Fixed-dose Combination Antituberculosis Therapy as a Risk Factor for Tuberculosis Recurrence: an Evidence-based Case Report

Arvin Pramudita[1], Cleopas M. Rumende[2], Ardi Findyartini[3]

[1] Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[2] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3] Department of Medical Education, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

Correspondence mail:
Ardi Findyartini, MD. Department of Medical Education, Faculty of Medicine Universitas Indonesia. Jl. Salemba Raya 6, Jakarta 10430, Indonesia. email: findyartini@yahoo.com.

ABSTRAK

Latar belakang: *seorang pasien dengan riwayat tuberkulosis (TBC) memiliki risiko hingga 27% untuk mengalami kekambuhan dalam 2 tahun setelah disembuhkan. Indonesia sendiri memiliki lebih dari 7.500 kasus berulang setiap tahun, terlepas dari reinfeksi atau kambuh. Ini adalah masalah penting, karena TB berulang dikaitkan dengan tingkat kesembuhan yang lebih rendah dengan terapi anti-TB dan risiko pengembangan resistansi obat yang lebih tinggi. Beberapa faktor risiko kekambuhan ini adalah merokok, kepatuhan pengobatan yang buruk, status ekonomi rendah, dan status kekebalan tubuh lemah. Laporan ini bertujuan mengidentifikasi apakah pasien dengan obat anti tuberkulosis (OAT) kombinasi dosis tetap (KDT) dalam pengobatan TBC lebih berisiko untuk kambuh dibandingkan pasien dengan pengobatan OAT dosis terpisah.* ***Metode:*** *pencarian literatur dilakukan di MEDLINE, ProQuest, EBSCO, ScienceDirect, dan Cochrane berdasarkan pertanyaan klinis dan pemilihan artikel sesuai kriteria inklusi dan eksklusi. Artikel yang terpilih dilakukan telaah kritis untuk menilai validitas, kepentingan, dan penerapannya.* ***Hasil:*** *hasil pencarian literatur didapatkan 5 studi kohort dengan validitas yang sama. Hanya satu studi yang memiliki nilai RR akurat sebesar 3,97 (1,14 – 13,80) dan NNH 18. Empat studi dapat diterapkan pada pasien kami.* ***Kesimpulan:*** *penggunaan OAT KDT dalam pengobatan TB meningkatkan risiko kekambuhan dibandingkan OAT dosis terpisah.*

Kata kunci: *kombinasi dosis tetap, tuberkulosis, kambuh.*

ABSTRACT

Background: *a patient with a history of tuberculosis (TB) has a risk up to 27% to develop recurrence within 2 years after being cured. Indonesia itself has more than 7,500 recurrent cases annually, regardless of reinfection or relapse. This is an important problem, as recurrent TB is associated with lower cure rates with the anti-TB therapy and higher risk of developing drug resistance. Some risk factors for this recurrence are smoking, poor treatment adherence, low economic status, and weak immune status. This study is aimed to identify whether the use of fixed-dose combination (FDC) anti-tuberculosis therapy increases the risk for tuberculosis recurrence compared with using separate drug formulation.* ***Methods:*** *the search was conducted on MEDLINE, ProQuest, EBSCO, ScienceDirect, and Cochrane according to clinical question. The studies were selected based on inclusion and exclusion criteria and led to five useful articles. The selected studies were critically appraised for their validity, importance, and applicability.* ***Results:*** *five cohort studies were found with comparable validity. Only*

1 study has accurate relative risk (RR) with 3.97 (1.14 – 13.80) and number needed to harm of 18. Other four studies fulfilled the applicability criteria for our case. ***Conclusion:*** *the use of FDC anti-tuberculosis therapy increases the risk for tuberculosis recurrence compared with using separate drug formulation.*

Keywords: *fixed-dose combination, tuberculosis, recurrent.*

INTRODUCTION

Tuberculosis (TB) remains a major global health problem, with an estimated 10.4 million incident cases and 1.4 million deaths in 2015 according to the World Health Organization (WHO).[1] In Indonesia, there were an estimated 441,940 new active TB cases in 2011 with total economic burden roughly US$ 2.1 billion.[2] Moreover, strains of Mycobacterium tuberculosis that are resistant to standard anti-TB therapy are emerging in 155 countries, accounting for more than 95% of the world's population.[1] Low compliance to treatment regimen and inappropriate prescription of TB therapy are believed to be major contributing factors to thus public health problems.[3,4]

