

**DETERMINANTS OF NON-COMPLIANCE TO ANTI-TUBERCULOSIS  
DRUGS AMONG PATIENTS IN IBADAN SOUTH EAST LOCAL  
GOVERNMENT AREA OF OYO STATE**

**Onawola, Motunrayo Risikat**  
*Primary Health Care Tutors' Course*  
*University College Hospital. Ibadan*  
*E-mail: onawolamotunrayo@gmail.com*

**Abstract**

This study assessed the level of knowledge on anti-tuberculosis drugs regimen and determinants of non-compliance to anti-tuberculosis drugs among patients in selected Directly Observed Treatment Short-course (DOTS) Centres of Ibadan South East Local Government Area, Oyo State. A cross sectional descriptive design was adopted, simple random sampling technique was used to select five DOTS while a convenience sampling technique was used to select one hundred (100) respondents. Self-structured questionnaire titled "Determinants of Non-Compliance to Anti-Tuberculosis Drugs Among Patients" In Ibadan South East Local Government Area of Oyo State was used for data collection. Data collected were analysed using Chi-square to test the hypotheses at 0.05 alpha level. The results from the findings revealed significant association between knowledge and non-compliance to anti-tuberculosis drugs ( $\chi^2=18.478$ , p-value <0.05). Finding also showed that there was significant association between age and non-compliance to anti-tuberculosis drugs ( $\chi^2=7.939$ , p-value <0.05). There was significant association between educational background and non-compliance to anti-tuberculosis drugs ( $\chi^2=6.108$ , p-value <0.05). In addition, it was revealed that there was no significant association between sex and non-compliance to anti-tuberculosis drugs ( $\chi^2=0.041$ , p-value >0.05). It was concluded that knowledge, age and educational background of the tuberculosis patients were determinants of non-compliance, while sex of patients was not a determinant factor of non-compliance to anti-tuberculosis drugs. Based on the conclusion, it was recommended that regular sensitization visits should be made by caregivers to places like market, motor parks and artisans on consequence of non-compliance to anti-tuberculosis drugs regimen.

**Keywords:** Anti-tuberculosis drugs, patients, Ibadan South East Local Government Area, Oyo State.

### **Introduction**

Non-compliance to anti tuberculosis treatment is one of the crucial problems in improving tuberculosis cure-rates and reducing extra healthcare costs. The poor compliance to anti-tuberculosis management among patients with tuberculosis is a major dilemma in Nigeria. According to World Health Organization (2017), Tuberculosis (TB) is airborne infectious disease caused by *Mycobacterium tuberculosis*. Multi drug resistant tuberculosis (2017) submitted that tuberculosis is one of the ten top causes of death worldwide from curable infectious diseases. World Health Organization Global strategy and targets for tuberculosis prevention, care and control (2015) and Floyd, Glaziou, Zumla and Raviglione (2018) reported that globally, there were estimated 10.4 million new TB cases and 600,000 new cases with resistance to Rifampicin. 490,000 had multidrug-resistant tuberculosis (MDR-TB) cases and 1.7 million people died from TB annually. Zegeye, Getnet, Fasil, Alemu, Sheikh, Islamid, Bekele and Dessalegn (2019) opined that globally, about one third of the world population is infected with Tubercle bacilli, which are at risk of developing active TB. Prevalence of TB cases in Africa accounted for (26%) and 75% of worldwide TB mortalities (World Health Organization, 2013). Consequently, there is need for adequate intervention through earlier diagnosis and prompt treatment of an infected person with anti Tuberculosis drugs.

