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Real-world impact of the fixed-dose combination on improving treatment outcomes of drug-susceptible tuberculosis: a comparative study using multiyear national tuberculosis patient data

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ABSTRACT

Background The fixed-dose combination (FDC) for first-line antituberculosis (TB) treatment has long been a standard practice worldwide; however, there is limited evidence on whether the use of FDC improves long-term treatment outcomes in the real-world setting.

Methods We identified 32 239 newly diagnosed patients with drug-susceptible (DS) TB in 2015 and 2016 who had been prescribed FDC or non-FDC TB treatment from a multiyear (2013–2018) national TB cohort database that linked the Korean National Tuberculosis Surveillance System, the National Health Insurance Database and the Health Insurance Review and Assessment Service database. Inverse probability of treatment weighting (IPTW) with a propensity score was used to control for differences in patient characteristics between 5926 patients with TB treated with FDC and 26 313 patients with non-FDC. Multivariable logistic regression analyses were performed to assess for the factors influencing treatment outcomes between the two groups.

Results After IPTW, new patients with DS-TB treated with FDC had higher treatment completion rate (83.9% vs 78.9%, p<0.01) and lower death rates (8.2% vs 9.8%, p<0.01) with similar TB recurrence rate (2.3% vs 2.4%) compared with those treated with non-FDC. In multivariable analyses, FDC use had higher odds treatment completion (adjusted OR 1.45; 95% CI 1.34 to 1.56). Patients with TB with younger age (relative to 70+ age) and higher income level had higher odds for treatment completion. Use of FDC did not influence TB recurrence after treatment completion (adjusted HR 0.94; 95% CI 0.77 to 1.16). The acquired drug resistance rate was similar between the two groups (drug-resistant TB in FDC 4.7% vs non-FDC 5.3%; p=0.80).

Conclusion In Korea, prescription of FDC to treat newly diagnosed patients with DS TB improved patient's treatment completion. Use of FDC did not increase the risks of TB recurrence or development of drug resistance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Currently, the use of fixed-dose combination (FDC) in the treatment of tuberculosis is adopted by the WHO guidelines and several national tuberculosis programmes. While clinical equivalence to single-drug formulations has been demonstrated, there is limited evidence on whether use of FDC improves treatment outcomes in the real-world setting.

WHAT THIS STUDY ADDS

⇒ In South Korea, where the burden of tuberculosis is high, the impact of FDC on patients with newly diagnosed, drug-susceptible tuberculosis was evaluated using an integrated multiyear national database. We observed that FDC use was independently associated with treatment completion rates and did not increase tuberculosis recurrence rate compared with single-drug formulation users.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may contribute to more effective management of tuberculosis by promoting the use of FDC in the initial treatment of drug-susceptible tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a major global health problem with an estimated 10.6 million developing TB and 1.6 million dying due to TB in 2021.[1] In 2015, the End-TB strategy was developed to end TB epidemic by 2035. This aims to reduce global TB incidence by 80% and TB deaths by 90% by 2030 relative to the baseline 2015 estimates.[2] One important pillar of the End-TB strategy is to provide 'integrated, patient-centred care and prevention', which includes goals to increase TB treatment coverage and success rate to more than 90%.

In this regard, the fixed-dose combination (FDC) for first-line TB treatment provides convenience for implementation and delivery of TB treatment and has the potential to improve patient acceptability and treatment outcomes and reduce risks of inappropriate dosing.[3] Given this benefit, WHO recommends use of FDC for treatment of drug-susceptible (DS) TB, over separate drug formulations in treatment of patients with DS-TB[4] and many National TB programmes have included FDCs in their TB treatment guidelines.[5]

Over the past decade, several clinical trials[6 7] and systematic reviews[8 9] on effectiveness of FDC have been published but provided contradicting results to the potential programmatic and clinical benefits of FDCs.[10] In one meta-analysis the risk of 'treatment failure' was similar with FDCs and single-drug formulations (pooled risk ratio 1.28, 95% CI 0.82 to 2.00).[9] However, in another meta-analysis, the pooled risk of 'treatment failure or disease relapse' in DS TB was higher with FDCs than separate drug group (pooled risk ratio 1.48, 95% CI 1.04 to 2.09) and implied the potential risk of worse outcome in patients with FDCs.[8] Furthermore, the bioavailability of FDC and lower drug levels, especially for rifampicin are of concern,[11] potentially contributing to higher relapse rate and acquired drug resistance in patients treated with FDCs.[12 13] Although one study reported improved patient satisfaction[14] there lacks clear evidence as to whether use of FDC can improve treatment adherence.

