

2017

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### Recommended Citation

Nguyen, Larry; Vazquez-Deida, Axel A.; and Chak, Veasna M. (2017) "Adherence to Drug Therapies in TB/HIV Patients: A Systematic Review of Fixed Dosed Combination Drug Therapy vs. Directly Observed Therapy," *Advances in Pharmacy: Journal of Student Solutions to Pharmacy Challenges*: Vol. 1 : Iss. 1 , Article 2.

Available at: <http://pubs.lib.umn.edu/advances/vol1/iss1/2>



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*Advances in Pharmacy: Journal of Student Solutions to Pharmacy Challenges* is published by the University of Minnesota Libraries Publishing.

# Adherence to Drug Therapies in TB/HIV Patients: A Systematic Review of Fixed Dosed Combination Drug Therapy vs. Directly Observed Therapy

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June 2017

## Abstract

The objective of this paper was to discern if there was a difference in adherence between fixed dose combination drug therapy (FDCT) and directly observed therapy (DOT) when treating patients with both tuberculosis (TB) and human immunodeficiency virus (HIV). Various search terms were used resulting in 1,646 related articles. 1,637 articles were eliminated using further screening and elimination criteria. A total of 8 peer-reviewed publications and reports classified either as primary or secondary were used for data extraction. These articles studied HIV/TB patients receiving either FDCT or DOT and included extractable data on the number of non-adherent patients versus total number of patients for their respective therapy. Information obtained during data extraction included: article definition of adherence, reasons for non-adherence, number of patients in the trial, and number of patients adherent to therapy. The results showed 70.2% of patients were adherent to directly observed therapy, and 92.5% of patients were adherent to fixed dosed combination drug therapy. This paper concluded that patients are more adherent to FDCT than DOT.

## 1 Introduction

According to the World Health Organization (WHO), it is estimated that people living with HIV have between 26 and 31 times greater risk of developing TB than those without HIV (1). In addition, the risk of progression to the active disease is much higher in HIV patients compared to those with healthy immune systems. While antiretroviral therapy can reduce the risk of TB by 70% to 90%, the incidence of TB among people that are HIV-positive is still two to four-fold higher. In 2015, TB was responsible for about 35% of deaths among HIV-positive people (2). Due to the infectious and potentially fatal nature of TB, adherence to therapy is important from a public health and patient safety standpoint.

Premature discontinuation and non-compliance to anti-TB therapy can also lead to the emergence of multidrug and extensively drug resistant strains, which in turn has an impact in health care costs (3). In the United States, there were 364 cases of multidrug resistant TB and 9 cases of extensively drug resistant TB during 2005-2007. These cases resulted in direct costs of approximately \$53 million to the health care system with an additional direct-plus-productivity loss cost of approximately \$100 million (4).

Two types of therapeutic regimens for TB/HIV are available: fixed dose combination therapy (FDCT), which is typically self-administered, and directly observed therapy (DOT), where administration of therapy is observed by a trained health care worker. There is limited research comparing adherence rates between the two treatment options, especially for TB/HIV patients, and the literature is conflicting regarding which therapeutic option is best. This article explored the differences in adherence between the two treatment options. Results from this study may help providers select a drug therapy regimen for patients with TB/HIV, lower the rate of non-adherence to therapy, and achieve lower rates of reactivation, spread, and mortality.

## 2 Methods

The literature search was focused on identifying articles related to adherence to FDCT and DOT for TB infections in HIV co-infected patients. The search was performed using Google Scholar, PubMed and OVID Medline. For PubMed and Google Scholar, the following search terms were used: HIV AND Tuberculosis AND pill burden, Adherence AND Latent tuberculosis, Adherence AND Latent tuberculosis HIV co-infection, Directly observed therapy AND Tuberculosis OR HIV, Fixed-dose combination therapy AND Tuberculosis OR HIV. For OVID Medline, a combination of keyword search and MeSH terms was used. The MeSH term latent tuberculosis, not focused, was combined with the terms medication adherence/sn, patient compliance/sn, fixed-dose combination keyword, and directly observed therapy/sn. These terms were auto exploded and assessed for which search strategy provides the least number of irrelevant articles. A not focused search combining HIV or HIV-Tuberculosis keyword, medication burden keyword, and pill burden keyword were performed and combined with previous tuberculosis-related search. Non-English, non-human, and non-adult studies were excluded from review. When searching for articles relating to pill burden, articles that did not reported adherence rates for DOT or FDCT were also excluded from review. Only peer-reviewed publications and reports classified either as primary or secondary literature were considered. Since the first FDA approved HIV antiretroviral drug was approved in 1987, articles from 1987 onward were included in our selection criteria.