Since 1994, WHO and the International Union against Tuberculosis and Lung Disease (IUATLD) have recommended the use of fixed-dose combination (FDC) anti-TB therapy.[5] This is to simplify the therapy, increase the compliance, and prevent the inadvertent medication errors.[3,6,7] However, concerns were raised about the possibility of poor rifampicin bioavailability, unstable blister-package of FDCs, and weak absorption rate.[6,8] Many observational studies and clinical trials have been conducted to assess the effectiveness of FDCs with conflicting results.[3] Currently, the main drugs for standard TB therapy are rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). The FDCs include two-drug formulations (R+H and H+E), three-drug formulations (R+H+E and R+H+Z), and a four-drug formulation (R+H+Z+E).

Despite all of that, recurrence of TB is quite high. A patient with a history of TB has a risk up to 27% to develop recurrence within 2 years after being cured.[9] Indonesia itself has more than 7,500 recurrent cases annually, regardless of reinfection or relapse.[10] This is an important problem, as recurrent TB is associated with lower cure rates with the anti-TB therapy and higher risk of developing drug resistance. Some risk factors for this recurrence are smoking, poor treatment adherence, low economic status, and weak immune status.[11] The aim of this evidence-based case report (EBCR) is to critically analyzed whether the use of FDC anti-TB therapy increases the risk for TB recurrence compared with using separate drug formulation.

CLINICAL QUESTION

A 56-year old woman came to the clinic with chronic cough for three months prior to admission. She was a merchant with a history of TB six years ago. She had had FDC anti-TB therapy for 6 months and had been declared cured by her attending physician at that time. In her family, his son had TB two years ago and has been cured, while her step father is being treated for TB right now. Her sputum smear was positive. The patient was diagnosed with recurrent TB and had a category II anti-TB therapy according to the Indonesian guideline. She lived in a small tenement with her two sons in a very dense district.

The patient's step father is being treated with separate drug regimen in a different clinic. She became curious of the difference between FDC and separate drug regimen. She was wondering whether there was a difference in terms of drug quality between those two and that was the cause of her recurrent TB.

In a woman with a newly diagnosed TB, does the use of FDC anti-TB therapy have a higher risk of TB recurrence compared with using separate drug formulation?

METHODS

A search of literatures was performed on June 23th to 25th, 2016 in six databases, including MEDLINE®, ProQuest®, EBSCO®, ScienceDirect®, and Cochrane®. The keywords were "tuberculosis", "fixed-dose", and "recurrent"