Although South Korea shares the largest TB burden among the countries in the Organisation for Economic Cooperation and Development, recent decade (2011–2021) represented an accelerated decline in TB incidence at a rate greater than 10% per year from 91.8 to 35.7 new cases per 100 000 population.[15] During this decade, the national TB control programme introduced and gradually increased coverage of the FDC treatment (isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z)) for patients with DS-TB in the routine practice. Majority of earlier studies evaluating the effectiveness of FDCs over single-drug formulations were clinical trials conducted in highly controlled and optimal research settings and there lack studies that evaluated longer-term, real-world effectiveness of FDC use of DS-TB treatment.

Using an integrated multiyear national database (the Korean National Tuberculosis Surveillance System (KNTSS), the National Health Insurance Database (NHID) and the Health Insurance Review and Assessment Service (HIRA)) of patients with TB reported between 2013 and 2018, we assessed the effectiveness of FDC use for treatment of newly diagnosed patients with TB. We assessed the comparative effectiveness of FDC use to single-drug formulation on patients' treatment outcomes (treatment completion rate), deaths and TB recurrence rate.

METHODS

Description of the main database

The integrated national database of patients with TB was developed by linking the following three databases: (1) KNTSS database established by the Korea Disease Control and Prevention Agency containing TB notification data for those reported between 2013 and 2018; (2) the NHID established by the National Health Insurance Service and (3) HIRA data of people with a history of TB and related diseases between 2007 and 2018. A total of 137 661 patients with TB reported in the KNTSS were linked with the matched data in NHID and HIRA. The KNTSS TB notification database includes individual patient data, which includes notification date, age, sex, nationality, type of TB, acid-fast bacilli (AFB) smear result and the patient's TB history. Matching the KNTSS database with the NHID and HIRA databases provides additional patient-level information on: (1) sociodemographic information in NHID (age, sex and household income level, death, insurance eligibility); (2) health services use types (inpatients procedure, operation, prescription, etc); (3) disease diagnosis and classification (according to the International Classification of Diseases); (4) drug and treatment prescriptions (generic name, quantity, total days, unit price, etc) and (5) health service provider information (location, level and types of health provider). Data linkage was established for the matched patients with TB reported to the KNTSS and those with a medical claim for TB and TB related disease in the NHID and HIRA.

Study design and population

The flow diagram illustrating the process of patients included for this study (see figure 1). Within the integrated national TB patient database, we selected our subset study population to patients with TB newly diagnosed patients with DS-TB between 2015 and 2016

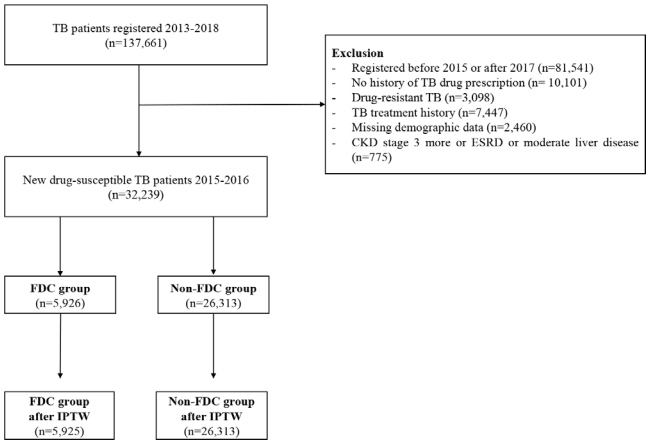

Figure 1 Flow chart of the participants. CKD, chronic kidney disease; ESRD, end-stage renal disease; FDC, fixed-dose combination; IPTW, inverse probability of treatment weighting; TB, tuberculosis.

because FDC was introduced and used generally in this period.

From the main integrated database, we excluded patients with TB registered before 2015 or after 2017 (n=81 541). We further excluded patients with drug-resistant (DR) TB (n=3098), without drug prescription history (n=10 101), those who had previous treatment history (n=7447). Patients with missing information in covariates (n=2460), chronic kidney disease (CKD, ≥stage 3), end-stage renal disease (ESRD), moderate liver disease (n=775) were additionally removed. Our final dataset included a total of 32 239 newly diagnosed patients with DS-TB: 5926 and 26 313 patients were classified as FDC and non-FDC users (figure 1).

