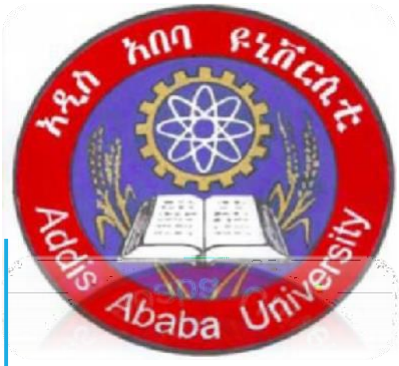

ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE

Department of Internal Medicine

Title: Effect of level of adherence of antimalarials on disease activity and its determinants in Systemic lupus erythematous patients on follow up at rheumatology clinic of Tikur Anbessa Specialized Hospital

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A thesis proposal submitted to Addis Ababa University, college of health sciences, school of medicine, department of internal medicine in preparation for partial fulfillment of the requirement for a specialty certificate in internal medicine.

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Title	Effect of level of adherence of antimalarials on disease activity and its determinants in Systemic lupus erythematous patients on follow up at rheumatology clinic of Tikur Anbessa Specialized Hospital
Study area	The study was conducted at the rheumatology outpatient clinic of Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia
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List of Acronyms

AAU	Addis Ababa University
AMs	Antimalarials
CI	Confidence Interval
CQ	Chloroquine
ESRD	End Stage Renal Disease
GC	Glucocorticoids
HCQ	Hydroxychloroquine
HMIS	Health Management Information System
HR	Hazard Ratio
IBM	International Business Machine
LLDAS	Lupus Low Disease Activity Score
LN	Lupus nephritis
MMAS	Morisky Medication Adherence Scale
MMF	Mycophenolate Mofetil
MRN	Medical Record Number
OR	Odds Ratio
RR	Relative Risk
SD	Standard Deviation
SLE	Systemic Lupus Erythematous
SLEDAI-2K	Systemic Lupus Erythematous Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SPSS	Statistical Package for Social Sciences
TASH	Tikur Anbessa Specialized Hospital
USA	United States of America

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Abstract

Background: Systemic lupus erythematous (SLE) is an autoimmune disease associated with accrual of organ damage and mortality. Antimalarials like Hydroxychloroquine/Chloroquine are important therapeutic options in SLE. But their effectiveness is impeded by non-adherence.

Objective: To assess the level of adherence of antimalarials, its determinants and its association to disease activity in SLE patients on follow up at the rheumatology clinic of Tikur Anbessa Specialized Hospital (TASH).

Methods: 106 SLE patients taking antimalarials and who had follow up visit from August 1 to October 31 2023 were included in the study. Structured questionnaire was used to assess their sociodemographic and clinical characteristics. Adherence was assessed using Morisky medication adherence scale (MMAS-8) and SLE disease activity was assessed using systemic lupus erythematous disease activity index 2000 (SLEDAI-2K). Data was analyzed using statistical package for social science (SPSS) version 26. Binary logistic regression was used to assess the association between level of adherence and disease activity and to look for clinical predictors of non-adherence. Statistical significance was determined using adjusted odds ratio at 95% confidence interval (CI) and P value <0.05.

Results: 98.1% were women and the mean age of the patients was 28.8 years. 91.5% were on chloroquine and 8.5% were taking hydroxychloroquine. 11.3% were on high dose prednisolone. 36.8% of patients were found to be non-adherent to their antimalarials and 53.8% had active disease. Non adherence was seen to have a significant association with active disease (AOR 9.86 95% CI 3.61, 26.87). None of the sociodemographic and clinical factors were found to be predictors of non-adherence. (P>0.2)

Conclusion: SLE patients in this study had a fair adherence to antimalarials. There is a strong association between non-adherence to antimalarial and active disease in SLE patients. Sociodemographic and clinical factors were not found to be predictors of medication adherence.

Key words SLE, Antimalarials, adherence, and Disease activity

1. Introduction

1.1 Background

Systemic lupus erythematous (SLE) is a multisystemic autoimmune disease characterized by the presence of autoantibodies. The chronicity and unpredictability of the disease contribute to organ damage and the long term use of immune suppressants as treatment can result in life threatening complications. (1)

Global SLE prevalence is estimated to be 43.7 per 100,000 persons with around 3.41 million people affected worldwide. (1) Women are more likely to have SLE than men with a sex ratio ranging from 7:1 to 11:1 (1, 2, 4). The highest SLE prevalence is reported to be in Latin America and the United Arab emirates. (1)

Mild lupus accounts for the majority of the cases with a possibility of progressing to severe disease. (2) Treatment strategies of SLE depend on disease activity and the organs involved. Antimalarials like hydroxychloroquine and chloroquine (HCQ/CQ) have become the cornerstone of lupus management as they are believed to reduce mortality, flares, renal involvement, cardiovascular events and disease progression. (2) They are also less toxic and costly than other disease modifying agents thus universal therapy with HCQ/CQ should be provided to all patients with SLE having no contraindications.(3)

Given the chronicity of the disease, patients are most often required to take antimalarials and other immmunomodulators for long duration making it challenging for patients to be adherent. Proportions of patients with SLE who are non-adherent to medications range from 43 to 75% in different studies (4-6) Non adherence is associated with disease progression, poor treatment outcome and increased mortality. (7)

