

Socioeconomic, Disease, and Biochemical Factors in Adherence to Anti Tuberculosis Treatment Regime in Benin City, Nigeria: A Comparative Study

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Abstract Tuberculosis is a re-emergent disease of great epidemiological concern with the directly observed treatment short course (DOTS) recommended by the World Health Organization falling short of targeted expectations. The aim was to compare the impact of socioeconomic, disease, and biochemical factors on the decision of patients to return to (comply with) the six-month treatment schedule. Effects of education, age, occupational and marital (socioeconomic) and biochemical (drug side effects and values of biochemical indices of liver function) factors were compared between 52 SLR and 49 SNR patients. The results suggest that socioeconomic factors play a more prominent role than factors related to drug side effects in determining whether a patient returns to treatment after initial stoppage. A more integrated multi-disciplinary approach to DOTS administration with professional and social inputs is recommended

Keywords: adherence, tuberculosis, regime, socioeconomic, liver enzymes

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1. Introduction and Review of Literature

Tuberculosis, according to the WHO, is an infectious bacterial disease, caused by *Mycobacterium tuberculosis* which commonly affects the lungs and is transmitted from person to person via droplets from the throat and nostrils of persons with the active respiratory disease [1]. A disease previously thought to have been globally put under control; tuberculosis has resurfaced as a major cause of morbidity and mortality worldwide primarily due to the global HIV/AIDS pandemics providing a platform for opportunistic infections. The disease remains an issue of great public health concern today despite the fact that effective treatment has been available for over fifty years [2]. The WHO found that the AR1 is highest in sub-Saharan Africa (1.5-2.5%) and Asia (1.0-2.0%). In Netherlands (a developed nation) the AR1 was estimated at 0.012% [4]. Without appropriate chemotherapy the death rate from tuberculosis is 50% [5] and the estimated annual number of deaths from TB in developing countries is greater than 2.5 million or approximately 6.7% of all deaths [6].

The WHO global program on tuberculosis advocates for the use of directly observed treatment short course (DOTs) for all patients which involves giving Isoniazid, Rifampicin, Pyrazinamide and ethambutol for two months, then Isoniazid and Rifampicin alone for further four months and the patients is considered cured at six months [3,5,7,8,9,10]. It also advocates for home-based care of patients [8,9,10]. Biochemical side effects of drugs may be one factor that may affect compliance with drug treatment regime. Socioeconomic factors may also play a role [8]. In addition it is known that sufferers of a disease may or may not embrace a given management approach depending on the perception they have of their susceptibility to complications or the severity of symptoms [11] which in the case of tuberculosis include prolonged productive cough exceeding three months duration, chest pain, low grade intermittent fever, hemoptysis, night sweat, weight loss, appetite loss, easy fatigueability etc [12,13]. Awofeso and others [8] observed non-attendance and defaulting trends among community based TB patients in northern Nigeria and opined that the extent of treatment adherence (avoiding the use of the word compliance) may be facilitated by positive or negative attributes related to the healthcare

The final content (after adding Biuret reagent) of each tube was mixed thoroughly by vortexing and then incubated for 30mins at 25°C. The contents were then transferred to suitable cuvettes and absorbance read at 540nm for test, standards, and blank. The concentrations of the standards were used to plot a standard curve. The absorbance of the test solution was derived by subtracting the blank absorbance after extrapolating from the standard curve.

The concentration of total protein mg protein/ml of test solution was calculated as

$$\text{Mg protein/ml} = \frac{\text{mg protein}}{\text{ml of patients sample}}$$

3.1. Quantitative Determination of Serum Albumin

The method of Corcoran and Durnan [15] was adopted. Albumin is bound by the modified Bromocresol Green (BCG) dye to bring about an increase in the blue – green colour measured at 630nm. The colour increase is proportioned to the concentration of albumin present. The reagents used were Bromocresol Green 0.15 g/dl, Buffer, pH 4.66 ± 0.1, reactive ingredient, stabilizers, and surfactant all purchased as a ready-to-use single reagent. To each labeled tube (blank, standard, Test) was added 1.0ml of reagent. 0.01ml of sample was added to each tube and all the tubes were incubated at room temperature for one minute. The spectrophotometer was zeroed with the blank at 630nm. The absorbance were then read and recorded.