Patients with TB were followed up in each health institution based on the Korean TB guideline[16] under the supervision of the Korean Disease Control and Prevention Agency. In general, patients visit the medical centre monthly to evaluate their TB status and treatment response. Since 2011, Private–Public Mix (PPM) programme nurses counsel the patients regularly and checked treatment adherence. All participants were followed up until 31 December 2018 or death. The median follow-up duration was 2.9 years (IQR 2.7–3.5).

Operating definitions of exposure, outcome and key covariates

Given the retrospective nature of our databases, exposure to FDC use, patient's TB treatment compliance, and other key covariates require operational definitions for required analyses for our study. In our study, the principal exposure variable was FDC use. We assigned patients in the FDC user group if the newly reported patient with TB was prescribed FDC within the first 6 months of TB diagnosis. New patients with DS-TB without any record of FDC prescription were classified as non-FDC users and were considered as the control to the FDC cohort.

Treatment outcomes at the patient's treatment end point were assessed as the following. First, we evaluated patient's treatment completion (or adherence) based on an operating definition of patients having received 80% of the recommended dose over a 6-month regimen within 9 months, or 9-month regimen within 12 months. Second, we considered patients did not complete their TB treatment (treatment incompletion) if they did not meet the treatment completion criteria. Third, we considered death as treatment outcome measure only when a patient died during their TB treatment. In addition, we considered TB recurrence for patients with more than one occurrence of TB notification after the completing the treatment of their initial TB episode.

Covariates

Household income level was categorised into a quintile (1=the lowest, 5=the highest) based on classifications used to assess patient's annual national health insurance premium. Patients receiving medical aid benefits were assessed as a separate income group (coded as '0'). They were in the lowest income bracket below the quintile group. Residential regions were categorised at the province level as metropolitan (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan and Sejong) and other regions (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam and Jeju). Variables that may influence the final treatment outcome, including age, sex, residential region, TB lesion site, sputum smear results, comorbidities and CCI were measured as covariates.

Statistical analyses

Inverse probability of treatment weighting (IPTW) was used to control for differences in patient characteristics between the two groups (FDC group and non-FDC group),[17] with standardised differences used to assess the balance of covariates. To calculate the probability of being prescribed FDC, we used a multivariable logistic regression model taking into account demographic and clinical characteristics for the propensity score: age, sex and CCI, type of TB, smear positivity, household income and year of diagnosis. The variables with an absolute standardised difference (ASD) of less than 0.1 between the two groups were considered to be accurately balanced. The love plot for standardised mean difference after IPTW was provided as online supplemental figure S1.

We performed descriptive analyses to assess the distribution of individual covariates. Continuous variables were assessed as means with 95% CI (or SD) if normally distributed. Otherwise, summaries of data were presented as median (IQR), or proportions/percentages (eg, categorical variables). The Student's t-test if the variable normally distributed or Mann-Whitney U test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables appropriately.

To assess the effect of FDC use on treatment outcomes, we conduced multivariable logistic regression analysis with IPTW. To assess the hazard of FDC use related to TB recurrence after successful treatment, the subdistribution hazard model with IPTW was used considering competing risks for death. All p values were two tailed, and a $p<0.05$ was deemed statistically significant. All statistical analyses were performed by using SAS Enterprise Guide V.7.1 (SAS Institute Inc., Cary, NC, USA) and Stata/MP version 18 (StataCorp LLC, College Station, TX, USA).

Patient and public involvement

To approve the data utility, the study protocol was reviewed by the committee operating 'Healthcare bigdata platform' where non-health sectors' reviewers participated. In addition, to approve the study design, the study protocol was reviewed by an Independent Review Committee operating by Yonsei University Health System where non-health sectors' reviewers participated.

Table 1 General characteristics of the newly diagnosed patients with TB according to the FDC use in 2015–2016: before and after inverse probability of treatment weighting