1.2 Statement of the problem

Despite advances in treatment, mortality rates from SLE remain high and it is among the leading cause of death in young women in the United States.(8) In hospital mortality is largely attributed to disease progression/activity, cardiovascular events, and infections. (9)

A Meta-analysis by Cai T et al showed that HCQ/CQ significantly reduced disease activity and risk of overall mortality in SLE patients including those with renal and cardiopulmonary involvement. (6) Most patients struggle with adherence and proportions of patients with SLE who

are non-adherent to antimalarials range from 43 to 75% in different studies (4-6) and non-adherence to HCQ/CQ is independently associated with the risk of SLE flare in the following year, early damage and a 5 year mortality. (10)

In a Caucasian predominant cohort of 1956 SLE patients in North Carolina, USA adherence rate of HCQ was only 58% (11) Similarly in a single center cross sectional study done in Brazil the non-adherence rate of SLE patients on treatment was 64% and identified duration of illness and comorbidities as important contributors. (12)

Another single centered cross sectional study done in china showed that 75% of SLE patients were non adherent to their medications and the main determinants were low education, drug side effects, and better physical health. (13)

There is limited data in Africa but a small study in Egypt showed that non-adherence of SLE patients was 51.7% and found adherence had a significant association with SLE disease activity. (14)

In Ethiopia, where young people comprise the majority of the population there is paucity of data regarding burden of the disease, medication use, clinical impacts of adherence.

1.3 Significance of the study

In Ethiopia, where access of SLE patients to advanced medical therapy is limited, the proper use of antimalarials which are more readily available is of paramount importance. So far there has not been any study done in the country or in the sub-Saharan Africa showing degree of adherence to antimalarials in SLE patients and its clinical impact. This study will assess the level of adherence and show the degree of association, if any, between adherence to antimalarial drugs and disease activity. As studies on SLE in Ethiopia are lacking, this study can serve as a reference for future large scale studies.

2. Literature review

2.1Epidemiology of SLE

SLE is a primarily female predominant chronic disease with peak of disease incidence for women being during reproductive years, while men tend to have a peak in later middle age years (45-60 years). (15)

In the USA the pooled prevalence of SLE is 72.8 per 100,000 person years with female prevalence being 9 times more than males and highest among Black females (230.9 per 100,000) followed by Hispanic females (120.7 per 100,000) with the least prevalence being in White females and Asian pacific population (84.7 and 84.4 per 100,000 respectively). (16)

Data from 35 European countries that studied 4375 SLE patients showed that the median age at SLE diagnosis was 30 years with the incidence ranging from 1.5 to 7.4 per 100,000 and females were primarily affected with a ratio of 10:1. (17)

A systemic review of different studies made on sub-Saharan natives showed that the pooled prevalence of SLE was 1.7% which is lower than the Asian pacific countries with the mean age at diagnosis being 28.8 to 39.2. The female proportions varied from 88% to 100 %.(18)

166 patients diagnosed with SLE between the years of 2007 and 2017 at a university hospital in Kenya showed that 92.2% of the patients were females with 79.5% aged between 18 to 40 years. (19)Similarly a healthy facility based study in Uganda concluded that the median age of SLE diagnosis is 29 years with a female to male ratio of 10:1. (20)

2.2 Rationale of antimalarial use in SLE patients

Antimalarial drugs like Hydroxychloroquine/Chloroquine reduce SLE activity, flares, accrual damage, serious infections, atherosclerosis, cardiovascular events and mortality thus universal therapy with HCQ/CQ should be provided to patients with SLE having no contraindications.(21) Beyond their immmunomodulatory effect they have also been shown to protect against thrombotic events,(22,23) improve glucose and lipid profile, and prevent renal damage.(23)

Patients with SLE have a 1.8 fold increased mortality rate compared with the general population. (24) Glucocorticoid use, female sex, and young age are associated with an increased mortality risk while low dose HCQ use significantly reduces the mortality rate. (24)

Mok C et al concluded the ever use of antimalarial was significantly associated with better survival from a study involving 803 SLE patients. (25) Similarly a meta-analysis of 21 studies with a pooled population of 26037 suggested that HCQ/CQ significantly reduced the overall mortality of SLE. (26) Furthermore HCQ use in SLE is associated with better patient reported health outcomes/ quality of life. (27)Having followed 3062 SLE patients taking AM in Canada for 6.4 years Hoque et al concluded that patients adhering to AM therapy had a 71% and 83% lower risk of death than patients who do not adhere or who discontinued AM respectively. (28)

A large cohort of 2,228 SLE patients in USA assessed predictors of LLDAS 50 which was patients being in lupus low disease activity for 50% or more of the observation time and found that a higher percentage of time taking HCQ is a positive predictor of LLDAS 50. (29)

Adherence level was studied in 276 SLE patients in china with blood assayed for HCQ levels by tandem mass spectrometry and disease activity was assessed using SLEDAI. 77% of the patients had sub therapeutic levels of HCQ (10-500ng/ml) and in patients having therapeutic serum levels, a lower disease activity and fewer incidences of flares was observed. (30)

As immunosuppression is the cornerstone of lupus management, infection is one of the leading causes of mortality and morbidity in SLE patients.(31, 32) A meta-analysis of 11 cohorts has shown that patients with SLE have significantly higher risk of infection compared with the general populationwith pooled RRs for pneumonia and TB being 2.58 and 6.1 respectively. Interestingly subgroup analysis of the study has indicated that the HR for the risk of serious infection was 3.9 for those starting on Glucocorticoids without antimalarials. (33)