The authors reviewed each article and looked for data that specified whether a patient was adherent or non-adherent to FDCT or DOT therapy for either TB or HIV. The total number of patients and number of non-adherent patients for each trial were recorded in a table based on the type of therapy used. For each article, a second author verified that the data extracted was consistent with the first authors findings.

For each regimen, the number of adherent patients across all the trials was totaled and divided by the total number of patients from all the trials. The percentage of patients adherent to FDCT was compared to the percentage of patients adherent to DOT.

## 3 Results

### 3.1 Study Selection

A total of 1,646 initial hits were obtained from three databases (Figure 1). The three investigators were randomly assigned a set of articles to screen for fulfillment of the eligibility criteria. A different author then re-screened a set of articles that was not initially reviewed by them to confirm accurate revision and eligibility. Upon completion of this process, a total of 8 articles were selected for data extraction.

### 3.2 Description of included studies

Of the eight studies included for data extraction, three only assessed DOT, four assessed only FDCT and one had a direct comparison between DOT and FDCT. Regarding adherence to the therapeutic regimen, six studies assessed TB therapies and one study assessed both TB and HIV regimens. Most of the studies included isoniazid among their treatment regimens, either alone or in combination with other drugs.

### 3.3 Data extraction

From the four articles that studied DOT, there were a total of 369 HIV patients who received DOT therapy and 259 who were adherent to therapy. For FDCT, 1614 of the 1744 HIV patients were adherent to FDCT therapy. Approximately 70.2% of patients were adherent to their TB/HIV therapy through DOT, while 92.5% of patients fulfilled adherence to FDCT as defined by the study they belonged to (Tables 1 and 2). Further insight regarding factors impacting adherence was obtained through individualized evaluation of each articles results. Despite the studies measuring adherence in different ways, there were common denominators in contributing factors for non-adherence regardless of the disease being treated. In the articles that assessed DOT, factors that led to failure of accomplishing adherence included: side effects,

adverse reactions, withdrawal from DOT programs, illicit intravenous drugs utilization, and immigration status. Difficulty obtaining medications and forgetting to take them were common reasons for non-adherence in the articles that studied FDCT.

The articles directly comparing adherence to TB and HIV therapies revealed that six-month optimal adherence was higher for antiretroviral (ART) than TB medications (88.2% vs 67.7%;  $p < 0.001$ ). Factors that affected adherence included low educational attainment, male gender, and year of enrollment (5). These were independently associated with dual suboptimal adherence. Other reasons for non-adherence included: running out of pills (22%), being away from home (19%) or forgetting to take the medication (17%) (6). Also, there was no statistically significant difference in adherence between HIV infected patients on antiretrovirals (ART) versus those not on ART. Other studies also concluded ART usage, socioeconomic status, sex, occupation and duration of HIV all have no effect on adherence (7).

