

Family Based Directly Observed Therapy on Culture Conversion in Newly Diagnosed Pulmonary Tuberculosis Patients

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Received January 26, 2014; Revised July 25, 2014; Accepted July 30, 2014

Abstract Background: The effectiveness of directly observed therapy (DOT) on TB treatment outcome has been debated and different findings regarding different DOT practices and settings were demonstrated. **Methodology:** The observational study was conducted in new sputum smear and culture positive pulmonary TB patients at Queen Savang Vadhana Memorial Hospital and Chonburi Hospital, Chonburi province, Thailand during April 2010 and July 2012. The aim of this study was to evaluate the effect of family based DOT toward sputum culture conversion. Sputum AFB smear, culture and drug susceptibility test were performed at the time of diagnosis, the second and the fifth month of treatment. Baseline characteristic, clinical and laboratory parameters, treatment regimens and adverse events were recorded. Descriptive statistics were applied as appropriate. **Results:** Proportion of patients with illiteracy, visual alteration and hepatitis was significantly higher in family based DOT group ($p=0.026$, $p=0.011$ and $p=0.031$). Sputum smear and culture conversion at 2 and 5 months after treatment were not significantly different between family based DOT and self administer groups. Patients in both group achieved over 90% cure rate without significant difference ($p=0.262$). **Conclusions:** Continuing patient education, counseling and AEs monitoring should be incorporated into family based DOT to achieved successful outcome. DOT can be interfered by many factors. Therefore appropriate implementing of DOT can enhance effectiveness of DOT toward patient adherence and further achieve success in TB treatment and control.

Keywords: DOT, family base DOT, culture conversion, new pulmonary TB

Cite This Article: Duangjai Duangrithi, Kamol Phojanamongkolkij, Vipa Thanachartwet, Varunee Desakorn, Yuthichai Kasetjaroen, Pasakorn Jitruckthai, Duangjai Sahassananda, and Punnee Pitisuttithum, "Family Based Directly Observed Therapy on Culture Conversion in Newly Diagnosed Pulmonary Tuberculosis Patients." *American Journal of Public Health Research*, vol. 2, no. 4 (2014): 147-152. doi: 10.12691/ajphr-2-4-4.

1. Introduction

Irregular, interrupt or incomplete treatment of tuberculosis (TB) could result in drug resistance, treatment failure, relapse as well as transmission [1-3]. Furthermore, approximately 50% of TB patients had ever missed at least one anti-tuberculous dose [3]. Directly observed therapy (DOT) was the method for sustaining patient adherence to anti-tuberculous treatment by observing patients swallowing drugs [1,3] and it was recommended concomitantly with rifampicin containing regimen in 1980s in order to improve treatment outcome [3]. In 1990s, World Health Organization (WHO) incorporated DOT with standard short course regimen and named directly observed therapy, short course (DOTS) which was the key

element of six principal components of The Stop TB Strategy [2].

DOT providers can be health care workers, community volunteers or family members [3]. DOT influencing treatment outcome of TB has been debated and different findings regarding different DOT practices and settings were demonstrated. Similar cure rates were reported between patients with DOT and self administration (SAT) [1]. Furthermore, lowest success rate was observed among patients provided DOT by health care worker [1,4] whereas similar clinical outcomes were reported among patients provided DOT by clinic staffs, community health workers and families [1]. However, family based DOT showed potential advantage in cure rate compared to clinic based DOT [1]. In Thailand, family based DOT was more acceptable than layperson and volunteer [3].

Cure rate defined by sputum culture for *Mycobacterium tuberculosis* (40.8%) and sputum acid fast bacilli (AFB) smear (32.4%) among new definite pulmonary TB were significantly different ($p < 0.05$) [5] and even none of patients with positive sputum AFB smear at the end of anti-tuberculous treatment were sputum culture positive for *M. tuberculosis* [6]. These may affect the benefit assessment of DOT toward treatment outcome.

To our knowledge, the association between family based DOT and sputum culture conversion among new definite cases of pulmonary TB was examined restrictedly. Therefore, this study aims to evaluate the effectiveness of family based DOT toward culture conversion rate of new pulmonary TB patients

2. Materials and Methods

2.1. Study Design and Study Sites

A prospective observational study was conducted at Queen Savang Vadhana Memorial Hospital and Chonburi Hospital in Chonburi province, Thailand during April 2010 and July 2012 in order to evaluate the effectiveness of family based DOT toward treatment outcome defined by sputum culture for *M. tuberculosis* in new pulmonary TB patients.