Tuberculosis symptoms include: feelings of sickness or weakness, fever, night sweat and weight loss. The symptoms of pulmonary TB (Tuberculosis of the lungs) also include coughing, chest pain, and the coughing up of blood. Extra pulmonary TB Symptoms (Tuberculosis of the other parts of the body) depend on the area affected. *Mycobacterium tuberculosis* infects one-third of the world's population and is the most common single death causing agent in young adults (WHO, 2010). Globally, however, the consequences of tuberculosis (TB) on society are enormous. Worldwide, one person out of three is infected with *Mycobacterium tuberculosis*, i.e. two billion people in total. Currently, it holds the seventh place in the global ranking of the causes of death. (Dye, 1999; Smith, 2004 as cited by UK

Essay 2018). Tuberculosis disease itself induces many consequences and makes the poor poorer. As a result of poverty-related physical illness, extensive malnutrition and subsequent decreased host resistance, the poor are likely to have more extensive and severe forms of TB disease and run higher risks of poor treatment outcomes (Dewan, Arguin, Kiryanova, Kondroshova and Khorosheva, 2004). The long course of the disease and treatment make the poor socially vulnerable and deprived and locks them in the poverty stricken condition, the poor suffers more from TB, and TB puts the poor in more vulnerable state (Hanson, 2002). UK Essay (2018) reported that Tuberculosis hinders socioeconomic development for the high percentage of the disease, and 75%, afflict the productive age group that ranges between 15-54 years. Furthermore, 95% of all cases and 99% of deaths occurred in developing countries, with the greatest burden in Sub-Saharan Africa and South East Asia.

Currently, anti-tuberculosis therapy consists of a mixture of drugs taken over a period of at least 6 months for new patients and 8 months for retreatment patients. Since the duration of the therapy is long, there is a menace of treatment interruption or default by the patients and this contributed to prolonged infectiousness, drug resistance, relapse and death (Sagbakken, Frich and Bjune, 2008; Jakubowiak, Bogorodskaya, Borisov, Danilova and Kourbatova, 2016) as a result of the long duration of the therapy, while Tuberculosis (TB) patients have difficulty following a long-term treatment regimen. Efforts to improve treatment outcomes require better understanding of compliance as a complex behavioural issue and of the particular barriers to and facilitators of patient compliance (WHO, 2009). In order to improve patients' compliance with anti Tuberculosis drug regimen, Directly Observed Treatment (DOT) was established and adopted in all TB clinics of Nigeria to monitor patient while swallowing his/her drugs and reduce the rate of non-compliance though, globally, the adoption of Directly Observed Treatment (DOT) has been associated with reduced rate of treatment failure, relapse and drug resistance. However, its impact on reducing TB incidence has been limited by non-compliance to DOT, which occurs when patients do not turn up for treatment at the health facility or community DOT point (Kudakwashe, 2010).

World Health Organisation (2016) reported that Nigeria is one of the nations included among 30 high burden nations for tuberculosis disease. World Health Organisation also estimated that TB cases in Nigeria to be 322 per 100, 000 population with only 15% of the total burden of the disease in the nation being notified in 2015. However, compliance to treatment for tuberculosis (TB) is observed as a major principle of the elimination framework of TB within low-incidence countries globally (World Health Organization, 2014). Wurie, Cooper, Horne and Hayward (2018) documented that in spite of elimination framework of TB, little is known of the individual's characteristics that mostly include social and cultural factors that drive non-compliance across different groups in these settings. Poor compliance was identified as the primary cause for suboptimal clinical benefit, which results into poorer clinical consequences, then increasing development of drug resistance, increased duration of infectivity and following onward transmission of infection (Wurie et al., 2018). Rehman, Raoof, Srinivasa, Hassan and Qurram (2017) submitted that most of the TB programmes were not successful because of the multidrug resistance due to non-compliance with drug regimen.

Empirical studies have reported some of the determinants of non-compliance to anti-tuberculosis drugs; Krasniqi, Jakupi Daci, Tigani, Jupolli-krasniqi, Pira, and Neziri (2017) opined that knowledge about the daily dosage of TB drug and knowledge on TB disease was the major determinants that showed the difference between compliance and non-compliance. Krasniqi, *et al.* (2017) in their study, agreed that the impact of knowledge on the question regarding the TB treatment had a significant impact on TB treatment compliance. The other factors include age group, which showed a significant difference in TB treatment compliance while marital status had no impact. Adane, Alene, Koye and Zeleke (2013) stated that the reasons why participants did not comply with their treatment regimen were due to forgetfulness (34.0%), vomiting (24.0%) and travelling to other places (17.0%). The other significantly associated factors for non-compliance to anti-tuberculosis were phases of chemotherapy, symptoms of TB, HIV co-infection experience of drug side effects, visiting quacks and taking additional drugs other than anti-TB. Akilew, Kefyalew, Digsu and Berihun (2013) reported that patients who were forgetful were seven times more likely to be non-compliance than their counterparts. Those