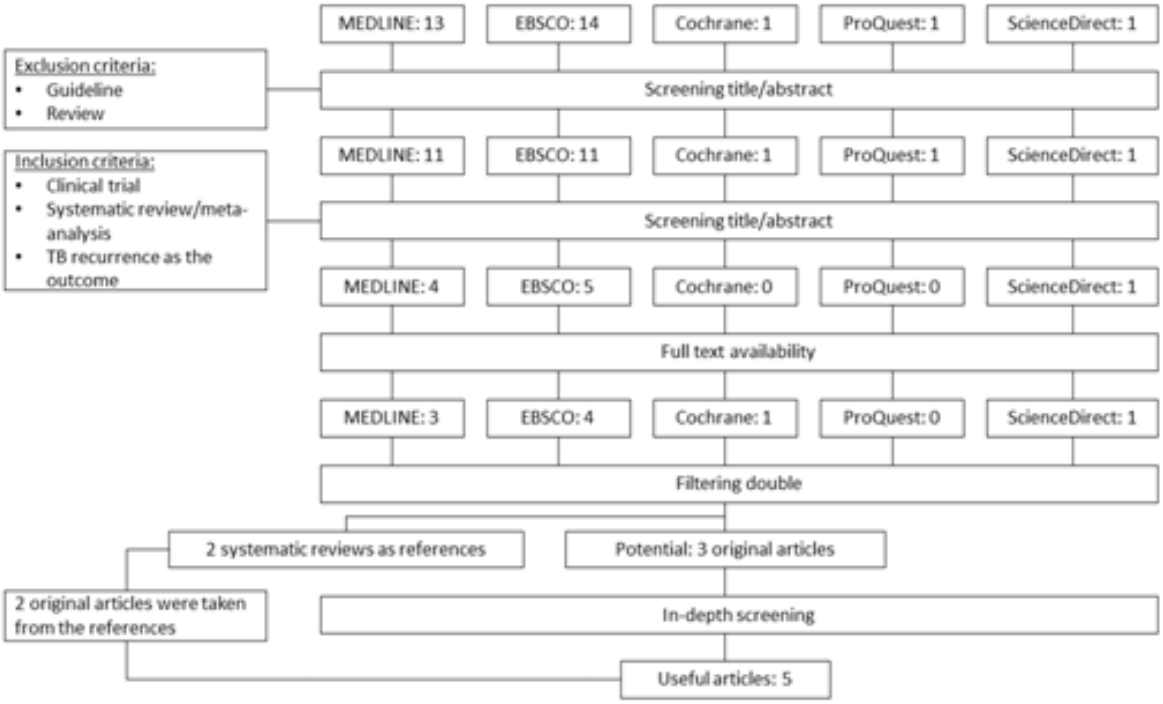

Figure 1. Flowchart of search strategy

Table 1. Terminology used in six databases

Database	Terminology	Hits
MEDLINE®	(("Tuberculosis"[Mesh]) AND ((((fixed-dose[Title/Abstract]) OR fixed dose[Title/Abstract]) OR fixed-drug[Title/Abstract]) OR fixed drug[Title/Abstract])) AND ((((recurrence[Title/Abstract]) OR recurrent[Title/Abstract]) OR relapse[Title/Abstract]) OR reinfection[Title/Abstract])	13
ProQuest®	ab(tuberculosis) AND ab((recurrent OR relapse OR reinfection)) AND ab((fixed-dose OR fixed dose OR fixed-drug OR fixed drug))	1
EBSCO®	AB tuberculosis AND AB (recurrent OR relapse OR reinfection) AND AB (fixed-drug OR fixed drug OR fixed-dose OR fixed dose)	14
Science Direct®	TITLE-ABSTR-KEY(tuberculosis) AND TITLE-ABSTR-KEY("recurrent" OR "relapse" OR "reinfection") AND TITLE-ABSTR-KEY("fixed-dose" OR "fixed dose" OR "fixed-drug" OR "fixed drug")	1
Cochrane®	"tuberculosis" in Title, Abstract, Keywords AND "fixed-drug" OR "fixed drug" OR "fixed-dose" OR "fixed dose" in Title, Abstract, Keywords AND "recurrent" OR "reinfection" OR "relapse" in Title, Abstract, Keyword	1

with their synonyms and related terms. Eligible articles were clinical trials, systematic reviews, or meta-analyses that point TB recurrence as the outcome. Guidelines and review articles were excluded. The search strategy, results, and the inclusion-exclusion criteria are shown in **Figure 1**. After literature selection, critical appraisal was done by consensus of all authors using several aspects based on Center of Evidence-Based Medicine, University of Oxford for harm or etiology study.

RESULTS

Following the search strategy, five original articles were eligible for this evidence-based case report.[8,12-15] The design and summary of result is available on **Table 2**. The critical appraisal is shown on **Table 3**. All articles were cohort studies with level of evidence 2b. Study from Nunn et al.[15] had the largest sample size