In patients with LN antimalarial therapy is associated with longer duration of renal remission and reduced GC use which has a number of side effects. (34) Continued HCQ use also hinders renal damage and progression to ESRD in patients with LN. (35)And persistently low HCQ blood levels are predictors of renal flares. (36)

A retrospective chart review of patients diagnosed with SLE in a 10 year period ascertained that continued use of HCQ reduced the risk of flares and is associated with low disease activity while discontinuation or never use can increase the risk of flares including renal flares. (37) A

prospective data analysis form the SLICC cohort of 1460 patients indicated that HCQ taper/discontinuation is associated with a higher flare risk and disease activity. (38)

2.3 The magnitude of Non adherence in SLE patients and its determinants

As there is no cure to SLE, patients tend to be on long term to lifelong pharmacological therapy. The disease is chronic and its management is complicated. The global incidence of SLE in young adults is estimated to be 7.31 per 100,000 person years. (1) so patients tend to be diagnosed early and have the disease for the majority of their life span. Antimalarials and other immunosuppressants are primarily used in the treatment of SLE and adhering to these medications for longer duration can be cumbersome for most patients.

In a cohort of 10,406 SLE patients on HCQ, proportion of days covered (PDC) was used to assess overall adherence and monthly patterns during the first year of use of HCQ and found that 17% were persistent adherers, 36% persistent non adherers and 47% had dynamic patterns of partial adherence and suggested that HCQ adherence is a dynamic behavior that declined over the first year of use. (39)

In a longitudinal cross sectional survey being conducted annually in Germany since 2001 adherence rate of various lupus medications are assessed and in 2012 out of 529 questionnaires 62.7% showed a high, 32.5% a moderate and 4.8% a low adherence. Higher adherence was reported with azathioprine (72%) and cyclosporine (73%) than in users of MMF or antimalarials (58%)). young age and better physical functioning contributed to low adherence. (40)

A single centered study in Jamaica showed that the non-adherence level of SLE patients was 44% and high cost and poor availability were implicated for low adherence.(41)

In Sweden, a cross sectional study was done in two tertiary hospitals using validated questionnaires to assess medication adherence of antimalarials and GC separately. 45.9% of the patients were on five medication or more and the non adherence rate was 66.8% and concerns regarding medication side effects had a negative association with adherence. The other predictors like sociodemographic status, disease duration, total medications used were not associated with adherence. (42)

Amalia et al concluded that the incidence of side effects is a significant predictor of medication adherencefor patients with SLE with 36.6% of the patients in the study being non adherent.

Duration of disease and the number of currently used medicines were not significantly associated with the level of adherence. (43)

In a single centered cross sectional study conducted among Egyptian SLE patients, the adherence to medication was reported to be quite low and attributed it to low socioeconomic status , rural residency, and more number of medications.(44)

3. Research question

What is the level of adherence of antimalarials, its determinants and association to disease activity in SLE patients on follow up at rheumatology clinic of TASH?

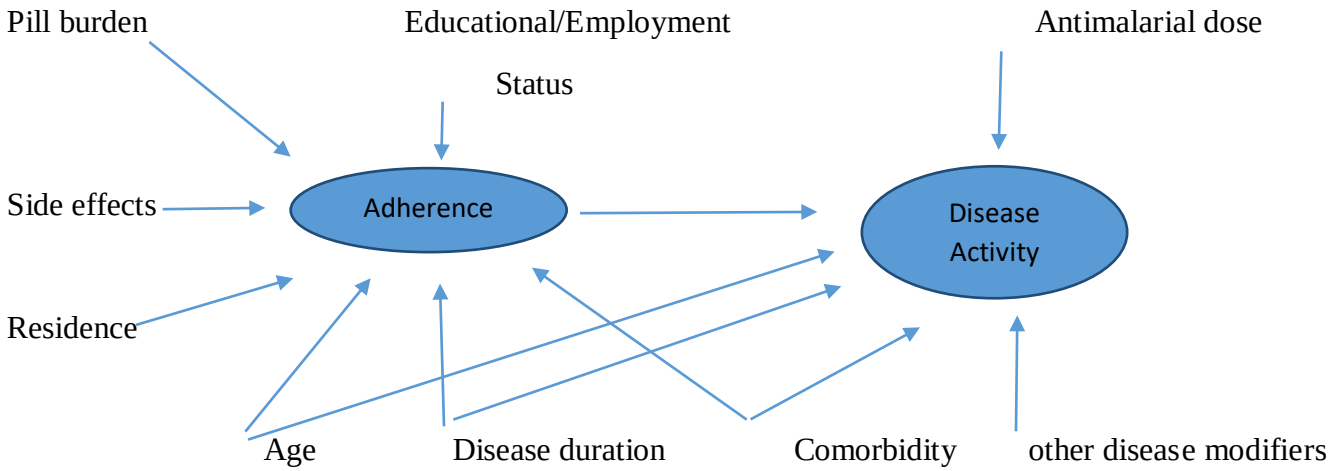

Fig 1: Conceptual framework on Determinants of adherence and disease activity and their association

