatment. WHO-recommended standard TB treatment requires a minimum duration of 6 months. The patients have to regularly take treatment without interruption to get a cure. However, discontinuation of treatment because of loss to follow-up (LTFU) is a significant problem, especially among patients suffering from multidrug-resistant tuberculosis (MDR-TB), requiring urgent attention. The proportions of LTFU and its associated factors differ among various countries. A clear understanding of these underlying causes is essential for the success and effectiveness of the National Tuberculosis Program (NTP) of every nation. Hence, appropriate measures targeting LTFU are needed to achieve the goals of the NTP.

2. Definition

In 2012, a large group of researchers from Africa, Asia, America, Europe, and the Pacific suggested that the term 'defaulter' is inappropriate for the patient [1]. Instead, they recommended using the term 'person lost to follow-up' to become more patient-centered. In 2013, the WHO decided to use the term 'loss to follow-up' instead of 'defaulter' for reporting treatment outcomes because the former is less judgmental [2]. They defined LTFU as "A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more." Since then, several papers have started reporting according to this new term and definition [3–10].

3. The problem of LTFU

The patients who were LTFU have not completed the treatment regime. This can cause serious public health problems because these patients are at higher risk of drug resistance [11]. They continue to spread the potentially resistant bacilli to the public, infecting the public. This has been proved in a Bayesian mapping where LTFU has served as an important indicator for the distribution of TB patients [12]. Therefore, LTFU should be one of our primary concerns in the battle against TB.

Even just a single case of LTFU could cause an outbreak of TB, as observed in countries with low incidence such as Norway [13, 14], USA [15], and Austria [16]. In such outbreaks, the index cases are mostly immigrants, spreading the infection to their families, friends, and other social networks. To further visualize this problem, we need to look into the proportion of LTFU among different countries in the world.

4. Proportion of LTFU

The proportion of LTFU varies considerably among different countries, different types of TB, and different patient populations. It has been studied extensively and was found to be ranging from 2.5 to 44.9% [17–23]. A very high proportion (44.9%) of the patients were LTFU in rural northern Mozambique revealing that LTFU is a very serious problem [19]. In addition, systematic reviews and meta-analyses have estimated the mean proportion of multidrug-resistant TB patients who were LTFU. A 2009 systematic review of MDR-TB patients has found that this proportion is 12% [24]. Another 2009 systematic review also found a similar proportion of 13% [25]. However, a 2012 individual patient data meta-analysis found a higher proportion of 23% [26]. A rough literature review has revealed that the proportion of MDR TB patients who were LTFU ranges from 2.2 to 47% [27–43]. The figures vary vastly among different years, countries, and institutions, suggesting that the underlying factors responsible for these variations should be studied carefully.

However, few studies have reported on the proportion of LTFU among patients with extra-pulmonary TB. According to a French study, this proportion was 25% among lymph node TB patients [44]. Another study from Gabon reported that the proportion among cervical lymph node TB patients was 24.3% [45]. In India, among the miliary tuberculosis patients presenting with neurological manifestations, the proportion was 10% [46]. However, in Saudi Arabia, the proportion among CNS tuberculoma patients was reported to be 25.8% [47].

Another area of interest is latent TB since developed countries such as the USA and the UK are giving much attention to latent TB and its LTFU rate. Studies from the USA reported proportions ranging from 12 to 35.6% [48, 49]. In the UK, this proportion is 22.8% [50], and in Switzerland, 11% [51].

Attention should also be paid toward LTFU among certain special populations. The proportion of LTFU among childhood TB patients ranges from 4 to 37% [52–57]. Among the children with drug-resistant TB, it ranges from 5 to 19.09% [58–60]. These figures are much similar to those of the adult population. On the other hand, researchers from Côte d'Ivoire found out that the proportion of LTFU was rising among the elderly TB patients [61]. This is an area that researchers should explore more in the future.

We should not forget about our fellow healthcare workers since LTFU could lead to serious problems in the healthcare service setting. They are expected to have low rates of LTFU because of the medical knowledge they possess. Fortunately, a study from Morocco confirmed that the proportion of LTFU among healthcare workers

in the public sector was only 0.8% [62]. However, many studies need to be done to explore this area of study.