	Unweighted population		Before IPTW			After IPTW		
Variable	FDC group N=5926	Non-FDC group N=26 313	FDC group (%)	Non-FDC group (%)	P value	FDC group (%)	Non-FDC group (%)	P value
Sex					0.16			0.91
Men	3391	15 319	57.2	58.2		58.1	58.0	
Women	2535	10 994	42.8	41.8		41.9	42.0	
Age; year, median (IQR)	58 (42–74)	57 (42–74)	58 (42–74)	57 (42–74)	0.50	57 (42–74)	57 (42–74)	0.50
Age group (year)					0.55			0.55
0–19	236	978	4.0	3.7		4.0	3.7	
20–29	531	2394	9.0	9.1		9.0	9.1	
30–39	561	2525	9.5	9.6		9.5	9.6	
40–49	808	3593	13.6	13.7		13.7	13.6	
50–59	1064	4864	18.0	18.5		18.3	18.5	
60–69	843	3896	14.2	14.8		13.9	14.8	
70+	1883	8063	31.8	30.6		31.6	30.7	
Region					0.41			0.24
Metropolitan	2756	12 393	46.5	47.1		46.2	47.1	
Others	3170	13 920	53.5	52.9		53.8	52.9	
Income level					0.32			0.86
0 (lowest, medical aid)	501	2304	8.5	8.8		8.7	8.7	
1	940	4357	15.9	16.6		16.4	16.4	
2	878	4082	14.8	15.5		15.1	15.5	
3	1003	4343	16.9	16.5		17.0	16.5	
4	1120	4813	18.9	18.3		18.8	18.4	
5 (highest)	1484	6414	25.0	24.4		24.2	24.6	
Lesion of TB					<0.001			0.98
Pulmonary	4571	20 974	77.1	79.7		79.2	79.2	
Extrapulmonary	1355	5339	22.9	20.3		20.8	20.8	
AFB smear					<0.001			0.86
Positive	1630	7894	27.5	30.0		29.4	29.5	
Negative	4296	18 419	72.5	70.0		70.6	70.5	
CCI score					<0.001			0.16
0	2448	11 579	41.3	44.0		42.8	43.6	
1	1350	5792	22.8	22.0		23.2	21.9	
2	697	3164	11.8	12.0		11.6	12.1	
3 or above	1431	5778	24.1	22.0		22.5	22.4	
Comorbidity								
Diabetes mellitus	1368	5661	23.1	21.5	0.01	22.5	21.7	0.16
Cerebrovascular disease	663	2830	11.2	10.8	0.33	11.2	10.8	0.97
Chronic pulmonary disease	2433	10 213	41.1	38.8	0.001	41.1	38.8	0.09
Malignancy	670	2239	11.3	8.5	<0.001	11.3	8.5	<0.001

AFB, acid-fast bacilli; CCI, Charlson Comorbidity Index; FDC, fixed-dose combination; IPTW, inverse probability of treatment weighting; TB, tuberculosis.

Table 2 Treatment outcome of the newly diagnosed patients with TB according to the FDC use in 2015–2016

Variable	Unweighted population		Before IPTW			After IPTW		
	FDC group (N)	Non-FDC group (N)	FDC group (%)	Non-FDC group (%)	P value	FDC group (%)	Non-FDC group (%)	P value
Total	5926	26 313			<0.01			<0.01
Treatment completion	4977	20 764	84.0	78.9		83.9	78.9	
Treatment incompletion	463	2983	7.8	11.3		7.9	11.3	
Death	486	2566	8.2	9.8		8.2	9.8	
Men	3391	15 319			<0.01			<0.01
Treatment completion	2803	11 954	82.7	78.0		82.6	78.0	
Treatment incompletion	284	1805	8.4	11.8		8.5	11.8	
Death	304	1560	8.9	10.2		8.9	10.2	
Women	2535	10 994			<0.01			<0.01
Treatment completion	2174	8810	85.7	80.1		85.8	80.1	
Treatment incompletion	179	1178	7.1	10.7		7.0	10.7	
Death	182	1006	7.2	9.2		7.2	9.1	

FDC, fixed-dose combination; IPTW, inverse probability of treatment weighting; TB, tuberculosis.

After those approvals, there were no public and patients involvement during the study implementation.

RESULTS

Baseline characteristics before and after IPTW

Table 1 provides the baseline characteristics of the FDC and non-FDC groups before and after IPTW. After IPTW, we did not observe significant differences between the two groups for all key variables (sex, age, region, household income level, lesion of TB, AFB smear positivity and CCI score). The FDC group had a higher rate of malignancy as comorbidities relative to the non-FDC group (FDC vs non-FDC: 11.3% vs 8.5%, p<0.001).

Given the key differences in exposure, outcome and key covariate measures by sex, we performed subgroup analyses for men and women separately. These results are provided in online supplemental tables S1 and S2. Similar statistical results for baseline characteristics were observed in the FDC and non-FDC groups according to subgroup analysis by sex.

Treatment outcomes in the FDC group and non-FDC group

Patients prescribed with FDC had better overall treatment outcomes compared with the non-FDC cohort after IPTW (p<0.01 for all outcome measures). FDC users had a higher treatment completion (83.9% vs 78.9%), lower treatment incompletion (7.9% vs 11.3%) rates and lower proportion of patients experiencing deaths (8.2% vs 9.8%) relative to the comparator. This trend was also consistent in our subgroup assessment for men and women (see table 2).