The inclusion criteria were: (1) patients with aged ≥ 14 years; (2) patients having at least 2 or more of pulmonary or constitutional symptoms including cough, hemoptysis, chest pain or discomfort, dyspnea, fever, malaise, fatigue, weight loss and night sweat; (3) patients who were defined as pulmonary TB due to having abnormal chest compatible with pulmonary TB and having at least 1 of 3 sputum smear positive for AFB; and (4) patients who had first episode of TB or have taken anti-TB drugs for < 1 month according to the 2010 WHO definition [7]. The exclusion criteria were: (1) patients having sputum culture negative for *M. tuberculosis*; and (2) patients having extrapulmonary TB without pulmonary TB.

Apart from education and counseling about TB and its treatment, DOT delivery was explained to all patients as well as their family members.

2.2. Laboratories and Sputum Examinations

Complete blood count, blood chemistries and HIV testing were performed at the time of diagnosis. All patients and their family members were educated about sputum collection procedure. The sputum AFB smear was routinely performed at 2, 5 and 6 months after treatment at each hospital using Kinyoun method. Only one leftover sputum specimen with the highest positive AFB smear, prior to treatment, at 2 and 5 after treatment of each patient was sent to national TB reference laboratory center, Bangkok Thailand for mycobacterium culture as well as drug susceptibility test (DST) by conventional method using Löwenstein–Jensen solid media and automated liquid media culture systems (MGIT 960, BACTEC, USA). However, if patient was sputum AFB negative after treatment, one leftover sputum with the best quality specimen was sent for culture and DST.

Baseline characteristics, clinical and laboratory parameters as well as treatment regimens were collected and recorded in a pre-defined case record form. Adverse

events (AEs) and treatment adherence were evaluated biweekly.

2.3. Definitions

Patients were classified into family based DOT group if DOT was delivered by their family members at least for the entire course of intensive phase according to Thai guideline for diagnosis and treatment of TB, otherwise were classified into SAT group. All patients as well as DOT observers were regularly supervised by telephone every 2 weeks. Treatment outcome was defined according to WHO Global Tuberculosis report 2012 [8]. Irregular adherence was identified if patients missed at least one dose of anti-tuberculous treatment according to Tuberculosis and Public Health, Policy and Principles in Tuberculosis Control [3].

2.4. Sample Size Calculation

The sample size was estimated based on the Thailand national TB program monitoring and evaluation report 2006-2007 which showed 77% cure rate of new AFB smear positive patients with a 95% confidence interval (CI) and the precision to be within 5% of the true value. A required sample size of at least 272 pulmonary TB patients was enrolled in our study.

2.5. Statistical Analysis

Data were analyzed using the statistical package SPSS for Windows version 18.0 (SPSS, Chicago, IL). Categorical variables were summarized as frequencies (percentages) and the comparison between 2 groups was performed by χ^2 test. Numerical variables were tested for normality using the Kolmogorov-Smirnov test, if non-normal distributed data, summarized as median (interquartile range; IQR) and 2 group comparisons was performed using Mann-Whitney *U*-test. The statistical significance was considered by two sided with $p < 0.05$.

2.6. Ethical Consideration

The study was approved by the ethics committee of faculty of Tropical Medicine, Mahidol University in Bangkok; and Queen Savang Vadhana Memorial Hospital and Chonburi Hospital in Chonburi province, Thailand. Written informed consent was obtained from all patients.