Other populations of interest are prisoners and migrants. Northern Ethiopian prisons reported a low LTFU proportion of only 2.5% [63], which is an excellent result. In contrast, among the Ugandan prison inmates, 43% were LTFU and the odds are greater among the transferred prisoners [64]. On the other hand, researchers from the USA found out that 25.8% of the cases in a public health intervention were LTFU, and they were mainly undocumented migrants [65]. In such countries, as discussed above, even a single case of LTFU can cause an outbreak of TB. The same problem is arising in Australia where all of the detained illegal foreign fishermen were LTFU [66]. They concluded that

"Treatment completion in illegal foreign fishermen may be as low as zero; deporting fishermen before curative treatment is completed undermines TB control efforts and may lead to an emergence of drug resistance and an increased burden of active TB disease in our region."

This is an area of concern that needs urgent measures. On the other hand, the International Organization of Migration is achieving great results among Vietnamese immigrants [67]. Only 7% of the MDR-TB patients from these migrants were LTFU. It is likely that such 'international intergovernmental' effort is necessary to tackle the problem of LTFU among the migrants since individual governments are facing difficulties handling this problem.

5. Factors associated with LTFU

5.1 Individual factors

Individual factors play a role in the process of being LTFU from treatment. Sometimes, the results may contradict between different studies, probably due to the cultural, social, and other variations of the study settings.

Among the various sociodemographic characteristics, age is a recognized factor associated with LTFU. Studies from India, Brazil, and China revealed that elderly patients have higher LTFU [4, 68–70], whereas studies from Norway, Botswana, and South Africa suggested that adolescents have significant risk [8, 30, 71]. One study from the UK even suggested a wider range of age of 15–44 years as a high-risk group for LTFU [11]. Regarding gender, studies uniformly suggest that higher LTFU was found in males, as seen in Kenya, Ethiopia, Georgia, and Uzbekistan [7, 18, 41, 72].

Residence plays a role in the mechanism of LTFU. In Pakistan, the rural residence is associated with LTFU [73], whereas in Uzbekistan, the urban residence is associated with LTFU [18]. This may be caused by access to the treatment center since being far from the treatment center is also associated with LTFU [74]. Transportation should be improved to increase accessibility toward the treatment center. Alternatively, they could be built in the hard-to-reach areas. Both approaches include challenges, and ultimately, these challenges may be what cause LTFU. Further discussion regarding different providers will be given in the next section.

Education plays a role in the development of LTFU. Brazilian researchers have found out that less than 8 years of schooling increases the risk of LTFU [4]. In addition, scarce TB knowledge is a risk factor for LTFU [75], and better TB knowledge a protective factor [5]. Therefore, health education and proper counseling should always be at the heart of every anti-TB treatment program.

Financial factors should also be considered while giving treatment, and programs without such considerations will likely to result in high LTFU. A study from

Uzbekistan found that joblessness contributes toward LTFU [18]. This is confirmed by a study from China which found that pre-school children, unemployed laborers, and retirees have a higher rate of LTFU [76]. Patients with low income have financial constraints to complete treatment leading to LTFU as seen in India [77], a lower middle-income country. A similar phenomenon has been observed in South Korea, a high-income country [78]. Even in the USA, it was found that homelessness is associated with LTFU [79, 80], which might be due to low income. Therefore, regardless of the country, patients with low income still have barriers against treatment completion.

LTFU is also associated with alcohol abuse, tobacco use, smoking, and illicit drug use. Association between alcoholism and LTFU was observed in India [77], Philippines [5], and Congo [74], tobacco use in Georgia [41], smoking in Brazil [75], and illicit drug use in Norway [30], Georgia [41], and the UK [81]. Therefore, before initiating treatment, personal history should be carefully taken to find out these risk factors, and special attention should be given to such patients.