4. OBJECTIVES

4.1 General objective

- To assess the effect of level of adherence of antimalarials on disease activity and it's predictors in patients with SLE on follow up at rheumatology clinic in Tikur Anbessa specialized hospital

4.2 Specific objectives

- To measure the level of adherence of antimalarials in SLE patients
- To determine the association between adherence of antimalarials and SLE disease activity
- To identify clinical predictors of non-adherence of antimalarials in SLE patients

5. Research methodology

5.1Study area

The study was conducted at the rheumatology clinic of Tikur Anbessa hospital, which is one of the tertiary hospitals found in Addis Ababa, Ethiopia giving specialty and subspecialty level patient care. The department of internal medicine is one of the earliest specialties in TASH that has branched out into numerous subspecialties and one of which is the rheumatology unit which provides both inpatient and outpatient services attended by 2 rheumatologists, medical residents and nurses. Over 1000 patients have follow up at the rheumatology clinic, out of which around 118 are SLE patients.

5.2 Study period

Data was collected from August 1 2023 to October 31 2023.

5.3 Study design

The study is a cross sectional study which assessed the degree of non-adherence using MMAS 8 and identified its association with disease activity and the various markers of high disease activity in SLE patients using a pretested questionnaire.

5.4 Source and study population

The source population was all patients with SLE on follow up at the rheumatology clinic of TASH with the study population being those that fulfill the inclusion criteria and who had follow up visit from 1st August 2023 to 31st October 2023.

5.4.1 Inclusion criteria

Males or females who are 18 years of age and above fulfilling the 2012 SLICC criteria for SLE
Given informed consent

5.4.2 Exclusion criteria

SLE patients on follow up not taking HCQ/CQ

Lack of good cognitive status to complete the questionnaire

5.5 Sample size

In the study done In Alexandria university hospital, Egypt the non-adherence rate was 51.7% (22) and assuming a confidence interval of 95%, margin of error of 5% and a 10% non-response rate with total SLE patients on follow up at the rheumatology clinic of TASH being 118 patients. The sample size was calculated as:

$n = Z\alpha/2^2 \times P(1-P)$

d^2

$= (1.96)^2 \times 0.483 \times 0.517 = 383.6 \approx 384$

0.05^2

n sample size 384

Zα/2 Z score for 95% CI is 1.96

d margin of error : 5% which is 0.05

P proportion 51.7%

Since source population (N) is 118 and is less than 10,000 sample size was adjusted as follows

nadjusted= $n \div (1+n/N)$

$= 384 \div (1+384/125)$

$= 94.5 \approx 95$

Considering a 10% non-response rate final sample size is calculated as follows

nfinal= $(1/ (1-0.1)) \times 95$

$= 105.5 \approx 106$

The sample size for the study was **106**

5.6 Sampling technique

Consecutive sampling was used and all patients fulfilling the inclusion criteria who had follow-up from August 1 to October 31 2023 G.C were included in the study.

5.7 Study variables

5.7.1 Dependent variables

- Disease activity

5.7.2 Independent variables

- Age
- Duration of SLE
- Dose of antimalarial drugs
- Drug adherence
- Use of immunosuppressive agents
- Comorbidities

5.8 Operational definitions

SLE diagnosed if a patient fulfills 4 of 17 criteria including at least 1 clinical and 1 immunologic criterion used in SLICC classification criteria or a biopsy proven lupus nephritis

MMAS-8 a scale with scores ranging from 0 to 8 used to assess medication adherence (45)

Adherent MMAS-8 score of 6 and above;

Non adherent MMAS-8 score of less than 6.

Disease activity is assessed using the SLEDAI-2K covering 9 organ systems and lab values with a score range of 0-105

Inactive disease Clinical SLEDAI 2K score of 4 or less

Active disease SLEDAI 2K score of more than 4

Low dose prednisolone less than or equal to 7.5mg po daily

High dose prednisolone more than 7.5mg po daily

- SLICC criteria, SLEDAI-2K and MMAS-8 are provided in the annex

5.9 Data collection

Data was collected using a structured questionnaire. The questionnaire was adopted from other literatures of similar content and was translated from English to Amharic for better understanding by the participants and to avoid bias. The primary investigator pretested the questionnaire on 5 individuals prior to the actual data collection. Data was collected by one general practioner after thorough training on the material.

5.10 Data analysis

Data was cleaned and entered into Excel before being exported into SPSS version 26 for analysis. Frequency was run for each variable with cross tabulations done to compare proportions. Categorical variables were summarized using proportions and continuous variables using mean and standard deviation. Association between disease activity and independent variables like age, duration of SLE, dose of antimalarial, drug adherence, use of immunosuppressive drugs and comorbidity was initially assessed using binary logistic regression and P value < 0.2 was taken as significant to be entered into the multivariable model. Association was measured using adjusted odds ratio with confidence interval of 95% and considered significant if P value <0.05 in the multivariate analysis.

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6. Ethical consideration

Ethical approval was obtained from the department of internal medicine before the study was commenced. Participants had enough explanations about the aim of the study and their participation. Collected data was accessible only for the primary investigator and data collector.