3. Result

3.1. Baseline Characteristics

Total of 233 new pulmonary TB patients were eligible for the study. Of these, 39 patients were treated under family based DOT and the rest were SAT. Baseline characteristics of patients in both groups were similar. Majority of patients in both groups were male (31/39, 79.5% VS 140/194, 72.2%, $p=0.456$) with median age (IQR) of 40 years (31-51) and 37 year (28-50) in family based DOT and SAT group ($p=0.290$). Over two third of patients in both group had history of smoking and alcohol consumption with the higher proportions in family based DOT group (30/39, 76.9% VS 122/193, 63.2%, $p=0.145$ and 29/39, 74.4% VS 132/193, 68.4%, $p=0.585$). Cough

was the most common symptoms in both groups (36/39, 92.3% VS 179/193, 92.7%, $p=1.000$) and cavity on chest radiography was presented in one third of patients similarly in each group (11/32, 34.4% VS 54/169, 32.0%, $p=0.950$). However, proportion of patients with illiteracy and low education in family based DOT group were significantly higher compared to SAT group (26/36, 72.2% VS 90/179, 50.3%, $p=0.026$) (Table 1).

3.2. Sputum Conversions

Smear conversion rate at the end of 2 and 5 months after treatment were not significantly higher in family based DOT group compared to SAT group (34/39, 87.2% VS 162/192, 84.4%, $p=0.841$ and 36/37, 97.3% VS 177/185, 95.7%, $p=1.000$). Similarly, culture conversion rate at the end of 2 and 5 month after treatment were not significantly higher in family based DOT group (29/38, 76.3% VS 166/191, 86.9%, $p=0.153$ and 35/37, 94.6% VS 181/185, 97.8%, $p=0.262$).

Table 1. Baseline characteristics, clinical and laboratory parameters of among new pulmonary TB

Characteristics	n	DOT		Self administer		P value
		n	no(%) / Median (IQR)	n	no(%) / Median (IQR)	
<i>Baseline characteristics</i>						
Age	233	39	40 (31-51)	194	37 (28-50)	0.290
Gender: male	233	39	31 (79.5)	194	140 (72.2)	0.456
Married	233	39	26 (66.7)	194	116 (59.8)	0.533
Education: illiterate or primary school	215	36	26 (72.2)	179	90 (50.3)	0.026
Occupation: laborer	233	39	18 (46.2)	194	106 (54.6)	0.428
Income \leq 10,000 Baht	223	38	25(65.8)	185	144 (77.8)	0.170
Smoking	232	39	30 (76.9)	193	122 (63.2)	0.145
Alcoholic drinking	232	39	29 (74.4)	193	132 (68.4)	0.585
BCG scar	229	39	27 (69.2)	190	153 (80.5)	0.176
HIV	225	37	4 (10.8)	188	21 (11.2)	1.000
Extrapulmonary TB	233	39	2 (5.1)	194	11(5.7)	1.000
<i>Clinical characteristics</i>						
Cough	232	39	36 (92.3)	193	179 (92.7)	1.000
Fever	232	39	24 (61.5)	193	141 (43.1)	0.210
Shortness of breath	232	39	24 (61.5)	193	127 (65.8)	0.745
Fatigue	232	39	23 (59.0)	193	99 (51.3)	0.484
Pleurisy	232	39	19 (48.7)	193	105 (54.4)	0.636
Anorexia	232	39	22 (56.4)	193	90 (46.6)	0.348
Night sweat	232	39	18 (46.2)	193	77 (39.9)	0.585
Hemoptysis	232	39	17 (43.6)	193	61 (31.6)	0.208
Vomiting	232	39	10 (25.6)	193	41 (21.2)	0.694
Nausea	232	39	4 (10.3)	193	17 (8.8)	0.761
Cavity on CXR	201	32	11(34.4)	169	54(32.0)	0.950
<i>Physical examination</i>						
Body weight (kg)	214	33	52.0 (44.6-55.0)	181	51.8 (45.0-56.6)	0.681
Body weight change (%)	204	31	-8.6 (-15.2 to -4.9)	173	-8.5 (-14.9 to -4.0)	0.634
Creptitation	233	39	6 (15.4)	194	26 (13.4)	0.942
<i>Laboratories</i>						
Hemoglobin (g/dL)	143	28	11.4 (10.0-13.0)	115	11.5 (9.7-13.2)	0.827
Hematocrit (%)	143	28	35.2 (28.2-38.5)	115	34.4 (30.3-39.3)	0.770
White blood cell ($\times 10^3/\text{mm}^3$)	143	28	10.0 (7.7-14.2)	115	10.4 (8.2-13.5)	0.867
Platelet ($\times 10^3/\text{mm}^3$)	143	28	386.5 (252.5-559.5)	115	416.0 (324.0-492.0)	0.389
Sodium (mmol/l)	91	21	136.0 (131.5-137.5)	70	134.0 (130.0-136.1)	0.216
BUN (mg/dl)	107	25	10.6 (7.5-13.0)	82	9.0 (7.0-12.0)	0.264
Creatinine (mg/dl)	118	26	0.8 (0.6-0.8)	92	0.8 (0.7-0.9)	0.290
Albumin (g/dl)	156	26	3.3 (3.0-3.8)	130	3.3 (2.9-3.7)	0.786
Aspartate aminotransferase (U/l)	160	29	28.0 (21.0-37.5)	131	25.0 (19.0-43.0)	0.569
Alanine aminotransferase (U/l)	161	29	21.0 (12.0-39.0)	132	19.5 (13.0-35.0)	0.862