There are also certain disease-specific factors that are associated with LTFU. Those who were previously LTFU tend to be LTFU again. This was confirmed by studies conducted in Brazil [4], Kenya [7], Uzbekistan [18], and Korea [78]. Caution should be taken while planning treatment for such patients. Studies from Nigeria and Ethiopia both point out that smear-negative TB patients were more likely to be LTFU [72, 82]. However, the opposite was observed in the UK where smear-positive pulmonary TB patients were more likely to be LTFU [11]. Researchers also found that patients with extrapulmonary TB were more likely to be LTFU [71, 83]. Co-morbid diseases such as diabetes mellitus and human immunodeficiency virus (HIV) infection also cause hindrance against TB treatment conditions [7, 71, 84].

5.2 Treatment support services

The treatment providers should give support to the patients since a perceived lack of provider support is a barrier to regular follow-up [77], and receiving any type of assistance and support from the providers can protect against LTFU [5]. They need to build up trust [5] from the patients. An intervention program targeting these factors will be described later in the chapter. Lastly, the timing of the treatment services should be flexible according to the needs of the patients [77], but this may not be an easy task to implement.

5.3 Diagnosis and treatment

The timing of the treatment is important since those who initiate the treatment late (beyond and within 30 days of onset) are more likely to be LTFU [85]. Those who initiate it late may not have enough motivation, will, or knowledge to continue taking treatment until they are cured. Moreover, the timing of treatment interruption is found to be the most important during the intensive phase [7]. This stage should be particularly targeted while conducting interventions against LTFU.

Different providers have different abilities to retain the patients. In Korea, patients treated by a non-pulmonologist were found to be more likely to default from TB treatment [78]. In Myanmar, patients treated by private practitioners were more likely to be LTFU [86]. An interesting situation was observed in Nigeria where patients treated at private, not-for-profit (PNFP) DOT facilities were more likely to be LTFU [87]. The researchers concluded that "Patients managed at PFP [private, for-profit] DOT facilities were probably richer, had better education, nutrition, and knowledge of TB than patients managed at PNFP

DOT facilities…" Indeed, the factors causing LTFU are not simple, and they are correlated with each other. Therefore, intervention should be addressed not only on a single problem but also targeted toward the patient as a whole. Furthermore, the provider should also be consistent throughout the different stages of treatment since different providers in the intensive phase and continuation phase are associated with LTFU [88].

5.4 Drug side effects

Studies from the USA and India have found that drug side effects are associated with LTFU [49, 77]. The researchers from the Philippines take one step further regarding this concept, stating 'patients' self-rating of the severity' as an associated factor [5]. Indeed, some side effects, such as hepatitis, of the anti-tuberculosis drugs are already severe. However, some side effects, such as vomiting, might need self-rating since different patients may perceive differently. It would be interesting to research which kind of patient rates which side effect as severe.

5.5 Social factors

Factors such as migration and social stigma also contribute toward LTFU. LTFU is common among the migrant population particularly in developed countries where there is an inward movement of people from the developing countries. Studies from the UK had repeatedly revealed this association [11, 50, 86, 89]. Researchers from the USA also found that birth outside the USA or Canada is associated with LTFU [80]. Higher LTFU among migrants has also been observed in Asian countries such as South Korea and China [70, 76, 90].

In countries where TB is a social stigma, treatment is very difficult and sensitive [77]. The patients may not want the health workers to give counseling. They do want to take treatment since the news of having TB may spread to the community, causing discrimination. In such places, secret treatment sessions should be initiated to control LTFU rates. In contrast, in Korea, the absence of TB stigma is associated with LTFU [78]. The authors wrote "TB stigma might motivate patients to receive TB treatment, thus increasing adherence to TB treatment." Therefore, before starting the TB treatment program, it is important to make community observations first to find out whether TB sigma can cause or prevent LTFU.

In theory, interpersonal factors such as family dynamics, household role, peer influence, and partner and family relationships were thought to influence LTFU [5]. However, to our knowledge, none of the studies to date supports the association of LTFU with these factors.

LTFU risk	Score
Immigration	1
Living alone	1
Living in an institution	2
Previous anti-TB treatment	2
Poor patient understanding	2
Intravenous drug use (IDU)	4
Unknown IDU status	1

Table 1.
A predictive scoring instrument for tuberculosis lost to follow-up outcome [86].