Table 2. Design and result of the selected articles

Article	Year	Design	Drug regimen	Result (adjusted with per-protocol analysis)
Zhang et al.[12]	1996	RCT	2RHZ/4RH The FDCs were Rifater® for the first 2 months and Rifinah® for the next 4 months. No information regarding the manufacturer of the separate drugs. Fixed-dose combination group: - Rifater® consists of R 120 mg + H 80 mg + Z 250 mg, 3 tablets for body weight 30-39 kg, 4 tablets for 40-49 kg, and 5 tablets for ≥50 kg. - Rifinah®-150 consists of R 150 mg + H 100 mg, 3 tablets for body weight <50 kg; or Rifinah®-300 consists of R 300 mg + H 150 mg, 2 tablets for ≥50 kg. Separate-drug group: - For the first 2 months; R 450 mg + H 300 mg + Z 1500 mg for body weight <50 kg, R 600 mg + H 300 mg + Z 1500 mg for body weight ≥50 kg. - For the next 4 months; R 450 mg + H 300 mg for body weight <50 kg, R 600 mg + H 300 mg for body weight ≥50 kg.	Relapse after 2 years - FDC group: 2 of 102 patients - Separate-drug group: 2 of 103 patients
Suryanto et al.[8]	2008	RCT	2RHZE/3R3H3 using WHO recommended formulation. The FDCs were produced by Svizera Netherlands. No information regarding the manufacturer of the separate drugs. Fixed-dose combination group: - Average 4FDC adult dose contains R 450 mg + H 225 mg + Z 1200 mg + E 825 mg. - Average 2FDC adult dose contains R 450 mg + H 450 mg. Separate-drug group: - Average adult dose for the first 2 months contains R 450 mg + H 300 mg + Z 1500 mg + E 750 mg. - Average adult dose for the next 3 months contains R 450 mg + H 600 mg.	Relapse after 3-6 years - FDC group: 10 of 236 patients - Separate-drug group: 2 of 198 patients
Nunn et al.[15]	2014	RCT	2RHZE/4R3H3 using WHO recommended formulation. The FDCs were produced by Svizera India. No information regarding the manufacturer of the separate drugs. Fixed-dose combination group: - 4FDC consists of R 150 mg + H 75 mg + Z 400 mg + E 275 mg, 2 tablets for body weight 30-37 kg, 3 tablets for 38-54 kg, 4 tablets for 55-70 kg, and 5 tablets > 70 kg. - 2FDC consists of R 150 mg + H 150 mg, 2-5 tablets respectively based on the body weight. Separate-drug group: - For the first 2 months; R 300 mg + H 150 mg + Z 800 mg + E 600 mg for body weight 30-37 kg, R 450 mg + H 250 mg + Z 1200 mg + E 800 mg for body weight 38-54 kg, R 600 mg + H 300 mg + Z 1600 mg + E 1200 mg for body weight 55-70 kg, or R 750 mg + H 350 mg + Z 2000 mg + E 1400 mg for body weight > 70 kg, - For the next 4 months; 2FDC consists of R 150 mg + H 150 mg, 2-5 tablets respectively based on the body weight.	Relapse after 30 months - FDC group: 5 of 683 patients - Separate-drug group: 0 of 671 patients

Table 2. Design and result of the selected articles

Article	Year	Design	Drug regimen	Result (adjusted with per-protocol analysis)
Su et al.[14]	2002	RCT	2RHZE/4RHE No information regarding the manufacturer of the separate drugs. Fixed-dose combination group: - Rifater® + E for the first 2 months, followed by Rifinah® + E for 4 months. - Rifater® consists of R 120 mg + H 50 mg + Z 250 mg, 3 tablets for body weight 30-39 kg, 4 tablets for 40-49 kg, and 5 tablets for ≥ 50 kg. - Rifinah®-150 consists of R 150 mg + H 100 mg, 3 tablets for body weight < 50 kg; or Rifinah®-300 consists of R 300 mg + H 150 mg, 2 tablets for body weight ≥ 50 kg Separate-drug group: - For the first 2 months; R 450 mg + H 300 mg + Z 1500 mg + E 1200 mg for body weight < 50 kg, R 600 mg + H 300 mg + Z 1500 + E 1200 mg mg for body weight ≥ 50 kg. - For the next 4 months; R 450 mg + H 300 mg + E 800 mg for body weight < 50 kg, R 600 mg + H 300 mg + E 800 mg for body weight ≥ 50 kg.	Relapse after 2 years - FDC group: 1 of 57 patients - Separate-drug group: 0 of 48 patients
Teo et al.[13]	1999	RCT	There were 3 variations of the regimen: 2SHRZ/4H3R3, 1SHRZ/5H3R3, or 2HRZ/4H3R3. No further explanation regardless the selection criteria. Fixed-dose combination group: - For the initial daily phase, RHZ was given as Rifater® (R 120 mg + H 50 mg + Z 300 mg). The daily dosage was 4 tablets for patients weighing ≤ 42 kg, 5 tablets for 43-57 kg, or 6 tablets for ≥ 58 kg. - Streptomycin was given in a fixed-dose injection of 750 mg, regardless of body weight. - For the continuation phase, H 600 mg for patients weighing ≤ 42 kg, 800 mg for 43-57 kg, or 1000 mg for ≥ 58 kg. Additional R 1200 mg were also given, regardless of body weight. Separate-drug group: - For the initial daily phase, R 450 mg + H 300 mg + Z 1500 mg for patients weighing ≤ 42 kg, R 600 mg + H 300 mg + Z 1500 mg for 43-57 kg, or R 600 mg + H 300 mg + Z 2000 mg for ≥ 58 kg. - Streptomycin was given in a fixed-dose injection of 750 mg, regardless of body weight. - For the continuation phase, H 600 mg for patients weighing ≤ 42 kg, 800 mg for 43-57 kg, or 1000 mg for ≥ 58 kg. Additional R 1200 mg were also given, regardless of body weight.	Relapse after 5 years - FDC group: 12 of 154 patients. - Separate-drug group: 3 of 153 patients.