## 4 Discussion

When combining the results from the various studies for each therapy, it appears that better adherence rates would be achieved in FDCT compared to DOT in TB/HIV patients. When comparing the adherence rates in each study for a particular therapy, however, one would see that they vary greatly from one another. This is especially true in the DOT studies, where the adherence rate ranged from 25% to 92% (8, 11). For FDCT, the difference between the highest and lowest adherence rates were less drastic and ranged from 61% to 98% (7, 8). Complexity and length of therapy may have also played a role in the different adherence rates. Narita et al. saw a 92% adherence rate for TB/HIV patients undergoing twice-weekly rifamycin and pyrazinamide DOT for two months (8). Meanwhile, in the DOT study that produced the lowest adherence rate of 25%, patients underwent a three-phase therapeutic regimen that lasted about 11 months (11). The method of DOT delivery may also change adherence rates. In the Oll-Goig study, DOT was delivered in home (11). In the Narita study, DOT was delivered in clinic (8). It is expected that more people would fail to adhere to therapy or drop out the longer the study is. Another reason for the discrepancy in adherence rates may be due to the various ways that DOT can be carried out. While all of the therapies are similar in that they require an individual to provide the medication and watch the patient swallow every dose, the DOTs can differ on where this meeting takes place and the individual designated to carry out these tasks. Having to travel to a pharmacy or medical office to receive treatment may be more difficult to accomplish than having someone come to the patients place of residence and administer the medications, especially considering that a portion of HIV/TB patients from the studies have unstable housing situations.

There were some similarities and differences between DOT and FDCT in terms of reasons for non-adherence. For DOT regimens, common reasons for non-adherence included: the requirement of office visit, inability to travel to the clinic, poor access to health care and adverse drug events. For FDCT, a common reason for non-adherence was an inability to collect the medications due to cost, work, family, and/or travel. Other reasons for non-adherence to FDCT were poor education about the disease or therapy, poor social and professional support, and forgetting to take the pill due to pill burden.

A possible solution that may address some of these problems is using mail-order pharmacy in combination with televideo meetings. This could address the issue of travel for both DOT and FDCT and may increase access to health care. For either therapies, education about the disease and their therapy is very important as well. Due to the chronic nature of both HIV and TB, pharmacists have an important role in promoting compliance to the therapy by providing education about lifestyle choices, medication side effects, optimization of therapies, and disease management. Reminding the patient of the consequences of poor compliance, such as reactivation or worsening of TB, development of drug resistance, and potentially death, may also improve adherence.

Limitations to our study include the various definitions of adherence used by each study, the various methods used to measure or quantify adherence, self-reporting of adherence, varying populations in each study, and the disproportionate number of patients in the FDCT arm versus the DOT arm. Another limitation is that different drug therapies were utilized in the studies analyzed, which can impact adherence outcomes from one study to another due to differing adverse events, therapy duration, access, effectiveness,

and cost.

This paper does not address the rates of adherence within specific populations. This paper included research from various countries such as the U.S., Spain, Haiti, South Africa, Kenya, Uganda, and Tanzania. Future research could look into how adherence differs with economic status, education, access to health care, social drug use, or age. This study also elucidates that more research directly evaluating DOT and FDCT is needed due to limited literature. In addition, the papers results follow the WHO recommendations of developing more tuberculosis FDCT to decrease the burden on healthcare systems and increase patient compliance just like current ARTs FDCT regimens for patients with HIV.

With the results of this research, other professionals will be able to have more confidence in following an FDCT regimen instead of a DOT regimen if general adherence is an issue. Professionals will see that both FDCT and DOT have their own flaws regarding adherence and hopefully will individualize care for their patients and take steps to help reduce rates of non-adherence based on this studys findings. The study also opens the opportunity for potential future research analyzing the use of short-term DOT followed by FDCT, especially in HIV-TB patients since they should receive a 9-month isoniazid treatment course (13). Short-term DOT would promote more frequent interactions between provider and patient, allowing for opportunities to monitor safety and effectiveness of treatment, to educate the patient about the disease and reinforce the importance of being adherent and compliant to treatment, and to improve the provider-patient relationship overall. Once it has been determined by the provider that the patient is willing and capable of being adherent to the therapy, switching to FDCT can increase convenience for the patient.

## 5 Conclusion

Our study found that patients with HIV and tuberculosis are more adherent to fixed dose combination therapy (FDCT) than directly observed therapy (DOT) for treating tuberculosis. While our results favor FDCT, it is difficult to make a strong recommendation as to which therapy should be used for this population group due to the variability in each studys patient population, study setting, therapy regimen and duration, and many other factors that contribute to the different adherence rates across the different studies. Future studies can be focused on comparing the adherence rates between two therapies in TB/HIV patients with certain characteristics, such as accessibility to care, age, or socioeconomic status, to better choose appropriate therapies for these individuals.