who were in the continuation stages of chemotherapy were seven times more likely to be non-compliance to anti-TB regimen. More so, those who had symptoms of TB during the interview and had co-infection with HIV were at higher risk of non-compliance than those who were non-symptomatic during the interview and HIV zero-negatives respectively. It was observed that fear of the adverse effect of the drugs also contributed to non-compliance by some of the patients. The researcher therefore assessed determinants of non-compliance to anti-tuberculosis drugs among patients in Ibadan South East Local Government Area of Oyo State

**The following hypotheses were formulated and tested:**

**H0<sub>1</sub>:** There will be no significant association between knowledge of anti-tuberculosis drugs and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State.

**H0<sub>2</sub>:** There will be no significant association between age and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State..

**H0<sub>3</sub>:** There will be no significant association between sex and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State..

**H0<sub>4</sub>:** There will be no significant association between educational background and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State.

**Methodology**

Cross sectional descriptive design was adopted for this study. A cross-sectional study is one, which has to do with the gathering of data from a relatively large and representative of the population at one occurrence of a particular period. Simple random sampling technique was used to select five (5) out of the existing seven DOTs facilities in Ibadan South East Local Government Area of Oyo State, while Convenience sampling technique was used to select twenty (20)

volunteers (TB patients) at each DOT centres. Thus, making a total of 100 respondents selected for the study.

**Below are the lists of DOTS Centres where Respondents were Selected**

s/n	Name of DOT Centre	Number of respondent selected
1	Agbongbon DOT. Centre	20
2	Boluaji DOT. Centre	20
3	Oranyan DOT. Centre	20
4	Orita Aperin DOT. Centre	20
5	Odinjo DOT. Centre	20

The instrument used for data collection was self-structured questionnaire titled "Determinants of Non-Compliance to Anti-Tuberculosis Drugs among Patients in Ibadan South East Local Government Area of Oyo State". The questionnaire instrument included section "A" on Knowledge of anti-tuberculosis drugs regimen. The knowledge on anti-tuberculosis drugs regimen was determined using a 'knowledge score' method where each item answered correctly=2, and those wrongly answered=0. Minimum score: Zero; Maximum score: 4. Scores: 0 – 2 = poor level of knowledge; 3 – 4 = good level of knowledge. Section "B" was on non-compliance to anti-tuberculosis drugs, while section "C" was on Determinants of non-compliance to anti-tuberculosis drugs. Non-compliance to anti-tuberculosis drugs was adopted from the parameters as developed by Adane, Alene, Koye and Zeleke (2013) who reported that non-compliance was viewed according to the following indicators for days and month respectively. This included the number of drugs consumed by patients against the actual drugs they were supposed to consume. TB medication in the last 4 days was classified as non-compliance (missed at least 1 (25%) of the pills prescribed over 4 days) and completely compliance (no missed pill in the last 4 days before the survey). Likewise, the last one month non-compliance was calculated as total reported missed pills over the total prescribed pills within that month and classified as compliance (no more than 10% of pills missed) and otherwise non-compliance. Also, Woimo, Yimer, Bati and Gesesew (2017) documented that anti-TB treatment compliance status was the response variable categorized as compliance and non-compliance. A patient belonging to either intensive or continuation phase under new or retreatment regimen

who missed  $\geq 10.0\%$  of the total prescribed dose was considered as non-compliance.

### Findings and Discussion

**H0<sub>1</sub>:** There will be no significant association between knowledge of anti-tuberculosis drugs and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South East Local Government Area, Oyo State.