There were no significant differences of drug resistances prior to treatment (2/38, 5.3% VS 21/191, 11.0%, $p=0.384$), at 2 months (0/38, 0 VS 5/190, 2.6%, $p=0.593$) and 5 months (1/37, 2.7% VS 2/184, 1.1%, $p=0.424$) after treatment (Table 2). Primary and acquired MDR TB was found in 2 patients in SAT group.

3.3. Treatment and Outcome

Treatment and outcome were similar in both groups. Majority of patients in family based DOT and SAT groups were treated with the standard regimens according to WHO treatment of TB guideline 2010 in both intensive phase (37/39, 94.9% VS 189/194, 97.4%, $p=0.332$) and continuation phase (39/39, 100.0% VS 192/194, 99.0%, $p=1.000$) with the similar median duration (IQR) of intensive [65.0 days (55.0-9.0) VS 62.5 (55.0-72.2), $p=0.773$] and continuation phase [118.0 days (101.0-144.0)

VS 120 days (112.0-145.0), $p=0.523$]. Irregular adherence was not significantly different between family based DOT and SAT group, however it was observed more during continuation phase (16/39, 41.0% VS 68/190, 35.8%, $p=0.663$) than intensive phase (7/39, 17.9% VS 17/194, 13.9%, $p=0.688$). Cure rate was not significantly higher in family based DOT group compared to SAT group (28/39, 71.8% VS 121/181, 66.9%, $p=0.682$) (Table 3). Extrapulmonary TB was found in 1 patient from SAT group at 1 year after treatment.

Overall AEs were similar in both groups. During intensive phase, AEs were found equally in family based DOT and SAT groups (30/35, 85.7% VS 143/168, 85.1%, $p=1.000$) and the incidence was lower in continuation

phase (9/13, 69.2% VS 54/70, 77.1%, $p=0.503$) (Table 3). Arthralgia and skin reactions were the most common AEs during intensive [50.0% (18/36) VS 52.1% (87/167), $p=0.965$ and 30.6% (11/36) VS 47.9% (80/167), $p=0.087$] and continuation phase [20.0% (3/15) VS 39.7% (27/68), $p=0.254$ and 33.3% (5/15) VS 26.5% (18/68), $p=0.751$] similarly in both groups. However, proportion of patients with visual alteration and hepatitis were significantly higher in family based DOT group [12% (20/167) VS 30.6% (11/36), $p=0.011$ and 5.6% (2/36) VS 0, $p=0.031$]. On the other hand, numbness was not significantly higher in SAT groups [31.1% (52/167) VS 13.9% (5/36), $p=0.060$].

Table 2. Sputum examinations and drug resistances among patients in DOT and self administer groups

Sputum examinations	n	DOT		Self administer		P value
		n	no (%)	n	no (%)	
Smear negative						
At 2 months	231	39	34 (87.2)	192	162 (84.4)	0.841
At 5 months	222	37	36 (97.3)	185	177 (95.7)	1.000
Culture negative						
At 2 months	229	38	29 (76.3)	191	166 (86.9)	0.153
At 5 months	222	37	35(94.6)	185	181 (97.8)	0.262
Drug resistance						
Prior to treatment	229	38	2 (5.3)	191	21 (11.0)	0.384
At 2 months	228	38	0	190	5 (2.6)	0.593
At 5 months	221	37	1(2.7)	184	2 (1.1)	0.424

Table 3. Anti-tuberculous treatment and outcome among patients in DOT and self administer groups