7. Results

7.1 Sociodemographic status

The study included 106 patients out of which 104 (98.1%) were females and 2(1.9%) were males with a sex ratio of 52:1. Most (46.2%) were in the 26-35 age group with the mean age being 28.8 with SD 8.5. The maximum age was 66 and the minimum age was 17. Two third of the patients had a university/college level of education but the majority were unemployed (55.7%). 97.2% of the patients lived in urban areas. The demographic characteristics of the patients are shown in table 1.

Table 1: Sociodemographic status of patients

Variable	Frequency	Percentage
Age		
15-25	38	35.8
26-35	49	46.2
36-45	15	14.2
>45	4	3.8
Sex		
Male	2	1.9
Female	104	98.1
Educational status		
Primary	11	10.4
High school	29	27.4
University/college	66	62.3
Employment		
Employed	47	44.3
Unemployed	59	55.7
Marital status		
Single	58	54.7
Married	43	40.6
Divorced	4	3.8
Widowed	1	0.6
Religion		
Orthodox	67	63.2
Muslim	13	12.3
Protestant	26	24.5
Residence		
Urban	103	97.2
Rural	3	2.8

7.2 Clinical characteristics

As presented on table 2, 24 (22.6%) patients had SLE for less than one year while 51 (48.1%) had it for more than 1 year but less than 5 years and 31(29.2%) had it for more than five years. The majority of patients (92 %) were on three medications or less. 41 (38.6%) patients were on two medications and 36 (33.9%) patients were on only one medication. 97(91.5%) were on chloroquine out of which 72(67.9%) were taking 250mg five times weekly and 19(17.9%) were on daily doses. Only 9 (8.5%) were on hydroxychloroquine.

36 (33.9%) patients were taking only antimalarial and no other disease modifying agent, while 30(28.3%) were on low dose prednisolone and 12 (11.3%) were on high dose prednisolone. 24(22.6%) were on different steroid sparing agent and the commonest agent was Methotrexate (7.5%). 20 (18.9%) had different comorbidities; the commonest were diabetes (3 patients), dyslipidaemia (3 patients). One patient was pregnant. 15 (14.2%) were on treatment for lupus nephritis.
22(20.8%) patients reported side effects with antimalarial use. The majority complained of gastrointestinal symptoms while 8(13.3%) had various eye complaints.

Table 2: clinical characteristics

Variable	Frequency	Percentage
Duration of SLE		
<1 year	24	22.6
1 to 5 years	51	48.1
>5 years	31	29.2
No of medications used		
one	36	33.9
Two	41	38.6
Three	21	19.8
Four	8	7.6
Antimalarial		
CQ	97	91.5
250mg 3x weekly	6	5.7
250mg 5x weekly	72	67.9
250mg daily	19	17.9
HCQ	9	8.5
Medications		
Antimalarial	36	33.9

Prednisolone <7.5mg	30	28.3
Prednisolone ≥7.5mg	12	11.3
MTX	8	7.5
Anti-Hypertensive	3	2.8
Other Immunosuppressant	16	15.1
Comorbidities		
No	86	81.1
Yes	20	18.9
Lupus Nephritis		
Yes	15	14.2
No	91	85.8
Side effects		
Yes	22	20.8
GI	14	79.2
Eye	8	13.3
No	84	7.5

7.3 Level of adherence and disease activity

67 (63.3%) patients were adherent to the antimalarial drug and the remaining 39 (36.8%) patients were non adherent as assessed by Morisky medication adherence 8 scale as depicted on figure 2. 57 (53.8%) patients had active disease and the remaining 49 (46.2%) patients had inactive disease based on SLEDAI2K as seen on table 3.

Figure 2: Level of adherence as assessed by Morisky medication adherence scale 8 (MMAS 8)