**Table 1: Cross tabulation of association between knowledge of anti-tuberculosis drugs and non-compliance to anti-tuberculosis drugs**

		Non-compliance		Total	Chi-square	P-value
		Compliance	Non-compliance			
Knowledge	Good	68	24	92	18.478	0.000
	Poor	0	8	8		
	Total	68	32	100		

Data from table 1 showed that there was a significant association ( $\chi^2=18.478$ , p-value  $<0.05$ ) between knowledge of anti-tuberculosis drugs regimen and non-compliance to anti-tuberculosis drugs. Therefore, the hypothesis which stated that there will be no statistically significant association between knowledge of anti-tuberculosis drugs and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State was rejected.

**H0<sub>2</sub>:** There will be no significant association between age and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South East Local Government Area, Oyo State.

**Table 2: Cross tabulation of association between age and non-compliance to anti-tuberculosis drugs**

	Non-compliance		Total	Chi-square	P-value
	Compliance	Non-compliance			
Age 18-23 years	0	2	2	7.939	0.047
29-33 years	3	4	7		
34-38 years	3	0	3		
39 years & above	62	26	88		
Total	68	32	100		

Data from table 2 showed that there was significant association ( $\chi^2=7.939$ , p-value  $<0.05$ ) between age and non-compliance to anti-tuberculosis drugs. Therefore, the hypothesis which stated that there will be no statistically significant association between age and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres of Ibadan South East Local Government Area, Oyo State was rejected.

**H0<sub>3</sub>:** There will be no significant association between sex and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South East Local Government Area, Oyo State.



**Table 3: Cross tabulation of association between sex and non-compliance to anti-tuberculosis drugs**

	Non-compliance		Total	Chi-square	P-value
	Compliance	Non-compliance			
Sex					
Male	63	30	93	0.041	0.84
Female	5	2	7		
Total	68	32	100		

Data from table 3 showed that there was no significant association ( $\chi^2=0.041$ , p-value  $>0.05$ ) between sex and non-compliance to anti-tuberculosis drugs. Therefore, the hypothesis, there will be no statistically significant association between sex and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South East Local Government Area, Oyo State was accepted.

**H0<sub>4</sub>:** There will be no significant association between educational background and non-compliance to anti-tuberculosis drugs among patients in selected DOT centre in Ibadan South East Local Government Area, Oyo State.

**Table 4. Cross tabulation of association between educational background and non-compliance to anti-tuberculosis drugs**

	Non-compliance		Total	Chi-square	P-value
	Compliance	Non-compliance			
Education					
SSCE	3	0	3	6.108	0.047
OND	0	2	2		
HND/BSc	65	26	91		
Total	68	28	96		

Data from table 4 showed that there was significant association ( $\chi^2=6.108$ , p-value  $<0.05$ ) between educational background and non-compliance to anti-tuberculosis drugs. Therefore, the hypothesis which stated that there will be no statistically significant association between educational background and non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South East Local Government Area, Oyo State was rejected.

### **Discussion of Findings**

The finding of the study on knowledge of anti-tuberculosis drugs regimen and non-compliance revealed that there was a significant association between knowledge of anti-tuberculosis drugs regimen and non-compliance to anti-tuberculosis drugs. This implied that TB patient had good level of knowledge on anti-tuberculosis drugs regimen. The outcome of this study was in contrast to the finding of Alotaibi et al. (2019), which established that knowledge gaps were identified in relation to the definition of MDR-/XDRTB and LTBI, length of standard TB treatment for drug-sensitive TB, smear microscopy results, 2<sup>nd</sup> line anti-TB drugs, BCG vaccination, and appropriate PPE to be used with active pulmonary TB patients. The discrepancy in the two studies could be due to the methodologies used in the previous and present study.

The finding of the study on association between age and non-compliance to anti-tuberculosis drugs revealed that, there was a significant association between age and non-compliance to anti-tuberculosis drugs. This implied that age of the respondents has a significant link with the inability to comply with anti-tuberculosis drugs. The outcome of this study was in line with the finding of Alotaibi, Yara, Mushi, Maashi, Thomas and Mohamed (2019) which revealed that gender, age, nationality, occupation and length of work experience dealing with TB patients were associated with knowledge scores.