The concentration (g/dl) of albumin in test was calculated as:

$$\frac{\text{Absorbance of test}}{\text{Absorbance of standard}} \times \text{concentration of standard (BSA)}$$

Calculated from

$$U/ml = \frac{\Delta A/\text{min}}{18.75} \times \frac{3.0}{0.10} \times 1000$$

$$U/ml = \Delta A/\text{min} \times 1000$$

Where 18.75 = the absorbance of 1µmol/L p-nitrophenol in working buffer at 404nm in a 1cm path.

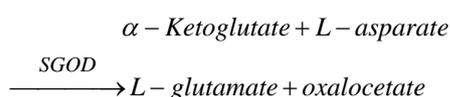
0.3 is the volume in the cuvette

0.1 is the sample volume

1000 is the factor converting to litre.

3.2. Estimation of Serum Glutamic Oxaloacetate Transaminase (SGOT, EC 2.6.1.1)

This was done using the colorimetric method of Reitman and Frankel [16]. SGOT catalyses the transformation of the substrate which contains α-ketoglutarate and L-aspartate to yield L-glutamate and Oxaloacetate. The Oxaloacetate formed reacts with 2,4-dinitrophenyl hydrazine to form Oxaloacetate hydrazone whose intensity is measured colorimetrically and is directly proportional to the activity of the aspartate aminotransferase in the reaction.



The reagents were solution 1 (100m M phosphate buffer pH 7.4 + L-aspartate + αketoghtarate, solution 2 (2, 4- dinitrophenyl hydrazine as concentration of 2nM, and sodium hydroxide is 0.4M, all stored at about 8°C in the refrigerator. Two test tubes were used; one for the blank and the other for the sample. 0.5mls of solution 1 was put in an empty test tube and in the tube containing 0.1ml of the patient's serum and incubated for 30min at 37°C. 0.5ml of 2,4 dinitrophenyl hydrazine was added to each tube and the content of each tube was mixed and allowed to stand for 20min at 25°C. Finally 5ml of Sodium hydroxide was added to each test tube. After mixing, the absorbance of the sample was read against the blank after 5 minutes at 546nm. The corresponding SGOT value was deduced from the available SGOT value – absorbance chart in iu/L.

3.3. Determination of Serum Glutamic Pyruvic Transaminase (SGPT, 2.6.1.2)

The same method of Reitman and Frankel [16] was adopted. This enzyme catalyzes the transformation of the substrate to yield L-glutamate and pyruvate. The pyruvate formed reacts with the 2,4-dinitrophenyl hydrazine to form pyruvichydrazone, a coloured complex, whose intensity is measured colorimetrically and is proportional to the activity of the alanine aminotransaminase. Phosphate buffer, L-alanine, and α-ketoglutarate made up the solution in this case.

3.4. Determination of Direct, Indirect and Total Bilirubin

This was done by the colorimetric method of Vanden Bergh as discussed by Lathe and Ruthven [17]. Two forms of bilirubin exist in plasma, both of which are bound to albumin. These are non-esterified or unconjugated bilirubin, and bilirubin diglucuronide (conjugated bilirubin). The concentration of the unconjugated fraction is obtained by subtracting the conjugated form from the total bilirubin. Bilirubin can be converted into an azodyewhich absorbance at specific wavelength can be measured. Both conjugated and unjugated forms are split at the middle by the diazo reaction to form two dipyrroles with loss of the methylene bridge at the scission point. Each dipyrrole forms an azo dye by coupling with the diazonium salt, with the resulting azobilirubins having essentially the same spectral absorbance value.