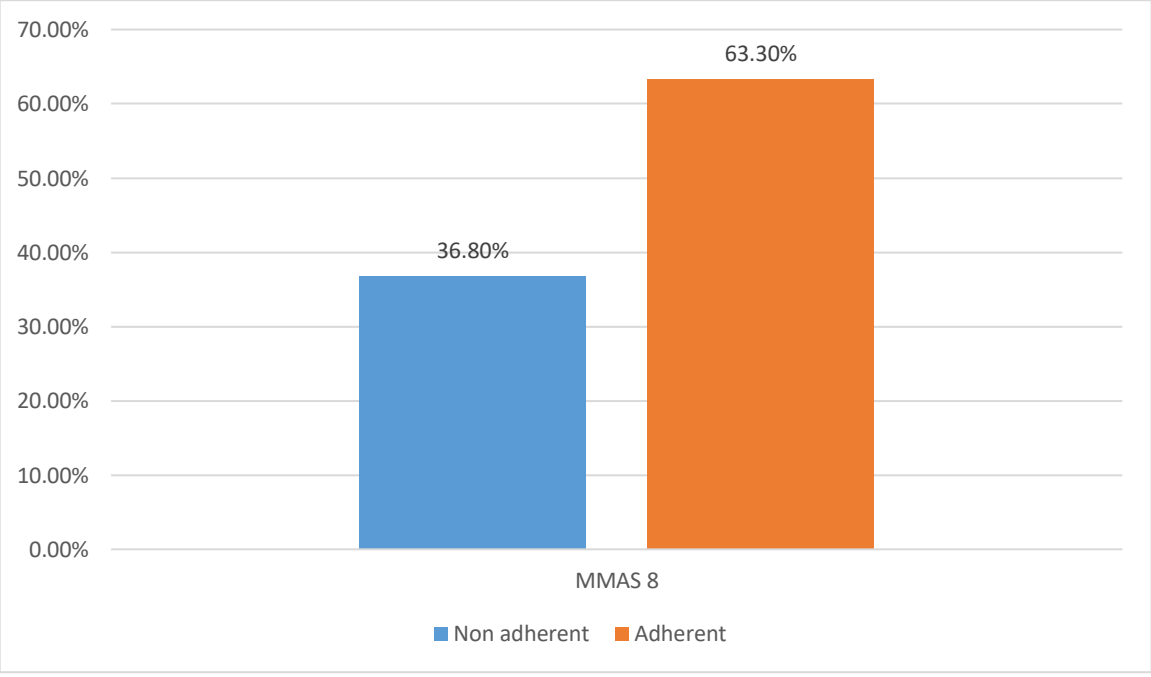
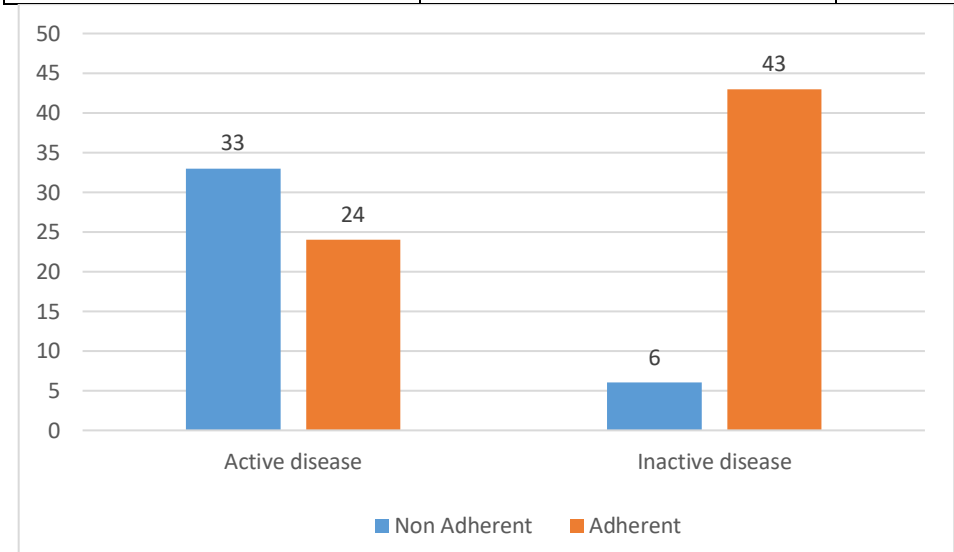


Table 3: Disease activity as assed by SLEDAI 2K

Disease Activity	Frequency	Percentage
Active	57	53.8
Inactive	49	46.2



7.4 Factors associated with disease activity

As shown in table 4 factors affecting disease activity were assessed using bivariate logistic regression and P value < 0.2 was considered significant accordingly four variables; Age, Duration of SLE, comorbidities and MMAS 8 were found to have significant effect on disease activity and these variables were accepted to the multivariable logistic regression (table 5) and out of the four variables only one was statistically significant (P <0.05). Using OR and 95% CI to show association; the odds of active disease in patients with SLE who are non-adherent is 9.86 times higher than those who are adherent to their antimalarial drugs. (AOR 9.86 95% CI 3.61, 26.87).

Table 4: Bivariable analysis of determinants of disease activity

Variables	Disease activity		COR (95%CI)	P value
Age*	Inactive (N= 49)	Active (N= 57)		
15-25	19	19	1.42 (1.06-6.50)	0.12
26-35	19	30	1.81 (1.31-7.22)	0.08
36-45	9	6	1.90 (1.42-8.02)	0.05
>45	2	2	1	
Duration of SLE*				
<1 year	19	5	0.24 (0.07-0.82)	0.02
1-5 years	15	36	1.29 (1.01- 2.04)	0.09
>5 years	15	16	1	
Antimalarial				
CQ 250mg 3x/week	3	3	1.25 (0.15-9.91)	0.83
CQ 250mg 5x/week	33	39	1.47 (0.36-5.95)	0.58
CQ 250mg daily	8	11	1.71 (0.34-8.50)	0.50
HCQ 200mg daily	5	4	1	
Medications				
Antimalarial	24	13	0.32 (0.09-1.09)	0.22
Prednisolone <7.5mg	11	19	1.03 (0.29-3.63)	0.95
Prednisolone ≥7.5mg	2	10	3.00 (0.48-18.6)	0.23
Methotrexate	4	4	0.60 (0.10-3.33)	0.56
Anti-Hypertensive	2	1	0.30 (0.02-4.06)	0.36
Other Immunosuppressant	6	10	1	
Comorbidities *				
No	41	45	0.23 (0.07- 0.96)	0.13
Yes	8	12	1	
MMAS 8*				
Non adherent	6	33	11.01 (3.40-35.59)	0.001
Adherent	43	24	1	

*significant in binary logistic regression; COR crudes odds ratio; CI confidence interval

Table 5: Multivariable analysis of determinants of disease activity

Variables	Disease activity		COR	AOR (95%CI)	P value
Age	Inactive (N=49)	Active (N= 57)			
15-25	19	19	1.42	0.61 (0.04-8.96)	0.16
26-35	19	30	1.81	0.73 (0.05-9.28)	0.10