Effect of FDC use on DS-TB treatment completion

To assess the factors influencing DS-TB patients' treatment outcomes, we further analysed the data using multivariable logistic regression analysis (see table 3). After IPTW, FDC users were 1.40 times more likely to complete the first-line TB treatment for their initial TB treatment compared with those not prescribed with FDC in the univariate analysis (OR 1.40; 95% CI 1.30 to 1.51). This estimate marginally improved in the multivariate analysis, favouring FDC use for newly diagnosed patients with DS-TB for treatment compliance (adjusted OR 1.45; 95% CI 1.34 to 1.56) (see table 3). Similar trends were observed in subgroup analyses performed separately for men and women (see online supplemental tables S3 and S4).

In addition, patients with TB with younger age (relative to 70+ age) and higher income level had higher odds for treatment completion. We added the result of the adjusted risk difference of treatment completion before and after IPTW in online supplemental table 5.

Effect of FDC use on TB recurrence after treatment completion

We analysed the effect of FDC use on TB recurrence after treatment completion using a subdistribution hazard model with IPTW in survival analysis. The recurrence rate of TB was 2.3% in the FDC group (112 of 4973 patients with treatment completion) and 2.4% in the non-FDC group (500 of 20 760 patients with treatment completion) (see online supplemental figure S2). In the multivariable analysis, FDC use was not associated with TB recurrence after treatment completion (adjusted HR (aHR) 0.94; 95% CI 0.77 to 1.16) (table 4). Sex (men,

Table 3 The impact of FDC use on the treatment completion in newly diagnosed patients with TB after inverse probability of treatment weighting

	Total patients		
	Univariable	Multivariable	
Variables	OR, 95% CI	aOR, 95% CI	P value
FDC			<0.001
No	Ref.	Ref.	
Yes	1.40 (1.30 to 1.51)	1.45 (1.34 to 1.56)	
Sex			<0.001
Men	0.87 (0.82 to 0.92)	0.72 (0.68 to 0.77)	
Age group (year)			<0.001
0–19	5.88 (4.78 to 7.24)	5.61 (4.54 to 6.93)	
20–29	4.81 (4.24 to 5.46)	4.54 (3.97 to 5.19)	
30–39	5.45 (4.78 to 6.20)	5.17 (4.51 to 5.92)	
40–49	3.57 (3.24 to 3.94)	3.68 (3.32 to 4.07)	
50–59	2.81 (2.59 to 3.05)	3.09 (2.83 to 3.36)	
60–69	2.59 (2.38 to 2.83)	2.77 (2.54 to 3.03)	
70+	Ref.	Ref.	
Region			0.002
Metropolitan	Ref.	Ref.	
Others	0.82 (0.78 to 0.87)	0.91 (0.86 to 0.97)	
Income level			
5 (highest)	Ref.	Ref.	
4	1.20 (1.10 to 1.31)	0.98 (0.90 to 1.07)	0.68
3	1.18 (1.08 to 1.29)	0.86 (0.78 to 0.95)	0.002
2	1.11 (1.02 to 1.22)	0.78 (0.71 to 0.86)	<0.001
1	0.95 (0.87 to 1.03)	0.72 (0.66 to 0.79)	<0.001
0 (lowest, medical aid)	0.49 (0.44 to 0.53)	0.53 (0.48 to 0.59)	<0.001
Lesion of TB			0.004
Pulmonary	Ref.	Ref.	
Extrapulmonary	1.04 (0.97 to 1.11)	0.90 (0.83 to 0.97)	
AFB smear			<0.001
Positive	0.77 (0.73 to 0.82)	0.85 (0.80 to 0.91)	
CCI score			
0	2.02 (1.89 to 2.16)	1.15 (1.06 to 1.24)	<0.001
1	2.11 (1.95 to 2.29)	1.58 (1.45 to 1.72)	<0.001
2	1.43 (1.31 to 1.57)	1.14 (1.04 to 1.26)	0.01
3 or above	Ref.	Ref.	

AFB, acid-fast bacilli; aOR, adjusted OR; CCI, Charlson Comorbidity Index; FDC, fixed-dose combination; Ref, reference; TB, tuberculosis.

aHR 1.65; 95% CI 1.38 to 1.98), lowest income level (aHR 2.00; 95% CI, 1.49 to 2.69) and AFB smear positivity (aHR 2.43; 95% CI 2.04 to 2.88) were identified as risk factors of TB recurrence (see table 4). In addition, there were no differences between the FDC and non-FDC groups in terms of acquired drug resistance when TB recurred (drug-resistant TB in FDC 4.7% vs non-FDC 5.3%; p=0.80).

