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Influence of Decentralization and Type of Patient on Loss to Follow-up among Multidrug-Resistant Tuberculosis Patients in Indonesia from 2014 to 2015

Pengaruh Desentralisasi dan Tipe Pasien terhadap *Loss to Follow-up* pada Pasien *Multidrug-Resistant Tuberculosis* di Indonesia tahun 2014-2015

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Abstract

Drug-resistant tuberculosis (TB) patients have a greater risk of loss to follow-up (LTFU) than drug-sensitive TB patients, due to their longer treatment duration. This study aimed to determine the influence of decentralization and patient type on LTFU among multidrug-resistant TB (MDR-TB) patients in Indonesia. A retrospective cohort study was conducted at all MDR-TB treatment healthcare facilities in Indonesia from 2014 to 2015. Using total sampling technique, 961 patients were examined and sampled. Of these patients, 86.03% were decentralized. Patients were classified into types as follows: 35.17% were "relapse" patients, 5.52% were "new," 13.94% were classified as "after LTFU" patients, 23.10% were "treatment failure category 1" patients, 20.29% were "treatment failure category 2" patients, and 1.90% were classified as "other types" patients. Decentralization reduced LTFU risk by up to 46% (HR = 0.54, 95% CI 0.35–0.84). LFTU in "after LTFU," "treatment failure category 2," and "other types" patients was higher by 50%, 53%, 74%, respectively compared to LFTU occurrence in "relapse" (baseline) patients. Among "treatment failure category 2 patients, female patients were 2.13 times more likely to have an occurrence of LFTU, while male patients were 0.55 times as likely to have an occurrence of LFTU, compared to "relapse" type patients of the same sex.

Keywords: Decentralization, loss to follow-up, multidrug-resistant tuberculosis, type of patient

Abstrak

Pasien tuberkulosis (TB) resistan obat memiliki kemungkinan *loss to follow-up* (*LTFU*) lebih besar dibandingkan pasien TB sensitif obat dikarenakan durasi pengobatan yang lebih lama. Penelitian ini bertujuan mengetahui pengaruh desentralisasi dan tipe pasien terhadap *LTFU* pada pasien *multidrug-resistant TB* (*MDR-TB*) di Indonesia. Sebuah studi kohort retrospektif dilakukan di semua fasilitas kesehatan yang merawat pasien TB-MDR di Indonesia pada tahun 2014–2015. Sampel diambil dalam *total sampling* dengan total 961 pasien. Sebanyak 86,03% pasien dilakukan desentralisasi. Berdasarkan tipenya, pasien terdiri dari 35,17% kambuh, 5,52% baru, 13,94% setelah *LTFU*, 23,10% kegagalan kategori 1, 20,29% kegagalan kategori 2, 1,90% pasien tipe lainnya. Desentralisasi mengurangi *LTFU* hingga 46% (HR = 0,54; 95% CI 0,35–0,84). *LTFU* pada "setelah LTFU", "kasus gagal pengobatan kategori 2" dan tipe lain-lain meningkat masing-masing sebesar 50%, 53%, dan 74% dibandingkan dengan pasien kambuh (*baseline*). Pada kategori kegagalan pengobatan kategori 2, pasien perempuan 2,13 kali dan pasien laki-laki 0,55 kali untuk terjadi *LTFU* dibandingkan pasien dengan tipe kambuh.

Kata kunci: Desentralisasi, *loss to follow-up*, *multidrug-resistant tuberculosis*, tipe pasien

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Introduction

According to the 2018 Global Tuberculosis Report, tuberculosis (TB) is one of the top 10 causes of death in the world.[1] Among infectious diseases, TB is the third major cause of death, after lower respiratory tract infections and diarrhea.[2] One of the new challenges in TB control is the emergence of multidrug-resistant tuberculosis (MDR-TB).[3] Management of drug-resistant TB is more complicated and requires more attention than non-resistant TB management.[4] MDR-TB is a type of TB resistance caused by the Mycobacterium tuberculosis bacteria. This etiologic agent in humans is resistant to isoniazid and rifampicin, two of the most effective medications for first line anti-TB treatment.[5]