The finding of the study on association between sex and non-compliance to anti-tuberculosis drugs revealed that, there was no significant association between sex and non-compliance to anti-tuberculosis drugs. This implication was that the sex of the respondents was not associated with non-compliance to anti-tuberculosis drugs. The outcome of this study was not in agreement with the finding of Alotaibi, Yara, Mushi, Maashi, Thomas, and Mohamed (2019) which revealed

that gender, age, nationality, occupation and length of work experience dealing with TB patients were associated with knowledge scores.

The finding of the study on association between knowledge of anti-tuberculosis drugs regimen, age, educational background and non-compliance to anti-tuberculosis drugs revealed that; there was a significant association between knowledge of anti-tuberculosis drugs regimen, age, educational background and non-compliance to anti-tuberculosis drugs. The outcome of this study corroborated the finding of Krasniqi et al. (2017), which established that that knowledge on the question regarding the TB treatment had a significant impact on TB treatment adherence. In addition, the present study was in line with Alotaibi, Yara, Mushi, Maashi, Thomas and Mohamed, (2019), which established that gender, age, nationality, occupation and length of work experience dealing with TB patients were associated with knowledge scores.

### **Conclusion**

The study made known that the level of non compliance to anti-TB drugs among TB patients in Ibadan South West Local Government was high and it was concluded that the following were determinants of non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South West Local Government Area of Oyo state. 1) Knowledge of the patients about anti-tuberculosis drugs regimen. 2) Age and Educational background of the patients have been proven to affect non-compliance to Tuberculosis drug. While sex of the respondents was not determinants of non-compliance to anti-tuberculosis drugs among patients in selected DOT centres in Ibadan South West Local Government Area of Oyo state.

### **Recommendations**

Based on the outcome of the study the following were recommended:

1. There should be concerted efforts from different agencies on the sensitization about anti-TB drugs regimen with the aim of promoting compliance to anti-TB drugs among infected patients.
2. Under age children and adolescents should always be accompanied by parents or care givers to DOTS centres to see that they take their drugs regularly.

3. Community tuberculosis volunteers should always follow up tuberculosis patients on daily basis to see that they take their drugs regularly.
4. There should be a regular advocacy visit to different institution to create awareness on the cause, prevention and compliance to anti-TB drugs regimen.
5. Regular sensitization visits should be made by community Health workers to market places, motor parks, and artisans' on consequence of noncompliance to anti-TB drugs regimen.
6. Defaulters should be regularly follow up and bring back to the clinics to continue the medication.
7. Sensitize community tuberculosis volunteers to tell members of the community benefits of anti tuberculosis drug compliance among the infected people

### References

- Adane, A. A., Alene, K. A., Koye, D. N., and Zeleke, B. M. (2013). Non-Adherence to Anti- Tuberculosis Treatment and Determinant Factors among Patients with Tuberculosis in Northwest Ethiopia. *PLoS One*, 8(11), e78791. <https://doi.org/10.1371/journal.pone.0078791>
- Akilew, A. A.; Kefyalew, A. A.; Digsu, N. and Berihun M. Z. (2013). Non adherence to anti Tuberculosis Treatment and Determinant factors among patient with Tuberculosis in Northwest Ethopia. Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia.
- Alotaibi, B., Yara, Y., Mushi, A., Maashi, F., Thomas, A., Mohamed, G., and Saber, Y. (2019). Tuberculosis knowledge , attitude and practice among healthcare workers during the 2016 Hajj. *PLoS ONE*, 14(1), e0210913. <https://doi.org/https://doi.org/10.1371/journal.pone.0210913>
- Dewan, P.K.; Arguin, P.M.; Kiryanova, H.; Kondroshova, N.V. and Khorosheva, T.M. (2004) Risk factors for death during tuberculosis treatment in Orel, Russia. *Int J Tuberc Lung Dis* 8(5): 598–602.
- Essays, U.K. (2018). Social and Economic Impact of Tuberculosis. Retrieved from <https://ukdiss.com/examples/social-effect-of-tuberculosis.php?vref=1> on 02/04/2020.