The reagents included 0.20M HCl. Diazo reactant prepared from sulfanilic acid (0.058M) and 0.072M NaNO₂ bilirubin standard solution (standard bilirubin + directly sulfoxide + Bovine serum albumin)

To determine the conjugated bilirubin test and blank tubes were set for each specimen and standard containing 0.75ml of water and 50ul unknown serum. The same was done for control serum and standard 0.2ml of diazo reagent was added to all tubes marked "test" and 0.2u Sulfanilic acid to all tubes marked "blanked". The tubes were allowed to stand for 5minutes and then read in sequence against a water blank at 50nm.

For the determination of total bilirubin 1.0ml methanol was added to all the tubes above, both test and blank, mixed well, and allowed to stand for 30 minutes at room temperature, and then read at 560nm.

Total bilirubin (mg/dl) was calculated as

$$= \frac{\Delta Au}{As} \times C$$

Esterified bilirubin (mg/dl) was also calculated using the same equation but methanol was not added before the absorbance were read.

Δ Au= difference in absorbance between unknown and blank.

As = the absorbance of the standard read at 5 minutes.

C= the bilirubin concentration of the Bovine serum (standard).

3.5. Statistical Analysis

The statistical program for the social sciences (SPSS) version 17.0 was used to determine the means of various indices of liver function tests for the SLR and SNR groups.

4. Results

The results of the sociodemographic and economic parameters of patients complains, and liver function indices compared between the SLR and SNR groups of

patients is presented in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6.

Table 1. Comparison of educational status of SLR and SNR patients

Highest level of Education	SLR (%)	SNR (%)
* No Contact with Education	7.69	24.44
* Primary School	17.30	2.04
* Secondary School	59.61	8.16
* Tertiary Education	13.46	65.31

Table 2. Comparison of mean age between SLR and SNR patients

	SLR	SNR
Meanage±SD (yrs)	38.23±12.46	52.16±31

Table 3. Comparison of marital status between SLR and SNR patients

Marital status	SLR(%)	SNR(%)
* Married	71.15	18.52
* Unmarried	17.31	05.97
* Divorced	07.69	34.69
* Separated	03.85	40.82

Table 4. Comparison of occupational affiliation (classified according to the ILO [18]) of SLR and SNR patients

OCCUPATIONAL AFFILIATION{20}	SLR(No of patients)	SNR(No of patients)
* Managers	Nil	14
* Professional Occupations	1	10
* Technicians and Associate Professionals	2	2
* Clerical Support workers	3	2
* Service and Sales workers	23	6
* Skilled Agricultural, Forestry and Fishery workers	8	3
* Craft and related trade workers	11	7
* Plant and Machine operators and assemblers	4	5
* Armed forces occupations	Nil	Nil

Table 5. Comparison of the major complains between SLR and SNR patients as at the last visit before stoppage of treatment

Complain as at the last review before stoppage of treatment (Number of patients)	SLR (No of patients)	SNR (No of patients)
* Frightening coloration of urine	15	13
* Yellowness of the eyes	8	11
* Unbearable itching	21	24
* Blurred vision or eye pain	--	--
* painful joints	25	23
* Unfriendly o disrespectful attitude of facility staff	6	14

Table 6. Comparison of the mean values of the liver function indices between the SLR and SNR patients

Values of liver function indices as at the last liver function test	SLR	SNR	P value
* Serum total protein(TB, g/dl)	5.741±0.434	5.726±0.396	P>0.05
* Serum albumin (Alb,g/dl)	4.125±0.625	4.127±0.411	P>0.05
* Serum globulin (Glob, g/dl)	1.544±0.526	1.567±0.296	P>0.05
* Alkaline phosphatase (iu/dl)	171.012±0.196	154.874±0.634	P<0.05
* Serum glutamate oxaloacetate aminotransferase (ku)	25.245±0.644	24.628±0.467	P>0.05
* Serum glutamic pyruvic aminotransferase (ku)	30.169±0.736	28.425±0.339	P>0.05
* Direct Bilirubin (g/dl)	0.439±0.025	0.431±0.397	P>0.05
* Indirect Bilirubin (g/dl)	0.381±0.023	0.384±0.022	P>0.05
* Total Bilirubin (g/dl)	0.812±0.109	0.799±0.147	P>0.05