In 2016, incidence of MDR-TB was 490,000 cases, 84% of which were from 20 high burden countries (HBCs). These countries had the highest number of MDR-TB cases in the world. Indonesia is a high burden country, ranking fourth after India, China, and Russia. The incidence of MDR-TB in Indonesia was estimated to be 32,000 cases in 2016.[6] In Indonesia, the situation is further complicated by the high rate of loss to follow-up (LTFU) during the treatment of MDR-TB patients. LTFU in MDR-TB patients for cohorts in 2009, 2010, 2011, 2013, and 2014 were 10.5%, 10.7%, 25.1%, 26.9%, 28.7%, and 27.1%, respectively.[7] Such high rates of LTFU overburden the treatment infrastructure and severely limit the successes of TB control programs. The re-treatment of MDR-TB patients due to LTFU is more complex than the treatment of regular TB patients.[4]

Due to the longer duration of drug-resistant TB therapy (19–24 months), drug-resistant TB patients have a greater risk of LTFU than drug-sensitive TB patients (6–12 months).[4,8] In addition, MDR-TB patients who do not complete treatment have a greater risk of dying from TB. A study on MDR-TB patients in Peru revealed that out of 47 (70.1%) LTFU patients successfully traced, 25 (53.2%) had died.[9]

Decentralization and patient type are factors which play an important role in the occurrence of LTFU in MDR-TB patients. Decentralization is the transfer of treatment and care for MDR-TB patients from MDR-TB treatment centers or hospitals to community-based Directly Observed Treatment Short course (DOTS) facilities.[10, 11] Patient type was determined based on previous TB treatment status (i.e., relapse, new, after LTFU, treatment failure category 1, treatment failure category 2, and other types). Patients were classified under the LFTU category if their treatment had been interrupted for two or more consecutive months.[4,12] This study aimed to explain the influence of decentralization and patient type on LTFU incidence among MDR-TB patients in Indonesia in the 2014–2015 cohort.

Method

This was a retrospective cohort study based on record review of patients enrolled in MDR-TB treatment. This study was conducted from May to June 2018 at the Subdirectorate of TB, Directorate of Prevention and Communicable Disease Control, Directorate General of Prevention and Disease Control, Ministry of Health of the Republic of Indonesia. The study population was MDR-TB patients who started treatment in 2014 and 2015 at all MDR-TB treatment facilities throughout Indonesia, and whose data had been stored in the e-TB Manager application. The study sample was derived from an eligible population that met the inclusion criteria. The inclusion criterion was adult patients with MDR-TB (age of 15 years), while the exclusion criteria were drug-resistant TB with resistance patterns other than MDR (RR, Monoresistant, Polyresistant, Extensively Drug-resistant/XDR, Pre-XDR, and unknown pattern of resistance), MDR-TB patients with no end-of-treatment status, and MDR-TB patients with no end-of-treatment date.

This study used secondary data based on medical records of MDR-TB patients stored in the e-TB Manager application. Using a structured data capture instrument, data collection and entry into the e-TB Manager had been routinely performed by recording and reporting officers at each MDR-TB treatment facility. Sample selection was carried out using the total sampling technique.

Independent variables included decentralization (no or yes), patient type (relapse, new, after LTFU, treatment failure category 1, treatment failure category 2, other types), sex (female or male), age (45 years or > 45 years), culture conversion (conversion 4 months, > 4 months, unknown/no data), location of TB disease (extra pulmonary or pulmonary), HIV status (negative, positive, unknown), and side effects (no side effects, unknown, or any side effects). The main outcome variable was LTFU. Patients were classified under the LFTU category if their treatment had been interrupted for two or more consecutive months for any reason.[12]

There were four stages of data processing carried out for this study.[13] The first stage was editing. The completeness of medical records data and variables drawn from e-TB Manager was checked. The second stage was coding. Coding involves changing the data from alphabetical form into numerical form. The third was processing. Processing involved entering data from the file format downloaded in e-TB Manager into the data analysis program used. The last stage was cleaning. In this stage, data already entered were rechecked, ensuring the data were ready to be analyzed.

One of the main independent variables in this study (namely decentralization) occured lost data more than 10%, so that multiple imputations were carried out on

this variable. The assumptions of missing data were tested. Statistical tests were conducted to examine missing data included for completely missing data or data missing at random. The mean of numerical variables that were complete with the variables that has the missing data (t-test). The relation of categorical variable that is filled with the variable that has the missing data (logistic regression).[14]

In this study, survival analysis was carried out. Survival analysis is a statistical procedure to analyze data, with the outcome variable being the time to event.[15] The event in this study was the occurrence of LTFU. The time of event was calculated from the beginning of an observation (starting treatment of MDR-TB) until LTFU occurred.