R: rifampicin; H: isoniazid; Z: pyrazinamide; E: ethambutol; S: streptomycin

Table 3. Critical appraisal of the five studies based on criteria by Center of Evidence-Based Medicine, University of Oxford

Article, year	Level of evidence	Sample size	Validity					Importance	Applicability	
			Loss to follow-up (%)	Clearly defined groups	Equal measurement	Adequate follow-up	Fulfill the criteria for causation	RR/OR (95% CI)	NNH	Patient similarity
Zhang et al.[12], 1996	2b	205	1,9	+	?	+	+	RR 1.01 (0.14 – 7.00)	5.253	+
Suryanto et al.[8], 2008	2b	434	19,3	+	?	+	+	RR 1.16 (0.58 – 2.31)	95	+
Nunn et al.[15], 2014	2b	1.354	n/a	+	-	+	+	RR 10.81 (0.60 – 195.07)	137	+
Su et al.[14], 2002	2b	105	51,4	+	?	-	+	RR 2.53 (0.11 – 60.82)	64	+
Teo et al.[13], 1999	2b	307	18	+	?	+	+	RR 3.97 (1.14 – 13.80)	18	+

+ stated clearly in the article; - not being done; ? not stated clearly; levels of evidence based on Oxford Centre for Evidence-based Medicine; RR: relative risk; OR: odds ratio; CI: confidence interval; NNH: number needed to harm.

compared to the others, yet its loss to follow-up was unknown.Only one study from Su et al. had more than 20% loss to follow-up.[14]

All studies were considered to have good validity, although there were some unfulfilled components. The groups were similar, clearly defined, and had complete and adequate follow-up. In terms of Hill's criteria for causation, all studies met the criteria of temporality, consistency, and plausibility.[16] Biological gradient could not be assessed because dose-response gradient and dechallenge-rechallenge could not be done in this type of study. The patients were not blinded as FDC had distinct appearance compared to separate drug formulation. No studies used additional method to make both regimens look alike. The studies also did not state whether they were all blinded or not for the assessment of the outcomes.

From the aspect of importance and applicability, all studies had a relative risk (RR) above 1. The RRs were adjusted to per-protocol analysis for the critical appraisal. Only one of which had a 95% confidence interval (CI) did not pass below the value of 1.13 All studies were relevant to our case with similar sample's characteristics.

DISCUSSION

All studies reported a tendency of increased risk of TB recurrence with the use of FDC regimen.[8,13-15] However, four studies had inaccurate 95% CI, probably due to the large number of loss to follow-up.

Based on the validity components, all five studies were adequately valid. These five studies were cohort with long exposure (six months) and a follow-up period of over a year, thus increasing the risk of loss to follow-up. Su et al. study had notably a 51.4% loss to follow-up that we fear will affect the validity of the study itself.[14] This was mainly caused by adverse effects and treatment defaults that were equal in both FDC and separate formulation groups. There was also a risk of unequal measurement in both FDC and separate formulation groups during the follow-up of these studies, as the patients were aware of their regimen and the investigators could realize it. From the importance aspect, only Teo et al.[13] study that can be said to be accurate with RR 3.97 (1.14–13.80). Therefore, his study is the best evidence we have at this time.

Another limitation of this report is the heterogenicity of intervention models. The drug's dose and treatment regimens were different between articles. The FDCs among the articles

were produced from different manufacturers, as three articles used RIfater® and Rifinah® while the rest used another FDC by Svizera. There was also no information about the manufacturer of the separate drugs. Hence, this could be a potential bias for comparing the efficacy of the tuberculosis treatments.