DISCUSSION

In this comparative study using a large, multiyear integrated national TB patient data, we found that patients with FDC had higher treatment completion rates than those without FDC. In our further analyses, we confirmed that FDC use was key factor in improving treatment completion. In long-term follow-up assessment of patients included in our study, we found that FDC use did

Table 4 The impact of FDC use on TB recurrence in newly diagnosed patients with TB after inverse probability of treatment weighting

	Total patients		
	Univariable	Multivariable	
Variables	HR, 95% CI	aHR, 95% CI	P value
FDC			0.56
No	Ref.	Ref.	
Yes	0.94 (0.77 to 1.15)	0.94 (0.77 to 1.16)	
Sex			<0.001
Men	1.72 (1.45 to 2.04)	1.65 (1.38 to 1.98)	
Age group (year)			
0–19	0.59 (0.35 to 0.98)	0.73 (0.43 to 1.23)	0.24
20–29	0.91 (0.68 to 1.23)	1.08 (0.79 to 1.49)	0.63
30–39	0.74 (0.54 to 1.01)	0.83 (0.59 to 1.16)	0.27
40–49	0.75 (0.57 to 0.99)	0.75 (0.55 to 1.01)	0.06
50–59	1.23 (0.99 to 1.54)	1.13 (0.89 to 1.44)	0.32
60–69	1.07 (0.84 to 1.37)	1.03 (0.80 to 1.32)	0.84
70+	Ref.	Ref.	
Region			0.53
Metropolitan	Ref.	Ref.	
Others	0.95 (0.81 to 1.11)	0.95 (0.81 to 1.11)	
Income level			
5 (highest)	Ref.	Ref.	
4	1.21 (0.93 to 1.58)	1.20 (0.92 to 1.57)	0.18
3	1.24 (0.94 to 1.62)	1.18 (0.89 to 1.55)	0.25
2	1.57 (1.21 to 2.04)	1.43 (1.09 to 1.86)	0.01
1	1.46 (1.12 to 1.89)	1.34 (1.03 to 1.74)	0.03
0 (lowest, medical aid)	2.24 (1.67 to 3.01)	2.00 (1.49 to 2.69)	<0.001
Lesion of TB			0.58
Pulmonary	Ref.	Ref.	
Extra-pulmonary	0.56 (0.44 to 0.71)	0.93 (0.72 to 1.20)	
AFB smear			<0.001
Positive	2.59 (2.21 to 3.04)	2.43 (2.04 to 2.88)	
CCI score			
0	0.83 (0.67 to 1.02)	0.87 (0.69 to 1.10)	0.25
1	0.95 (0.76 to 1.20)	0.98 (0.77 to 1.25)	0.86
2	0.85 (0.63 to 1.13)	0.90 (0.67 to 1.20)	0.46
3 or above	Ref.	Ref.	

AFB, acid-fast bacilli; aHR, advanced HR; CCI, Charlson Comorbidity Index; FDC, fixed-dose combination; Ref, reference; TB, tuberculosis.

not increase the risk of TB recurrence or development of drug resistance compared with the FDC-non-user group.

A major benefit of using FDC for DS-TB treatment is the simplified delivery of the TB therapy, improved patient experience in taking the anti-TB drugs and the logistics of patient management. These factors conceptually favours to improved patient adherence to TB treatment in a variety of clinical settings.[3 9] The WHO guidelines recommend the use of FDC rather than separate drug formulations, emphasising the improvement of adherence and aspects of patient satisfaction.[18] Adherence to TB medications is critical for the success of TB treatment, control of TB transmission and prevention of the development of drug resistance.[19–22] However, treatment completion rates for TB are not satisfactory, with 16%–49% of patients reporting not completing the standard treatment regimen.[21] Treatment adherence for TB is challenging due to the exceptionally long treatment

period, multiple medications and intolerability that can occur due to the side effects of TB medications.[21] In a systematic review of clinical trials using directly observed therapy (DOT), the treatment completion rate was reported to be 75.1% when using DOT and 70.9% when using self-administered therapy.[23] Thus, improving adherence to TB treatment by using FDC could contribute to achieving the success of TB treatment.

The FDCs used in this study included isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z), which reduced the pill burden and was convenient for taking and prescribing drugs. Although the FDC in this study were mainly four drugs that could be used only in the intensive phase, the effect of reducing the pill burden and adherence to treatment could work in the critical phase of TB treatment.