Patient characteristics were summarized using descriptive statistics. To identify the relationship between the independent variable and survival time, and to test proportional hazard (PH) assumption, bivariate analysis was performed. PH assumption was tested by using graphical analysis of ln-ln survival estimates and time-dependent variables. The assumption of PH was met if the curve on the graph of In-ln survival estimates did not intersect and the test of time-dependent variables yielded a p-value > 0.05. The Cox Extended Regression method was used to measure the influence of a main independent variable on outcome, because some covariate variables did not meet the PH assumption. The next step was to test the interaction between the main independent variable and the covariate variable. A p-value < 0.05 indicated the presence of a relationship between both variables. Moreover, a confounding test was conducted by introducing all covariate variables gradually one by one starting from the variable with the largest p-value. A variable was included in the model if it was considered as confounder. A variable was considered a confounder if it caused a 10% change in the main independent (model without interaction) or on the main independent variable interact (model with interaction). A confounder may also cause a <10% change, if the variable was related to the outcome and main independent variable.

This study has been reviewed and approved by the Research Ethics Committee of the Faculty of Public Health, Universitas Indonesia dated on May 14th, 2018 No.452/UN2.F10/ PPM.00.02/2018.

Results

This study showed that of the 961 selected samples, 272 patients (28.40%) were LTFU; making the hazard rate of 2.88/100 person-months. This means that of any 100 patients with MDR-TB, approximately three patients were LTFU every month (Figure 1). As presented in Table 1, all patients were classified according to the following categories: decentralization status, patient status, and covariate variables. Statistically, the proportion of decentralized patients categorized as LFTU was lower than the proportion of LFTU non-decentralized patients (24.43% vs. 47.06%; p-value < 0.0001). Considering patient type, the proportion of LTFU patients among "after LTFU" patients and "other types" patients was higher than LTFU proportions among "relapse" patients (40.63% vs. 26.30%, p-value = 0.007 and 50.00% vs. 26.30 %; p-value = 0.019). The occurrence of LTFU among patients aged > 45 years was higher than the occurrence of LTFU among patients aged 45 years (37.05% vs. 23.63%; p-value < 0.0001). The occurrence of LTFU in patients with an unknown culture conversion status was higher than the occurrence of LTFU in patients who had achieved culture conversion status for four months (59.02% vs. 16.43%; p-value < 0.0001). The occurrence of LTFU among patients with an unknown HIV status was also higher than the occurrence of LTFU among HIV negative (32.89% vs. 24.31, p-value = 0.001) patients.

In the multivariable analysis, the location of TB as a variable was not included in the modeling, because only 1 (0.1%) patient had extra pulmonary TB. Conversion variables, HIV status and side effects were excluded in the modeling because they had a very high occurrence of missing data (unknown group). Based on the interactions test on the association between decentralization and patient type with LTFU in MDR-TB patients, it was found that there was an interaction between patient type and sex (p-value < 0.05) (Table 2). As for the confounding test on the relationship between decentralization and patient type, it was determined that the one confounder was age group (Table 2).

Decentralized patients had a smaller LTFU hazard rate compared to non-decentralized patients. After adjusting for patient type, sex and age, decentralization decreased LTFU rate by 46% compared to non-decentralized patients (HR 0.54; 95% CI 0.35–0.84) (Table

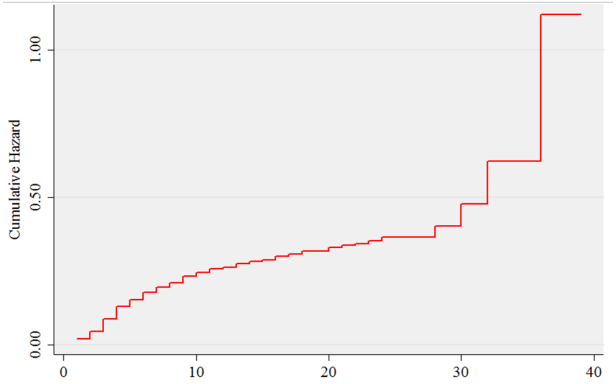

Figure 1. Graph of LTFU Cumulative Hazard Estimates of MDF-TB Patients in Indonesia from 2014 to 2015