36-45	9	6	1.90	1.20 (0.92-4.36)	0.11
>45	2	2		1	
Duration of SLE					
<1 year	19	5	0.24	0.22 (0.04-1.09)	0.07
1-5 years	15	36	1.29	1.19 (0.39- 5.04)	0.13
>5 years	15	16		1	
Comorbidities					
No	41	45	0.23	0.18(0.03- 1.02)	0.06
Yes	8	12		1	
MMAS 8***					
Non adherent	6	33	11.01	9.86 (3.61-26.87)	0.001
Adherent	43	24		1	

***very strong significance; COR crudes odd ratio; AOR adjusted odds ratio; CI confidence interval

7.5 Clinical predictors of Non adherence

Clinical and sociodemographic predictors of non-adherence were assessed using bivariate logistic regression with a P value of <0.2 considered significant and none of the variables (Age, educational status, employment, residence, duration of SLE, pill burden, comorbidities and side effects) have a significant association with non-adherence as depicted on table 6. So they could not be included in a multivariable analysis.

Table 6: Bivariable analysis of predictors of non-adherence

Variables	MMAS 8		COR (95% CI)	P value
Age	Nonadherent (N=39)	Adherent (N=67)		
15-25	14	24	0.57(0.05-6.03)	0.64
26-35	19	30	0.52(0.05-5.44)	0.59
36-45	5	10	0.67(0.05-8.16)	0.76
>45	1	3	1	
Educational status				
Primary	8	3	0.79(0.39-2.12)	0.32
High school	7	22	0.23(0.05-1.89)	0.21
University/College	24	42	1	
Employment				
Employed	15	32	2.06(0.73-5.82)	0.27
Unemployed	24	35	1	
Residence				
Urban	37	66	9.47(0.42-21.4)	0.25
Rural	2	1	1	

Duration of SLE				
<1 year	3	21	2.91(0.39-21.54)	0.29
1-5 years	25	26	0.41(0.10-1.63)	0.23
>5 years	11	20	1	
Current number of meds				
1	11	25	1.69(0.20-14.29)	0.63
2	14	27	9.33(0.59-14.94)	0.32
3	10	11	3.65(0.49-27.33)	0.21
4	4	4	1	
Comorbidities				
Yes	30	56	0.64(0.16-2.58)	0.53
No	9	11	1	
Side effects				
Yes	11	11	0.38(0.12-1.22)	0.22
No	28	56	1	

MMAS 8 Morisky medication adherence scale 8; COR crude odds ratio

8. Discussion

A total of 106 people were included in the study out of which 104 were females and 2 males. Females were predominant with a sex ratio of 52:1. Though the ratio is bigger, the female predominance was in line with other studies (1, 5, 9). The mean age was 28.8 SD 8.5 and the majority (more than 80%) of the study population were below the age of 35 which was comparable with other studies (13, 17, 19).

Hydroxychloroquine was used as the primary antimalarial in the majority of the studies (5, 10, 11) while 91.5% of the patients in this study were on Chloroquine. MMAS 8 of less than 6 was used to define non adherence and the rate of non-adherence of antimalarial witnessed in the study was 36.8% which is almost similar to the study done be Amelia et al (36.6%) (43) But is much less than most of the studies (5, 39, 44). The Egyptian study that was taken as a reference to determine the sample size of this study indicated that 51.7% of the patients were non adherent. (14)

A study done in Sweden showed 66.8% of the participants were non adherent and determined that close to 50% of the study population were on five different medications or more and had a strong association with non-adherence (42). Though the association was not studied, more than three quarter of the patients in this study were on three medications or less.

Adamichou et al showed that not being compliant to HCQ, male sex, duration of SLE, and the presence of comorbidities were risk factors for flares and high disease activity. (47) This study was consistent with non-adherence to antimalarial being a predictor for high disease activity even though duration of SLE and comorbidities did not show a significant association with disease activity and male sex was not powered enough to predict association.

Dose and type of antimalarial were not associated with disease activity in this study. This was also reflected in a study done in china which used both the prescribed dose and serum levels of HCQ to correlate with disease activity. Even though there was no association between prescribed doses of HCQ and disease activity, therapeutic serum level of HCQ was a predictor of low disease activity and flare. (30)

Predictors of low disease activity were age, duration of SLE and greater percentage of time taking HCQ while immunosuppressive use was associated with high disease activity in a study done by Babaoglu et al (29) even though greater adherence was associated with low disease activity in this study. Age and duration of SLE were not significantly associated with disease activity. 62.2% of the study participants

were on immunosuppressant including glucocorticoid but none of the medications had significant association with disease activity.

In this study 53.8% of the participants had high disease activity which was comparable with the study done in china (52.1%), UK (54.2%). (5,24). These studies have also stated that having a higher SLEDAI2K score was an independent predictor of non-adherence, even though such associations could not be made from this study.

Various studies have indicated that aside from social and economic factors, clinical characteristics of patients can affect adherence. (40, 42, 44) A Jamaican study has shown that adherence was strongly affected by cost of living and availability of the drugs. (41) Unlike this study, a Swedish and an Egyptian study (42, 44) have shown that factors like age, residence, educational status and pill burden significantly affected adherence. Much like this study disease Amalia et al concluded that duration, pill burden and comorbidities did not have a significant association with adherence, though side effects were found to have a strong association (43) which could not be replicated in this study.