5. Discussion

Tuberculosis remains an important public health issue especially in developing countries where the predisposing factors are commonly found. Poor housing, inadequate nutrition as a result of poverty are some important factors. A comparison of educational status between the SLR and SNR groups (Table 1) shows that at the extremes of the scale of educational status (no contact with education and tertiary education) were found those who absconded and never returned. It may be easily understood why those with absolute illiteracy may never return after absconded. The reason why those who are very well educated (tertiary education) did not return to treatment may however be difficult to decipher. However their presumably better socioeconomic status may suggest that they are able to afford treatment at more organized and sophisticated centers which may be more expensive than the private facilities where this study was conducted and so they can afford better ones when they get dissatisfied with a DOT facility. Some may even opt for home based care.

Age was also found to be a factor (Table 2). Older persons were found to be less likely to return after stoppage. The reason for this is not so clear but the perceived threat of tuberculosis, which Rosenstock [11] identified as a major factor in the decision whether to embrace a health programme or not, is more likely to be exaggerated by the young, who may also tolerate imperfections because of their lower self esteem, than the older ones. The older ones may also have a higher propensity to endure the symptoms of the disease and drug side effects instead of running back to the facility.

Marital status was found to be a determinant of whether a patient will return or not. From Table 3 it can be seen that those who are separated or divorced are less likely to return to treatment. Stable marriage comes with more social responsibility and accountability. Most marriage persons not only think of their welfare but also that of their spouses and children. This thought of the welfare of their dependants may make them return to treatment to avoid plunging these dependants into suffering which may be the case if they (the patients) die. The comparison between occupational affiliation of SLR and SNR patients is also remarkable (Table 4). There were more SNR than SLR patients up the ladder according to the ILO classification of occupational status [18]. Most of those who stopped and later returned were in the middle class while a higher percentage of those who stopped and never returned were in the upper class than in the middle and lower classes. This is closely related to the effect of education and further emphasizes the importance of education to health-seeking behavior. High educational rating also translates to high economic rating which is a major factor in the making of health related decisions.

Complaints related to side effects (Table 5) and the indices of liver function test (Table 6) are related to the biochemical processes involved in both the natural history and chemotherapy. From these tables it can be seen that there are no sharp differences between the two groups. Apart from the difference in complains about the unfriendly or disrespectful attitude of facility staff which is actually a social issue. In this regard it was seen that far

more SNR patients than SLR patients indicating that social issues are very important determinants of health-seeking behaviors.

The current study is in support of Awofeso et al [8] who had earlier stated that social and family issues may facilitate the extent of TB treatment adherence. It also betrays the common attribution of stoppage of DOTS regime to the effect of drug side effects.

6. Conclusion and Recommendation

Tuberculosis has been unearthed by the ravaging claws of HIV/AIDS. The menace of TB is especially worrisome in many developing countries where housing conditions are poor and government budgetary commitment to health are laughably pretentious. It can be seen from the present study that while there were clear differences between the average age, educational status, occupational affiliation, marital status, and complain about attitude of facility staff (socioeconomic factors) between the SLR and SNR patients, there were no clear differences between complains of drug side effects and biochemical indices of liver function. This suggests that socioeconomic factors play a more important role in determining whether a patient returns to treatment or not after stopping and hence are more important determinant of patient adherence to the DOTS regime or not. A multidisciplinary approach to the DOTS strategy is therefore recommended with emphasis on a clearly defined role for the social scientist. We also recommend that private, and not only public health facilities, be well integrated into the DOTS scheme since these are usually closer to the local communities and many patients shy away from government-run health facilities. The overall purpose is to ensure that we scale up to meet targets in global tuberculosis control [19,20,21,22,23].

Abbreviations

DOTS	Directly observed treatment short course
SLR	Stopped treatment but later returned
SNR	Stopped treatment and never returned
HIV/AIDS	Human immunodeficiency virus, acquired. Immunodeficiency
WHO	World Health organization
AR1	The probability that any person will be infected with mycobacterium. Tuberculosis in 1 year
TB	tuberculosis
BCG	Bromocresol Green
ILO	International labour organization.

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