Despite several advantages, such as reduced pill burden and ease of prescription and transport, there have been several issues with the use of FDC in TB treatment. Studies investigating differences in rifampicin bioavailability between FDC and single-drug formulations published in the 2000s generally suggested decreased bioavailability of rifampicin when taken as an FDC.[10 11 24–26] In relatively recent studies reported in 2014, 2015 and 2018, not all FDCs were bioequivalent to the single drug reference.[27–29] A decrease in the bioavailability of rifampicin is related to instability in the acidic environment of the stomach when isoniazid coexists,[11] drug product formulation[30] and food intake.[31] Rifampicin is a key drug driving the treatment response in DS TB, and low rifampicin exposure could be associated with poor outcomes, including the development of drug resistance.[32] Thus, validation of the bioavailability of FDCs and implementation of quality-assured drugs are important in the national TB control programme.

In addition, FDC use tends to be more associated with TB relapse compared with single-drug formulations.[8 9] A slightly higher rate of disease relapse and acquired drug resistance among patients treated with FDCs compared with those treated with separate drug formulations has been reported, although the difference was not statistically significant.[8 9] In a subgroup analysis of subjects with DS TB, the increased risk of treatment failure or disease relapse was more evident in patients using FDC compared with patients not using FDC (pooled risk ratio 1.48 (95% CI 1.04 to 2.09)).[8] This may be partly related to the bioavailability of FDCs. However, previous reviews were based on studies performed from the mid-1990s to the 2010s, and the number of participants was insufficient. In addition, the quality of FDCs could be improved over time.

In our study using recently introduced FDCs in Korea, we did not find any differences in TB recurrence rate and acquired drug resistance between FDC users and non-users. We need to follow further outcomes in other various settings using quality assured FDCs for the treatment long-term outcomes. Even with favourable outcomes of FDCs in TB treatment, there are several circumstances in which the use of FDC is restricted. Single-drug formulations are more appropriate for patients with renal dysfunction (CKD and ESRD) or advanced liver disease, who require dose adjustment. When patients experience adverse drug reactions and require adjustment of the treatment regimen, a single-drug formulation is preferred. Accordingly, WHO guidelines also recommend that a single drug formulation be stocked along with the FDC.[18]

This study has several strengths. First, this was a nationwide comparative study that investigated the effects of FDCs on TB treatment. This cohort included a large number of patients with TB and had a long follow-up period. Second, we used an integrated dataset by linking three national databases; thus, we could analyse more relevant covariates such as socioeconomic status and comorbidities. Despite these strengths, this study had a few limitations. We could not access some information since we used data from a retrospective cohort. First, although we collected covariates such as age, household income, history of TB, AFB smear and culture, we were unable to account for potential confounding factors that could have been linked to TB outcome, including smoking, drinking, body mass index and occupation. Additionally, we could not access the direct treatment outcome via KNTSS. Thus, we tried to validate each participant's treatment duration by drug prescription history. Second, FDC group had heterogeneous regimen combined with single drug formulation, because four-drug FDC has been used widely in 2015 but two-drug FDC was just introduced in 2015 and was not widely implemented during the study period. In addition, three-drug FDC was not available in Korea. Third, there were residual differences in clinical characteristics and there may be unobserved confounding factors even after applying IPTW. Although we tried to overcome this with multivariable analysis, it is necessary to interpret the result with this limitation.

In conclusion, our study demonstrated that FDC use is independently associated with treatment completion in patients with newly diagnosed DS TB. During the follow-up period, FDC use was not associated with TB recurrence or acquired drug resistance. Thus, our study may promote the appropriate usage of FDC and better management of patients with TB.