5.6 Scoring instrument

Based on the factors associated with LTFU, Rodrigo et al. have developed a scoring instrument to predict the probability of LTFU (**Table 1**) [91]. According to their original paper, "Scores of 0, 1, 2, 3, 4 and 5 points were associated with a lost to follow-up probability of 2.2% 5.4% 9.9%, 16.4%, 15%, and 28%, respectively." Incorporating the instrument in the process of history taking could help the healthcare providers in identifying patients who have the potential to be LTFU. Further interventions should be carried out to prevent these patients from becoming LTFU. Similar scoring systems could be developed in different regions, since there are always country-specific variations.

6. Interventions

6.1 Directly observed treatment (DOT)

Indeed, DOT is a part of the WHO-recommended 'Directly Observed Treatment Short Course' (DOTS) strategy. Although it cannot be denied that this strategy has saved the lives of millions of TB patients, the strategy itself is not flawless. Several authors have questioned the effectiveness of DOT as summarized in a review article by Otu [92]. The 2015 Cochrane systematic review and meta-analysis on DOT compared it with self-administered treatment, and the authors concluded that "TB cure and treatment completion were low with self-administered therapy in these trials, and direct observation did not substantially improve this" [93]. They called for complementary and alternative strategies in addition to DOT. Since DOT is a well-known and well-documented intervention in the field of TB, we felt that it need not be described in further detail in this chapter. Some interventions that have the potential to correct the weaknesses of DOT will be discussed below.

6.2 mHealth

Recently, mHealth has emerged as a popular choice for health programs around the world. The Global Observatory for eHealth (GOe) has defined mHealth as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [94]. Among these mHealth initiatives, appointment reminders and treatment compliance initiatives are of interest in reducing the rate of LTFU. However, there are limited interventional studies evaluating the effectiveness of these interventions in reducing the risk of LTFU.

In 2017, Hermans et al. have evaluated a text message service in the Infectious Diseases Institute (IDI) in Kampala, Uganda [95]. In this quasi-experimental study, appointment reminders were sent the day before the appointment, and adherence reminders were sent on days 2, 7, and 11 after the appointment. A total of 96% of the participants rated the messages as being helpful, and qualitative results also confirm these findings. However, data analysis has revealed that there was no statistically significant difference in the risk of LTFU between the intervention and control group. The lack of statistical significance may be due to the small sample size. Therefore, further studies with larger sample sizes are needed to further evaluate the program.

6.3 eCompliance

eCompliance is a biometric-based program, developed by Operation ASHA (OpASHA) [96], an Indian not-for-profit organization founded in 2006. The

system is similar to mHealth in using text message alerts to inform the missed dose. However, the unique fingerprint verification system for the patient and the health worker takes mHealth to the next level. The OpASHA website explains the working mechanism of eCompliance as follows.

> *"During each patient visit, the patient and healthcare worker simultaneously scan their finger in the system, the medication is dispensed, and the treatment is recorded in the system's database. If a patient misses a dose, an SMS message alert is sent to the patient, healthcare worker and supervisor. The healthcare worker is then responsible to meet the patient within 24–48 hours to administer and record the treatment."*

This system can be used to reduce the risk of LTFU since the data from OpASHA stated that the LTFU rate is less than 4% using their system [96].

This claim by OpASHA has been put to test in Uganda by Snidal et al. in 2012 [97]. Community health workers (CHWs) were selected and trained to use the system. The intervention was conducted at the Millennium Villages Project (MVP) cluster in Ruhiira, Uganda. The patients were followed-up by CHWs until the end of the treatment period. The proportion of LTFU is surprisingly 0% in the intervention group, which is a significant reduction compared to the control group, yielding an excellent result. However, since this study suffers from a limited sample size, a large-scale interventional study is still necessary to confirm the results. Local adaptation to the software is available from OpASHA, and they should be incorporated into local national tuberculosis programs to lower the proportions of LTFU.