Table 1. Characteristics of MDR-TB Patients in Indonesia in 2014–2015 Cohort

Variable	Category	Patients (n)	LTFU, n (%)	Cox Regression		
				HR	95% CI	p-Value
Decentralization	No	57	24 (47.06)	Ref		
	Yes	351	85 (24.43)	0.47	0.31-0.71	0.0001
Patient type	Relapse	338	86 (26.30)	Ref		
	New	53	19 (36.54)	1.54	0.94-2.53	0.089
	After LTFU	134	52 (40.63)	1.61	1.14-2.27	0.007
	Failed category 1	222	54 (25.00)	0.91	0.64-1.27	0.572
	Failed category 2	195	45 (23.44)	0.86	0.60-1.24	0.420
	Others	19	9 (50.00)	2.28	1.15-4.53	0.019
Sex	Female	405	114 (29.16)	Ref		
	Male	556	151 (27.86)	0.94	0.74-1.20	0.643
Age	≤ 45 years	618	142 (23.63)	Ref		
	> 45 years	343	123 (37.05)	1.88	1.47-2.39	0.0001
Conversion	≤ 4 months	633	104 (16.43)	Ref		
	> 4 months	35	4 (11.76)	0.69	0.25-1.86	0.458
	Unknown	293	157 (59.02)	8.93	6.89-11.56	0.0001
Location of TB**	Extra pulmonary	1	0	Ref		
	Pulmonary	960	265 (28.43)	-	-	-
Baseline AFB smear status	Negative	213	62 (29.67)	Ref		
	Positive	748	203 (28.04)	0.95	0.72-1.27	0.735
Amount of drug-resistant TB strains	2	380	112 (30.19)	Ref		
	3	320	84 (27.18)	0.89	0.67-1.19	0.446
	4	261	69 (27.27)	0.95	0.70-1.28	0.736
HIV status	Negative	477	115 (24.31)	Ref		
	Positive	9	1 (14.29)	0.63	0.09-4.53	0649
	Unknown	475	149 (32.89)	1.52	1.19-1.94	0.001
Side effects	Unknown	893	246 (28.44)	Ref		
	Yes	68	19 (27.94)	0.92	0.58-1.47	0.730

Notes:
*significant, p-value < 0.05, **cannot be analysed, MDR-TB = Multidrug-Resistant Tuberculosis, LTFU = Loss to Follow-up, AFB = Acid-Fast Bacilli, HIV = Human Immunodeficiency Virus, HR = Hazard Ratio, CI = Confidence Interval, Ref = Reference

2).

The following patient types: "after LTFU," "treatment failure category 2," and "other types" increased risk of LTFU by 50% (HR 2.02; 95% CI 1.18–3.45), 53% (HR 2.13; 95% CI 1.24–3.66), and 74% (HR 3.80; 95% CI 1.54–9.36), respectively, compared to "relapse" patients (baseline), after adjusting for decentralization, sex and age.

Female patients in the "treatment failure category 2" group were 2.13 times (95% CI 1.24–3.66) and male patients in the "treatment failure category 2" were 0.55 times (95% CI 0.15–1,98) as likely to have an incidence of LTFU than patients of the same sex in the "relapse" patient type group (Table 2).

Discussion

The percentage of patients with LTFU in this study was similar to the conclusion from a report by Subdirectorate of TB which stated that LTFU in MDR-TB patients in Indonesia for 2014 was 27.1%. Any variation in results may be attributed to differences in inclusion and exclusion criteria during sampling, such that not all MDR-TB patients were included in the study. The time reference for the study was between 2015 and 2016. The proportion of LTFU cases among MDR-TB patients in Indonesia was above the WHO target of 5%.[16]

The proportion of LTFU patients found in this study is similar to that LFTU proportions in a study conducted in Georgia among in MDR-TB patients, which estimated LFTU occurrence at 29.0%.[17] Another study in India found a lower occurrence of LTFU, at 19.2%.[18] The differences in these findings and figures are probably due to different patient characteristics. In this study, 94.5% of patients had a previous record of TB treatment, and therefore, had a greater risk of LTFU. However, only 45.8% of subjects in the Indian study had a previous record of TB treatment.[18]