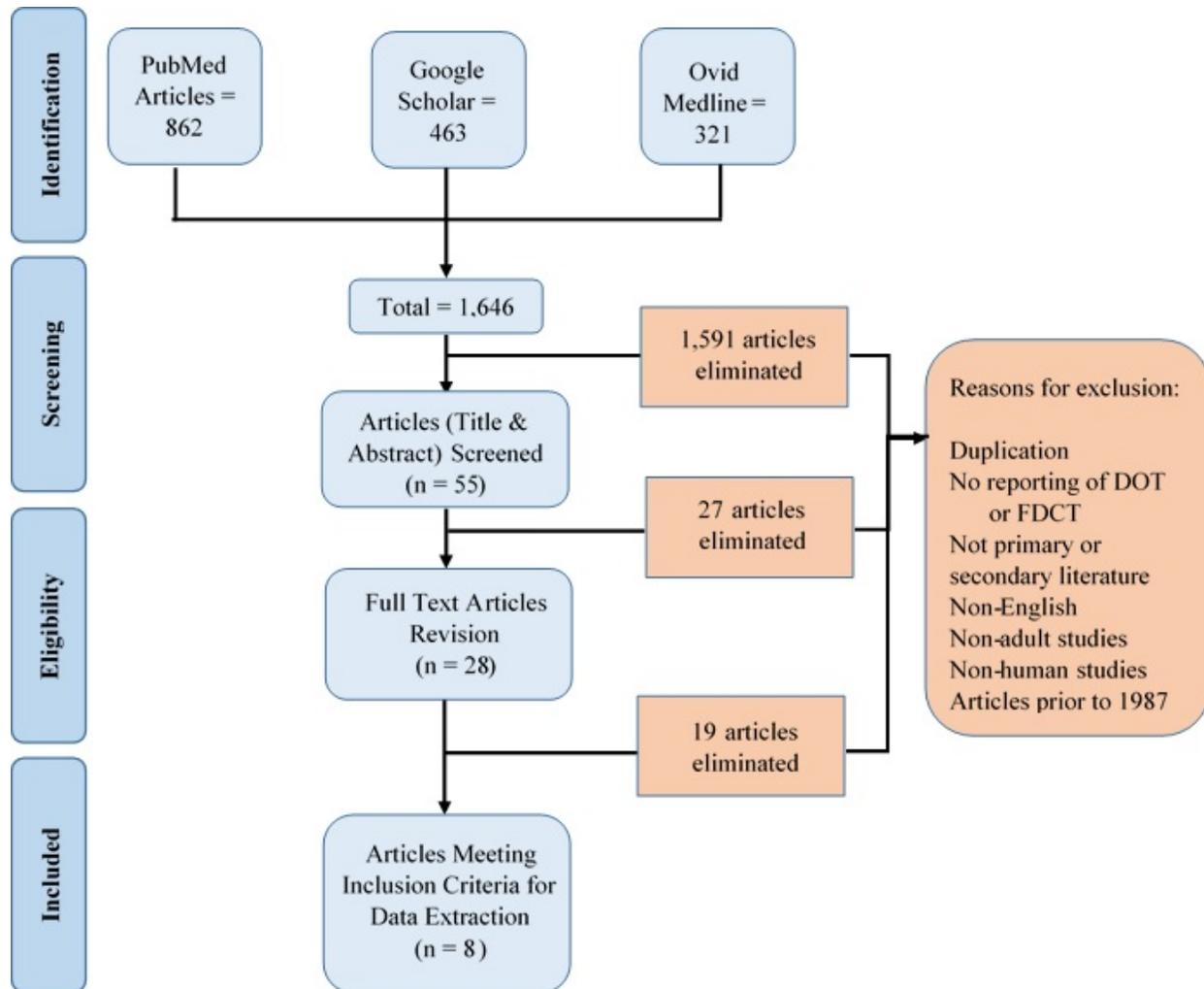
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Figures/Tables:

Figure 1: Study Selection Flow Diagram



**Table 1: Directly Observed Therapy Adherence Outcomes in Patients with TB/HIV**

Directly observed therapy (DOT)				
Study	Study's definition of adherence	Reasons for non-adherence (Percent of non-adherent patients if provided)	Total number of HIV patients	Number of HIV patients adherent to therapy
Narita, M. et al. (2002) <sup>(8)</sup>	Completion of 2 month course of rifamycin and pyranzinamide by DOT for LTBI in HIV patients	Allergic skin reaction (36%), hepatitis (9%)	135	124
Lopez, G. et al (2011) <sup>(9)</sup>	Completion of various LTBI therapies under DOT conditions  Therapy I (9H): isoniazid (H) for 9 months Therapy II (2R2Z2): rifampicin for 2 months Therapy III (3RH): rifampicin and isoniazid for 3 months Therapy IV (4R): rifampicin for four months	*Across all (both HIV+ and HIV-) patients  9H: Voluntary withdrawal (49%), adverse events (27%), release or transfer, (20%), unknown (1%), TB development (< 1%), suicide (< 1%)  Therapies II-IV: Adverse events (56%), voluntary withdrawal (38%), unknown (3%), release or transfer (1%), psychotic break (1%), idiopathic acute hepatitis (1%)	9H: 114 2R2Z2: 7 3RH: 2 4R: 0 Total: 123	9H: 64 2R2Z2: 4 3RH: 2 4R: 0 Total: 70
Juan, G. et al (2006) <sup>(10)</sup>	Completion of DOT program (isoniazid and rifampicin for 9 months, with pyrazinamide and ethambutol for first 6 weeks) through pharmacy offices	*Across all (both HIV+ and HIV-) patients  Loss to follow-up (half were unstably housed), transferred to different center or incarcerated, death due to HIV-related disease	67	54
Olle-Goig, JE (2001) <sup>(11)</sup>	Completion of DOT program (11 month, triphasic therapeutic regimen) under direct supervision of a trained TB supervisor	Not provided	44	11
Total:			369	259
Percent of patients adherent to DOT therapy:			70.2%	

Directly observed therapy (DOT); tuberculosis (TB); latent tuberculosis infection (LTB)

**Table 2: Fixed Dose Combination Therapy Adherence Outcomes in Patients with TB/HIV**

Fixed dose combination therapy (FDCT)				
Study	Study's definition of adherence	Reasons for non-adherence (Percent of non-adherent patients if provided)	Total number of patients	Number of patients adherent to therapy
Narita, M. et. al. (2002) <sup>(8)</sup>	Monthly isoniazid prescription picked up for 12 months (for self-administered therapy)	Not provided  None discontinued treatment due to adverse reactions	93	57
O'Donnell, MR. et al. (2014) <sup>(5)</sup>	Patient stated not having missed a dose of antiretroviral or TB medications according to a 7-day recall questionnaire given monthly by staff over 6 months	Not provided  Risk factors: male gender and low educational level	68	45
Nackers, F. et al. (2012) <sup>(6)</sup>	Adherence to self-administered FDC therapy for TB treatment based on various assessment tools (questionnaire, VAS, isoniazid urine test, pill count)	Running out of medications, being away from home, forgetting to take medication	212 **	195 **
Amuha, MG et. al. (2009) <sup>(12)</sup>	>89% of anti-TB medications taken over the past 5 days based on interviewer administered questionnaire	Unable to collect medications due to: lack of transport money (49%), busy at work (9%), family emergency (3%), sickness (3%), forgetting appointment date (3%)  Forgetting to take medications (17%)  Factors associated with non-adherence: knowledge about TB, alcohol, facility distance, smoking, being on ART, phase of TB regimen	140	105

Shayo, GA. et. al. (2015) <sup>(7)</sup>	>89% of monthly isoniazid prescription consumed over 6 months as determined by pill counts	Lost to follow up, withdrawal of consent, side effects, transferred out, pregnancy, active TB, death	1231	1212
Total:			1744	1614
Percent of patients adherent to FDCT therapy:			92.5%	

Fixed dose combination (FDC), visual analogue scales (VAS)

\*\* Total number of patients and number of adherent patients each averaged among 4 categories