Fixed-dose combination has been the main preference of anti-TB therapeutic regimen since about 20 years ago, especially due to its simplicity.[5] However, recent meta-analysis concludes that there is no evidence of improved compliance and treatment satisfaction with the use of FDC.[3] Recent findings from Indonesia also show that patient's adherence is multifactorial, not only affected by the treatment regimen but also healthcare accessibility, knowledge, and especially perception of TB therapy.[17,18]

The exact cause of how FDCs affect TB recurrence is still not clearly known. It was reported that the bioavailability of rifampicin was reduced in FDCs, due to its enhanced decomposition in the presence of isoniazid.[3,8] The blister-packed FDCs have also been shown to be unstable, and their absorption was insufficient in immunocompromised patients.[8] The fixed-dose model may also impede further dose adjustments.[6]

For the application in our case, we should explain to our patient that the evidence is still limited, yet there is a tendency that the FDC formulations are inferior compared to separate drug regimen. However, the patient should be educated that recurrence is also multifactorial, as her family history and environmental factors also play important roles.[19]

CONCLUSION

In conclusion, FDC therapy is associated with a trend toward increased risk of TB recurrence. Even though FDC is easier and simpler for both the patient and the physician, this report does not support the use of FDC for treating newly diagnosed TB patients. Further research with better trial designs are needed to simulate real-world clinical practice while minimizing confounding, thus providing high-quality evidence for health care policies and clinical decisions.

ACKNOWLEDGMENTS

We thank Listya Tresnanti Mirtha, MD for his general support to this report. In addition, we thank all staffs of Department of Community Medicine, Faculty of Medicine Universitas Indonesia

REFERENCES

1. World Health Organization. Glocal Tuberculosis Report 2016. WHO. 2016.
2. Collins D, Hafidz F, Suraratdecha C. The Economic Burden of Tuberculosis in Indonesia. TB CARE I - Management Sciences for Health. 2013.
3. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. Eur Respir J. 2013;42(3):721–32.
4. Shin HJ, Kwon YS. Treatment of drug susceptible pulmonary tuberculosis. Tuberc Respir Dis (Seoul). 2015;78(3):161–7.
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. Tubercule Lung Dis. 1994;75:180–1.
6. Gallardo Carmen R, Rigau Comas D, et al. Fixed-dose combinations of drugs versus single drug formulations for treating pulmonary tuberculosis. Cochrane Database Syst Rev. 2012;(7).
7. Monedero I, Caminero JA. Evidence for promoting fixed-dose combination drugs in tuberculosis treatment and control: A review. Int J Tuberc Lung Dis. 2011;15(4):433–9.
8. Suryanto AA, Van Den Broek J, Hatta M, De Soldenhoff R, Van Der Werf MJ. 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(2):174–9.
9. Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: Relapse or reinfection? Lancet Infect Dis. 2003;3(5):282–7.
10. World Health Organization. Glocal Tuberculosis Report 2015. WHO. 2015.
11. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: adequatley treated patients are still at high risk. Int J Tuberc Lung Dis. 2007;11(October 2006):828–37.
12. Zhang L-X, Kan G-Q, Tu D-H, Wan L-Y, Faruqi AR. Fixed-dose combination chemotherapy versus multiple, single-drug chemotherapy for tuberculosis. Curr Ther Res. 1996;57(11):849–56.
13. Teo SK. Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater) in the initial phase of chemotherapy in three 6- month

regimens for smear-positive pulmonary tuberculosis: A five-year follow- up report. Int J Tuberc Lung Dis. 1999;3(2):126–32.
14. Su WJ, Perng RP. Fixed-dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two-year follow-up. Int J Tuberc Lung Dis. 2002;6(11):1029–32.
15. Nunn AJ, Cook S V., 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(10):1252–4.
16. Hill AB. The environment and disease: Association or causation? Proc R Soc Med. 1965;58:295-300.
17. Putera I, Pakasi TA, Karyadi E. Knowledge and perception of tuberculosis and the risk to become treatment default among newly diagnosed pulmonary tuberculosis patients treated in primary health care, East Nusa Tenggara: a retrospective study. BMC Res Notes. BioMed Central. 2015;8:238.
18. Widjanarko B, Gompelman M, Dijkers M, van der Werf MJ. Factors that influence treatment adherence of tuberculosis patients living in Java, Indonesia. Patient Prefer Adherence. 2009;3:231–8.
19. Lienhardt C, Fielding K, Sillah JS, et al. Investigation of the risk factors for tuberculosis: A case-control study in three countries in West Africa. Int J Epidemiol. 2005;34(4):914–23.