Characteristics	n	DOT		Self administer		P value
		n	no(%) /Median (IQR)	n	no(%) /Median (IQR)	
Standard regimens	233					
Intensive phase		39	37 (94.9)	194	189 (97.4)	0.332
Continuous phase		39	39 (100.0)	194	192(99.0)	1.000
Duration of follow up	179	33	289.0 (262.0-342.5)	146	287.0 (267.0-336.0)	0.773
Duration of treatment						
Intensive phase	233	39	65.0 (55.0-90.0)	194	62.5 (55.0-72.2)	0.288
Continuous phase	232	39	118.0 (101.0-144.0)	193	120.0 (112.0-145.0)	0.523
Irregular adherence						
Intensive phase	233	39	7 (17.9)	194	27(13.9)	0.688
Continuous phase	229	39	16 (41.0)	190	68 (35.8)	0.663
Missing days						
Overall	85	17	3.0 (1.5-10.0)	68	5.0 (2.0-21.8)	0.326
Intensive phase	31	6	5.5 (1.8-15.0)	25	5.0 (2.0-19.0)	0.841
Continuous phase	66	13	3.0 (1.0-8.0)	53	4.0 (2.0-9.5)	0.553
Adverse events						
Intensive phase	203	35	30 (85.7)	168	143 (85.1)	1.000
Continuous phase	83	13	9 (69.2)	70	54 (77.1)	0.503
Outcome ^a						
Cure	233	39	28 (71.8)	181	121 (66.9)	0.682
Default	233	39	2 (5.1)	181	10 (5.5)	1.000
Success	233	39	37 (94.9)	181	164 (90.6)	0.538

^a World Health Organization, Global tuberculosis report 2012.

4. Discussion

Factors influencing treatment adherence is multi-factorial. Among TB patients, treatment adherence were affected by several factors e.g. socio-economic status, social support, accessible and patient friendly health systems, treatment duration, clinical improvement, adverse drug reactions, co-morbidities and the most

importance, disease knowledge and its treatment [3, 9]. As comparing to other study in Bangkok, Thailand, most patients in family based DOT and SAT groups were illiterate (72.2% and 50.3% VS 67.7% and 57.0%), unemployed or laborer (46.2% and 54.6% VS 53.0% and 54.7%) and low income earning (65.8% and 77.8% VS 81.3% and 87.8%) [4]. Cavity on chest radiography was not significantly different between family based DOT and SAT groups (34.4% VS 32.0%) compared to study from northern Thailand (27.1% VS 22.2%) [10].

Although WHO recommends DOT for TB control; many studies showed no benefit of DOT over treatment outcomes [1,4,11-13]. This study supported those previous findings since culture conversion rates at 2 and 5 months after treatment between family based DOT and SAT groups were not significantly different. At the end of intensive phase, 87.2% and 84.4% of patients in family based DOT and SAT groups were sputum smear negative compared to 62% and 30% of the previous study [13]. The lower proportions from this previous study were due to missing data of sputum smear found in 15% and 46% of patients in family based DOT and SAT groups at the end of intensive phase [13]. Smear conversion rates at 2 and 5 months after treatment were slightly higher in family based DOT group than SAT group while culture conversion rates were slightly higher in SAT group. These could be explained by false positive sputum AFB smear after treatment caused by nonviable bacilli and probably misled to the effectiveness of DOT. However, culture conversion rates at 2 and 5 months after treatment in SAT group and family based DOT group were similar. Education was the most likely influencing factor since significantly higher education was observed in SAT group while the rest of factors were similar between both groups. It could be as effective as DOT toward treatment outcome. Therefore, knowledge of TB and its treatment should be intensively educated especially in patients with illiteracy or low educated as well as their family member. Then continuing education is strongly recommended.