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REFERENCES

1 World Health Organization. Global tuberculosis report 2022 [Internet]. n.d. Available: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
2 World Health Organization. Implementing the end TB strategy: the essentials. 2015. Available: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy
3 Bangalore S, Kamalakkannan G, Parkar S, *et al*. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713–9.
4 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017. Available: https://www.who.int/publications/i/item/9789241550000
5 The promise and reality of fixed-dose combinations with Rifampicin. A joint statement of the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the World Health Organization. *Tuber Lung Dis* 1994;75:180–1.
6 Lienhardt C, Cook SV, Burgos M, *et al*. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the study C randomized controlled trial. *JAMA* 2011;305:1415–23.
7 Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/british Medical Research Council. *Am Rev Respir Dis* 1991;143:700–6.
8 Albanna AS, Smith BM, Cowan D, *et al*. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. *Eur Respir J* 2013;42:721–32.
9 Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, *et al*. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. *Cochrane Database Syst Rev* 2016;2016:CD009913.
10 Iftikhar S, Sarwar MR. Potential disadvantages associated with treatment of activetuberculosis using fixed-dose combination: a review of literature. *J Basic Clin Pharm* 2017;8.
11 Shishoo CJ, Shah SA, Rathod IS, *et al*. Impaired bioavailability of rifampicin in presence of isoniazid from fixed dose combination (FDC) formulation. *Int J Pharm* 2001;228:53–67.
12 Nunn AJ, Cook SV, Burgos M, *et al*. Results at 30 months of a randomised trial of FDCs and separate drugs for the treatment of tuberculosis. *Int J Tuberc Lung Dis* 2014;18:1252–4.
13 Suryanto AA, van den Broek J, Hatta M, *et al*. Is there an increased risk of TB relapse in patients treated with fixed-dose combination drugs in Indonesia *Int J Tuberc Lung Dis* 2008;12:174–9.
14 Bartacek A, Schütt D, Panosch B, *et al*. Comparison of a four-drug fixed-dose combination regimen with a single tablet regimen in smear-positive pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2009;13:760–6.
15 Korea Disease Control and Prevention Agency. Annual report on the notified tuberculosis in Korea [Internet]. 2021. Available: https://www.kdca.go.kr/npt/biz/npp/portal/nppPblctDtaMain.do
16 Joint Committee for the revision of Korean Guidelines for Tuberculosis. *Korean guidelines for tuberculosis*. 2020.
17 Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. *JAMA* 2020;323:466–7.
18 World Health Organization. WHO Consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment. n.d. Available: https://www.who.int/publications/i/item/9789240007048
19 Pradipta IS, Forsman LD, Bruchfeld J, *et al*. Risk factors of multidrug-resistant tuberculosis: a global systematic review and meta-analysis. *J Infect* 2018;77:469–78.
20 Bea S, Lee H, Kim JH, *et al*. Adherence and associated factors of treatment regimen in drug-susceptible tuberculosis patients. *Front Pharmacol* 2021;12:625078.
21 Horsburgh CR, Barry CE, Lange C. Treatment of tuberculosis. *N Engl J Med* 2015;373:2149–60.
22 Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *Int J Tuberc Lung Dis* 1998;2:10–5.
23 Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev* 2015;2015:CD003343.
24 Sadaphal P, Chakraborty K, Jassim-AlMossawi H, *et al*. Rifampicin bioavailability in fixed-dose combinations for tuberculosis treatment: evidence and policy actions. *J Lung Health Dis* 2019;3:9–15.
25 Milán-Segovia RC, Domínguez-Ramírez AM, Jung-Cook H, *et al*. Relative bioavailability of rifampicin in a three-drug fixed-dose combination formulation. *Int J Tuberc Lung Dis* 2010;14:1454–60.
26 Bargaje M, Bharaswadkar S, Lohidasan S, *et al*. Plasma drug concentrations of 4-drug fixed-dose combination regimen and its efficacy for treatment of pulmonary tuberculosis under national tuberculosis elimination programme: a prospective pilot study. *Indian J Tuberc* 2022;69:311–9.
27 Court R, Chirehwa MT, Wiesner L, *et al*. Quality assurance of rifampicin-containing fixed-drug combinations in South Africa: dosing implications. *Int J Tuberc Lung Dis* 2018;22:537–43.
28 Zhu H, Guo S-C, Hao L-H, *et al*. Relative bioavailability of rifampicin in four Chinese fixed-dose combinations compared with rifampicin in free combinations. *Chin Med J (Engl)* 2015;128:433–7.
29 Hao L-H, Guo S-C, Liu C-C, *et al*. Comparative bioavailability of rifampicin and isoniazid in fixed-dose combinations and single-drug formulations. *Int J Tuberc Lung Dis* 2014;18:1505–12.
30 Henwood SQ, de Villiers MM, Liebenberg W, *et al*. Solubility and dissolution properties of generic rifampicin raw materials. *Drug Dev Ind Pharm* 2000;26:403–8.
31 Kumar AKH, Chandrasekaran V, Kumar AK, *et al*. Food significantly reduces plasma concentrations of first-line anti-tuberculosis drugs. *Indian J Med Res* 2017;145:530–5.
32 Pasipanodya JG, McIlleron H, Burger A, *et al*. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. *J Infect Dis* 2013;208:1464–73.