It has been shown that decentralization decreased the risk of LTFU by 46% (HRadjusted 0.54; 95% CI 0.35–0.84). The results of this present study are in line with studies conducted in the Philippines which showed that transfer of MDR-TB patients to a Directly Observed Treatment Short Course (DOTS) provider close to the

Table 2. Effect of Decentralization and Patient Type on LTFU MDR-TB Patients in Indonesia from 2014 to 2015

Variable	Categoriy	LTFU, n (% Basis)	HRcrude (95% CI)	p-Value	HRadj (95% CI)	p-Value
Decentralization	No	24 (47.06)	1		1	
	Yes	85 (24.43)	0.47 (0.31–0.71)	0.0001	0.54 (0.35–0.84)	0.006
Patient type	Relapse	86 (26.30)	1		1	
	New	19 (36.54)	1.54 (0.94–2.53)	0.089	1.33 (0.55–3.24)	0.527
	After LTFU	52 (40.63)	1.61 (1.14–2.27)	0.007*	2.02 (1.18–3.45)	0.010
	Treatment failure category 1	54 (25.00)	0.91 (0.64–1.27)	0.572	0.91 (0.52–1.60)	0.755
	Treatment failure category 2	45 (23.44)	0.86 (0.60–1.24)	0.420	2.13 (1.24–3.66)	0.006
	Other types	9 (50.00)	2.28 (1.15–4.53)	0.019	3.80 (1.54–9.36)	0.004
Interaction	New#male				1.24 (0.42–3.62)	0.694
	After LTFU#male				0.63 (0.31–1.27)	0.199
	Treatment failure category1#male				0.92 (0.45–1.86)	0.818
	Treatment failure category 2 #male				0.26 (0.12–0.54)	0.0001
	Other types#male				0.26 (0.06–1.17)	0.08
Sex	Female	114 (29.16)	1		1	
	Male	151 (27.86)	0.94 (0.74–1.20)	0.643	1.35 (0.86–2.11)	0.185
Age	≤45 years	142 (23.63)	1		1	
	>45 years	123 (37.05)	1.88 (1.47–2.39)	0.0001	2.69 (1.81–4.02)	0.0001
Interaction	Tvc age				0.95 (0.92–0.99)	0.026

Notes:
MDR-TB = Multidrug-Resistant Tuberculosis, LTFU = Loss to Follow-up, HR = Hazard Ratio, CI = Confidence Interval, Tvc = Time-Varying Covariates

patient's residence could reduce risk of LTFU by 70% (HRadjusted 0.3, 95% CI: 0.2–0.7). Decentralization was implemented after health workers in DOTS healthcare facilities had been trained to manage and monitor treatment using second-line drugs.[11]

Another study in Russia showed that adherence to treatment among MDR patients increased from 56% to 88% when they were treated by a DOTS provider in the community. In this program, the time and place of daily medical supervision was chosen by the patient. Nurses were responsible for only five to seven patients. This was aimed at creating a sense of community with patients, close relatives, and colleagues.[19] These results were confirmed in a systematic review that showed that the involvement of public health officers as DOTS providers via referrals played a role in decreasing LTFU rates among MDR-TB patients.[20]

MDR-TB patients without severe drug side effects or uncontrolled comorbidities may be referred to and continue treatment at the closest DOTS provider designated and prepared as an MDR-TB satellite facility by the local District Health Office.[4] The decentralization or handover process aims to carry treatment access closer to the patient's home; hence, reducing the likelihood of a patient being lost to follow-up.[10] LTFU may be due to the high transportation costs to the hospital. Decentralization can be more cost-effective, as hospital service costs are usually higher than service costs at primary healthcare facilities.[21]

Currently, acceptance of decentralized treatment is still low due to several factors, including inadequate knowledge and experience with MDR-TB treatment (side effects) among local health staff, limited hours of public health care, lack of patient confidence in local health staff, and inadequate monitoring of remote primary health care.[22]