There are some limitations to this study. Due to limited amount of time and finance, the study was only done in a single tertiary center hence it will be difficult to make inferences based on the results. Given the small number of patients studied, the study may not be powered enough. As adherence was assessed using interviewer administered questionnaires, there could have been a response bias and this can overestimate the level of adherence among the study subject and may not be a true representation of what is actually going on. The level of adherence cannot also be ascertained as serum measurement of the drug level was not done and it would have been a far better estimate of adherence. Details regarding lab values of patients including DNA binding and complement level were not found and this information would have been substantial in assessing disease activity more accurately. In addition since this is a cross sectional study it will not show causation rather association of adherence to antimalarial drugs and disease activity.

9. Conclusion

This study shows that in SLE patients, the non-adherence rate to antimalarial drugs is much less as compared to the ones from literatures reviewed and it has also indicated that high adherence to antimalarial drugs is associated with low level disease activity.

10. Recommendation

We must advice patients on strict adherence to these agents, even though the non-adherence rate is less in this study. Though none of the clinical factors were found to be predictors of non-adherence, further study on other clinical, social and economic factors is needed.

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12. Annex

12.1 Participant information sheet and consent

My name is Eden Tesfaye, a final year internal medicine resident at TASH and I would like to seek for your kind assistance in filling out the questionnaire below for a study conducted to assess the level of adherence of antimalarials, its predictors and association to disease activity of SLE.

A data collector will fill in your personal information on the questionnaire. The data will only be accessible to the data collector and principal investigator, if you decide to be included in the study.

You have all the right to choose not to participate in the study and withdraw at any time. If you choose to participate, your personal information will be confidential and your identity will not be exposed. You will not get any personal benefit from the study but the final results of the study will highlight on the most important management issues, identify gaps and suggest interventions to tackle them.

If you are clear with the information above and have agreed to participate In the study, kindly put your signature down below.

12.2: Questionnaire

1. Sociodemographic Status

MRN:

No	Variables	Response
1.1	Age	_____Years
1.2	Sex	1. Male 2.Female
1.3	Educational status	1.Primary 2.Highschool 3. College/university 4. other specify_____
1.4	Employment	1. Yes 2. No
1.5	Marital status	1. Single 2. Married 3. Divorced 4. Widowed
1.6	Religion	1. Muslim 2. Protestant 3. Orthodox 4. Catholic 5. Otherspecify_____
1.7	Residency	2. Urban 2. Rural

2. Clinical factors

Duration of SLE	1. <1 year 2. 1 – 5 years 3. >5 years
Currently used number of medications and mention them	
HCQ/CQ	dose
Lupus nephritis	1.Yes 2.No
Comorbidities	1.Yes 2. No If yes specify
Side effects	1 yes 2 No If Yes specify

3. Morisky medication adherence scale MMAS-8-item

	Yes	No
Do you sometimes forget to take your medication?		
People sometimes miss taking their medications for reasons other than forgetting, over the past 2 weeks were there any days when you did not take your medication?		
Have you ever cut back or stopped taking your medicationwithouttelling your doctor because you felt worse when you took it?		
When you travel or leave home, do you sometime forget to bring your medication with you?		
Did you take all your medication yesterday?		
When you feel like your symptoms are under control do you sometimes stop taking your medication?		
Taking medicationevery day is a real inconvenience for some people. Do you hassle about sticking to your treatment plan?		
How often do you have difficulty remembering to take all your medications?	Never/rarely Once in a while Sometimes Usually All the time	

SLEDAI-2K disease activity assessment

SLEDAI 2K SCORE	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	> 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Urinary casts	Heme-granular or red blood cell casts.
4	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	Proteinuria	>0.5 gram/24 hours
4	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	Rash	Inflammatory type rash.
2	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	Mucosal ulcers	Oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory

2	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	Fever	>38o C. Exclude infectious cause.
1	Thrombocytopenia	<100,000 platelets / x109/L, exclude drug causes.
1	Leukopenia	< 3,000 white blood cells / x109/L, exclude drug causes.
Total score		

2012 SLICC Criteria to diagnose SLE

Requirements for SLE diagnosis are 4 or more (at least 1 clinical and 1 immunologic criteria) or a biopsy proven lupus nephritis with positive ANA or Anti-dsDNA

Clinical criteria	**Immunologic criteria**
Acute cutaneous Lupus (malar rash, bullous lupus, toxic epidermal necrosis)	ANA level above laboratory reference range
Chronic cutaneous lupus (discoid rash, hypertrophic lupus)	Anti-dsDNA level above laboratory reference range
Non scarring alopecia (diffuse hair thinning or fragility)	Anti-sm(presence of antibody to sm nuclear antigen)
Oral or nasal ulcers	
Joint disease (synovitis involving 2 or more joints)	Antiphospholipid antibody positivity
Serositis (pleural or pericardial effusion)	Low complement(low C3,C4)
Renal (24hour urine protein>500mg/24 hour)	Direct coombs test positive in the absence of hemolytic anemia
Neurologic(seizures, psychosis, neuropathy, confusional state)	
Hemolytic Anemia	
Leukopenia(<4000) or Lymphopenia(<1000)	
Thrombocytopenia (<100,000)	