Success rate in DOT group were not significant different to SAT group similarly to other findings [1,4,10]. Interestingly, cure rate in DOT group was 71.8% compared to 81-96% from previous study providing incentive [12]. Since most TB patients had low socio-economic status, incentive such as transportation payment could be one of the strategies to achieve successful outcome. On the other hand, other previous study including relapse and failure cases showed the significantly different of treatment outcome among patients provided DOT and SAT with lower success rate compared to this study in both family based DOT (74.1% VS 94.9%) and SAT groups (77.4% VS 90.6%) [10]. Similarly, low cure rate by 34-76% and 41-67% among patients with family based DOT and SAT groups were reported from studies included retreatment cases as well as cases treated with non standard treatment regimens [1]. In addition, similar success rate was found in new pulmonary TB patients with DOT delivered by either health care workers or family members and SAT [13] indicating that DOT has no benefit for new TB cases [3]. However, the success rate obtained from this study was higher compared to latest national success rate of 85% reported in 2010 [8]. This might be due to two important strategies using in this study. First, patients who could not attain clinic visit due to their work, prescription filled were provided after office hour and next appointment was arranged as soon as possible regarding patient convenience. Second, patients who missed doctors' appointments, they were immediately called and discussed for problems and their solutions.

Irregular adherence and default from treatment are the major causes of drug resistance and DOT has been proposed as the effective strategy by WHO and International Union Against Tuberculosis and Lung

Diseases [2,3]. However, similar treatment adherence, missing day and defaulted rate observed between both groups indicated that duration of DOT delivery modified from entire short course TB treatment as recommended by the stop TB strategies to at least in intensive phase as recommended by Thai guideline for diagnosis and treatment of TB may not be appropriate and might decrease effect of DOT over treatment outcome. Moreover, treatment adherence can be interfered by many factors as described previously [3,9]. Major cause of irregular adherence in both groups was alcoholic consumption similar to previous finding [3] while difficulty in asking sick leave and prioritized work over clinic visit were the major causes of missed appointment similar to previous studies [14]. Furthermore, significantly higher proportions of patients with AEs in DOT group could affect treatment adherence as reported previously [15]. Therefore, regular adherence assessment is necessary.

This study has some limitations. Recall bias is unavoidable for data obtaining by interview. Specimens after treatment were poor in quality because patients felt better and productive cough consequently subsided. This could influence isolation of *M. tuberculosis*, however it happens in the routine practice.

5. Conclusion

This study demonstrated that family based DOT had no effect on sputum culture conversion rate at 2 and 5 months after treatment as well as success rate. Since DOT delivery to all TB patients was unlikely in low income high burden TB countries like Thailand. Therefore, DOT should be focused on retreated or relapse cases while good quality TB service should be provided. Continuing patient education and counseling are fundamental necessity leading to understanding and co-operating in treatment. Emphasis on TB transmission among their families can increase their awareness and desire to cure of TB. Furthermore, TB affects predominately male in working active aged group and most of them were family leaders. Regular follow up should be feasible and accessible regarding patients working hours and cost for traveling. Fast tract services including direct clinic access and separated pharmacy service as well as patient friendly service should be established. In addition, treating TB needs the combination of several drugs with long duration so close monitoring for AEs should be performed. All these can enhance patient adherence and further achieve success in TB treatment and control.

Acknowledgements

We would like to thank our study participants for their co-operations. We also thank Dr. Pongsak Chunpongthong, Dr. Chureeratana Bowonwatanuwong, Dr. Ongard Kosintarajit, Dr. Apichart Chinnawan, Dr. Arun Lerdworawiwat, Dr. Poonlarb Panjaluk, Dr. Natcha Laopichainpong, nurses and staffs of TB clinic at Savang Vadhana Memorial Hospital and Chonburi Regional Hospital, Chonburi province, Thailand for participants enrollment; all staffs of Microbiology Unit at Savang Vadhana Memorial Hospital and Chonburi

Regional Hospital, Chonburi province, Thailand for specimen handling and Mr. Somsak Rienthong, National TB Reference Laboratory, Bureau of Tuberculosis, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand for Mycobacterium culture and sensitivity testing. Special thanks are extended to Assoc. Prof. Pratap Singhasivanon, Dean of the Faculty of Tropical Medicine and Dr. Arthit Ourairat President of Rangsit University for their support on this manuscript.

This study was supported by Faculty of Graduate Studies and Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Conflict of Interests

The authors have no competing interests.

List of Abbreviations

AEs:	Adverse events
AFB:	acid fast bacilli
CI:	confidence interval
DOT:	directly observed therapy
DOTS:	directly observed therapy, short course
DST:	drug susceptibility test
IQR:	inter-quartile range
SAT:	self administration

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