Patient type influences LTFU incidence. Patient types such as "after LTFU," "treatment failure category 2," and "other types" exhibited an increased risk of LTFU compared to "relapse" (baseline) patients. Having a previous LTFU record increased the risk of LTFU by 50% (HRadjusted 2.02; 95% CI 1.18–3.45). In other words, LTFU patients were 2.02 times more likely to have another LTFU episode than patients who returned for treatment after successful on previous treatment. The risk of a LFTU occurrence was 53% higher (HRadjusted 2.13; 95% CI 1.24–3.66) in "treatment failure category 2" patients compared to patients who returned for treatment after previous successful treatment. In other words, "treatment category 2" were 2.13 times more likely to have a LTFU occurrence than patients who returned for treatment after previous successful treatment. The risk of a LFTU occurrence was 74% higher (HRadjusted 3.80, 95% CI 1.54–9.36) in "other types" patients, meaning patients with no information about previous records of TB treatment were 3.80 more likely to have a LTFU occurrence than patients who returned for treatment after previous successful treatment. These results are in line with a Sri Lankan study which showed that patient type influenced LTFU risk. This present study demonstrated that "after LTFU" patients were 2.44 times (95% CI: 1.03–5.78) more likely to have an occurrence of LTFU compared to TB patients returning after successful treatment. Therefore, when restarting treatment in previous LTFU patients, it is important to continuously emphasize adherence to treatment. In these patients,

prompt follow-up with additional support from local healthcare facilities may be useful in decreasing LTFU occurrence.[23]

A study in Bangalore City, India, showed that the "after LTFU" patients were 2.5 times (95% CI: 1.3–4.9) more likely to have an occurrence of LTFU compared with TB patients who returned after previous successful treatment.[24] The higher LTFU risk among patients undergoing re-treatment could be attributed a high percentage of "after LFTU" patients (78%) who had interrupted previous treatment. Close supervision, motivation and ensuring that DOT facilities are accessible to patients at high risk of LFTU should be prioritized at the initiation of treatment. This may improve the success of treatment, given that majority (64%) of patients are undergoing retreatment.

The results of a study conducted in Nairobi, Kenya showed that TB patients who returned for treatment after LTFU were 2.33 (95% CI: 1.16–6.48) more likely to have an occurrence of LFTU compared to untreated (new) TB patients and patients who had returned for treatment after successful treatment.[25] Another study published similar results, showing that "after LFTU" patients returning for treatment were 6.4 times (95% CI: 2.9–14.0) more likely to have an occurrence of LTFU among retreatment patients (relapse, failed, and other types) during subsequent treatment.[26] It is important to prevent initial LFTU occurrence among new patients. Furthermore, due to greater risk of LFTU, "after LTFU," "treatment failure category 2," and "other types" patients must be quickly identified and monitored.

Our results showed no association between sex and LTFU, and is supported by results from a different study.[11] However, other studies have shown an association between sex and LFTU occurrence, suggesting that males had a greater odds of LTFU during MDR-TB treatment (1.43 times (95% CI 1.15–1.78)) than females.[24]

This study had several limitations. The retrospective cohort study design meant that quality control of previously recorded measurements was not possible. Data were missing for several variables due to incomplete medical records, possibly affecting the ability to detect relationships between the outcomes and certain variables, including culture conversion status, HIV status, and adverse events. Furthermore, unavailability and incompleteness of data limited the analysis of other potential confounding variables. Some potential confounding variables that were not considered in this study included conversion status, HIV status, adverse events, employment status, incarceration status, home ownership, drug use, tobacco use, alcohol use, and treatment disturbance rates. Therefore, the presence of several residual confounding effects in this study cannot be ruled out.

Conclusion

In conclusion, decentralization and patient type are influential risk factors for LFTU occurrence. Decentralization reduces the risk of developing LTFU. Certain patient types ("after LTFU," "failed treatment category 2," and "other types") have a higher risk of LTFU occurrence. Hence, supplementary strategies may be necessary to prevent occurrence of LTFU, so that the continuity of MDR-TB treatment can be improved.

Recommendation

Health workers should prioritize communication. MDR-TB patients should be informed and educated about treatment, side effects and duration of proper treatment. Furthermore, the benefits of decentralization should be demonstrated to MDR-TB patients (especially those without serious adverse events or uncontrolled comorbidities) and their families at the time of visits.

The risk of LTFU is higher in "after LTFU," "treatment failure category 2," and "other types" patients compared to "relapse" patients. Therefore, patient type screening should be conducted at initiation of treatment to determine a patient's risk of LTFU. For high LFTU risk patient types, it is necessary to communicate, inform and educate the patients on a routine basis on the benefits of adherence to treatment regimen and duration.

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