- Floyd, K., Glaziou, P., Zumla, A., and Raviglione, M. (2018). The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *The Lancet Respiratory Medicine*, 6(4), 299–314. Retrieved from [https://doi.org/10.1016/S2213-2600\(18\)30057-2](https://doi.org/10.1016/S2213-2600(18)30057-2) on 06/12/2019.
- Global strategy and targets for tuberculosis prevention, care and control after (2015).the end TB strategy. Geneva: World Health Organization; 2015.
- Hanson, C.L. (2002). Tuberculosis, poverty and inequity: a review of the literature and discussion of issues. Stop TB Partnership. *World Health Organization, Geneva*.
- Jakubowiak, W., Bogorodskaya, E., Borisov, S., Danilova, I. and Kourbatova, E. (2009). Treatment interruptions and duration associated with default among new patients with tuberculosis in six regions of Russia. *Int J Infect Dis.*, 13 (3): 362-368. 10.1016/j.ijid.2008.07.015.
- Krasniqi, S., Jakupi, A., Daci, A., Tigani, B., Jupolli-krasniqi, N., Pira, M. and Neziri, B. (2017). Tuberculosis Treatment Adherence of Patients in Kosovo. *Tuberculosis Research and Treatment*, 2017(4850324), 8. <https://doi.org/https://doi.org/10.1155/2017/4850324> Retrieved on 06/12/2019.
- Kudakwashe, C.H.(2010). "Factor affecting compliance to tuberculosis treatment in Andra Kanvango region in Namibia," *Journal of Compliance to TB Treatment*, pp. 5-6, WHO, Global Tuberculosis Control: Surveillance, Planning, Financing, WHO Press, Geneva, Switzerland, 2008.
- Rehman, F., Raoof, M. A., Srinivasa, R. A., Hasan, A. and Qurram, M. (2017). Knowledge about Tuberculosis and its Complication among the Patients in a Teaching Hospital Pulmonary & Respiratory Medicine. *Journal of Pulmonary & Respiratory Medicine*, 7(1), 1–4. <https://doi.org/10.4172/2161-105X.1000390>
- Sagbakken, M., Frich, J.C. and Bjune, G. (2008). Barriers and enablers in the management of tuberculosis treatment in Addis Ababa, Ethiopia: a qualitative study. *BMC Public Health*. 8: 11-10.1186/1471-2458-8-11.

- WHO. (2015). *Global tuberculosis report 2015*. Geneva, Switzerland.
- Woimo, T. T., Yimer, W. K., Bati, T. and Gesesew, H. A. (2017). The prevalence and factors associated for anti-tuberculosis treatment non-compliance among pulmonary tuberculosis patients in public health care facilities in South Ethiopia : a cross-sectional study. *BMC Public Health*, 17(269), 1–10. <https://doi.org/10.1186/s12889-017-4188-9>
- World Health Organisation. (2014). *TB elimination framework*. Geneva.
- World Health Organisation. (2016). *Global Tuberculosis Control: WHO report 2016*. Geneva, Switzerland.
- World Health Organisation. (2017). Multi drug resistant tuberculosis (MDR-TB) Up-to-date WHO Global tuberculosis program; Geneva: World Health Organization
- World Health Organization (2010) Global Tuberculosis Control. WHO Report 2011. Geneva: *World Health Organization. WHO/HTM/TB/2011.16*
- World Health Organization. (2009). *Global tuberculosis control: a short update to the 2009 report*. Geneva:
- World Health Organization. (2013). *Global tuberculosis report 2013*. Geneva, Switzerland.
- Wurie, F. B., Cooper, V., Horne, R. and Hayward, A. C. (2018). Determinants of non-compliance to treatment for tuberculosis in high- income and middle-income settings : a systematic review protocol. *BMJ Open*, 8, e01928. <https://doi.org/10.1136/bmjopen-2017-019287>
- Zegeye, I. D. A., Getnet, D., Fasil, W., Alemu, G., Sheikh, M., Islamid, S. and Dessalegn, K. (2019). Prevalence and determinants of antituberculosis treatment non-compliance in iopia: A systematic review and metaanalysis. *PLoS ONE*, 14(1), e0210422.