6.4 Community-based programs

An innovative community-based intervention to improve TB treatment outcomes was conducted in Sidama zone, Ethiopia [98, 99]. The core health workers mainly responsible for delivering the intervention to the grass-root level were called the health extension workers (HEWs). The HEWs were trained and salaried female health workers from the respective intervention regions. Active case finding and sputum smear preparation were conducted by the HEWs. The supervisors process the smears and initiate anti-TB treatment. Again, HEWs provide treatment support which includes provision and monitoring of treatment. Evaluation of the program over 4.5 years revealed that the proportion of patients lost to follow-up decreased significantly up to 3% [99]. The authors concluded that

> *"We have thus demonstrated that bringing simple services that detect disease and provide treatment support close to where patients live is critical to increase access to TB diagnosis and treatment adherence and minimise the number of patients LTFU."*

Therefore, such community-based programs should be implemented in modified forms in different countries around the world to reduce the proportion of LTFU. Another important thing to note is that both this program and eCompliance mentioned above employed 'task shifting' toward basic health workers (CHWs and HEWs) to support TB treatment at the grass-root level, not the experts.

6.5 Social support programs

In 2013, a novel social support program was developed in India by forming groups called "treatment support group (TSG)" [100].

> *"A TSG is a non-statutory body of socially responsible citizens and volunteers to provide social support to each needy TB patient safeguarding his dignity and confidentiality by ensuring access to information, free and quality services and social welfare programs, empowering the patient for making decision to complete the treatment successfully."*

A TSG supports the various needs of the patient so that they can complete the anti-TB treatment without any worries. The package includes transportation service, treatment counseling, emotional and spiritual support, and providing accommodation for homeless TB patients. After the program was implemented, the rate of LTFU fell until it strikes zero in the latest cohorts. It is because it tackles the social dimension associated with LTFU. This is one program that the interviewed patients from Ethiopia, who were LTFU, had hoped for [101].

6.6 Legislation

In some countries, under certain circumstances, law enforcement is controversially used to solve the problem of LTFU. Usually, the patients who were LTFU were isolated in hospitals, but in some countries, they were isolated in prisons. Usually, this method was used against patients who were homeless and had a history of alcohol abuse [102]. When all the other methods fail, the medical officer, with the power given by the health laws, has to conduct a short-term incarceration of the patients who were LTFU.

Detention of patients includes ethical and human right problems. The controversy surrounding this issue has been discussed in detail in a review article by Mburu et al. [103]. They discussed that the primary reason for detention is to protect public health, according to the Siracusa Principles adopted by the UN Economic and Social Council. However, they argued that this conflicts with the international human right laws and the 1979 Alma-Ata Declaration.

> *"...incarceration and detention approaches curtail the rights to health, informed consent, privacy, freedom from non-consensual treatment, freedom from inhumane and degrading treatment, and freedom of movement of people lost to follow-up. Detention could also worsen social inequalities and lead to a paradoxical increase in TB incidence."*

In the light of this information, the interventions which tackle the risk factors associated with LTFU are far superior to detention, which provides just a temporary solution to the problem, not a permanent one.

Another form of federal public health intervention is used in the USA to solve the problem of LTFU among the migrants [65]. These tools called the Do Not Board (DNB) and Border Lookout (BL) list are managed by the Department of Homeland Security (DHS) according to requests from the Centers for Disease Control and Prevention (CDC) Travel Restriction and Intervention expert workgroup. They are designed to detect land border travelers who were LTFU from TB treatment. State health departments and local health jurisdictions supply the list of patients and were reviewed under the following criteria:

> *"(1) infectiousness or potential infectiousness with a communicable disease that would pose a public health threat if the individual travelled internationally;*
>
> *(2) the person is unaware of his/her diagnosis, fails to adhere to public health recommendations, including treatment, or public health authorities are unable to locate the person; and*
>
> *(3) the person poses a risk to travel internationally or on a commercial flight" [65].*

Analysis revealed that most of the patients from this list were successfully treated but most of the migrants remain LTFU, suggesting that some improvement to the program is still needed to handle this problem.

7. Conclusion

LTFU from treatment is a serious problem that cannot be ignored. Throughout this chapter, the consequences of LTFU, the magnitude of this problem in different countries, and the underlying factors have been discussed. Various researchers have designed potentially powerful interventions to tackle LTFU. But, we still need further evidence and actions to be able to successfully lower the number of patients that are LTFU. With these points in mind, it is suggested that an ambitious approach should be taken to reduce the number of LTFU patients up to 0%.

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Conflict of interest

None declared.

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