Medication Nonadherence in Rheumatic Diseases

MEDICATION NONADHERENCE IN RHEUMATIC DISEASES

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Abstract

Medication nonadherence is the largest driver of avoidable healthcare costs in the United States. More than 40 percent of patients with rheumatic diseases are nonadherent. Among patients with systemic lupus erythematosus (SLE), adherence to hydroxychloroquine (HCQ), the standard of care medication, is especially poor. This dissertation defined predictors of nonadherence to HCQ among Medicaid beneficiaries with SLE and developed a rheumatology-specific intervention to address adherence-related barriers.

In Paper 1, group-based trajectory models were used to explore longitudinal patterns of HCQ nonadherence among adult SLE patients in Medicaid. Multinomial logistic regression models allowed for the assessment of predictors of nonadherent trajectories compared to the most adherent. In Paper 2, hierarchical multilevel logistic regression models were used to describe the association between area-level sociodemographic variables, health resource concentration and adherence behavior. In Paper 3, an intervention involving a patient navigator- a layperson trained in advocacy, care coordination and basic rheumatology- was designed, implemented and evaluated comparing baseline and post-intervention adherence.

In Papers 1 and 2, we identified more than 10,000 Medicaid beneficiaries with SLE who newly initiated HCQ. A four-group trajectory model provided the best fit for the data with a persistently adherent trajectory (17%), two intermediate trajectories (47%), and a persistently

nonadherent trajectory (36%). A number of factors were associated with nonadherent patterns including black race, Hispanic ethnicity, younger age, increased SLE-related comorbidities and antidepressant medication use. In Paper 2, we added contextual variables and found an association between higher zip code-level percent black and higher odds of nonadherence, after adjusting for individual-level factors. Residing in counties with more hospitals per capita decreased the odds of nonadherence; living in a health professional shortage area increased the odds. In Paper 3, we did not find a significant improvement in medication adherence 6-months following the patient navigator intervention, however medication-related concerns were reduced.

Overall, adherence was poor among Medicaid beneficiaries with SLE. Individual and contextual factors were associated were nonadherence, however there were no dominant predictors that could explain the complexity of the behavior. Additional interventions are needed particularly among the most vulnerable rheumatology patients, to better understand and improve adherence.

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Paper 1

Dynamic Patterns and Predictors of Hydroxychloroquine Nonadherence in a Nationwide Cohort of Medicaid Beneficiaries with Systemic Lupus Eyrthematosus

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Abstract

Background: Hydroxychloroquine (HCQ) is the standard of care medication for most SLE patients, however nonadherence is common. We investigated longitudinal patterns and predictors of nonadherence to HCQ in a U.S. SLE cohort of HCQ initiators.

Methods: We used Medicaid data from 28 states to identify adults 18-65 years with prevalent SLE. We included HCQ initiators following ≥6 months without use, and required ≥1 year of follow-up after first dispensing (index date). We used the proportion of days covered (PDC) to describe overall HCQ adherence (<80%=nonadherent) and group-based trajectory models (GBTM) to examine monthly patterns (<80% of days/month covered=nonadherent), during the first year of use. Multivariable multinomial logistic regression models were used to examine predictors of nonadherence.

Results: We identified 10,406 HCQ initiators with SLE. Mean age was 38 (±12) years, 94% were female, 42% black, 31% white; 85% had a mean PDC <80%. In our 4-group GBTM, 17% were persistent adherers, 36% were persistent nonadherers, and 47% formed two dynamic patterns of partial adherence. Adherence declined for most patients over the first year. Compared to persistent adherers, the odds of nonadherence were increased for blacks and Hispanics vs. whites and for younger ages vs. older; increased SLE-related comorbidities were associated with reduced odds of nonadherence for persistent nonadherers (0.95, 95% CI 0.91-0.99).

Conclusions: In the first year of use, we observed high rates of HCQ nonadherence with three trajectories of increased nonadherence over time. Interventions targeting new users of HCQ are needed to promote sustained adherence during this critical period.

Background

Medication nonadherence is a particularly serious problem among patients with systemic lupus erythematosus (SLE); in past studies, less than half of patients adhere to their SLE-related medications as prescribed.(1) Clinical and epidemiologic factors unique to SLE may increase nonadherence including cognitive and psychological manifestations, a high disease burden among lower socioeconomic status groups, the complexity and toxicity of the medication regimens, and SLE disease activity fluctuations. Hydroxychloroquine (HCQ) is considered the backbone of SLE therapy regardless of disease severity, and it is now standard of care for all SLE patients to take HCQ continuously beginning at the time of diagnosis.(2-4) HCQ use is disease stabilizing and associated with fewer disease flares, reduced disease activity overall and less organ damage accrual.(2, 4-7) Medically indicated discontinuation is uncommon with the exception of evidence of retinal toxicity, which results in most cases from cumulative exposure and occurs in 4-7.5% of patients taking HCQ for 10 years and in <1% during the first 5-7 years.(7, 8)

To date, the majority of studies of HCQ adherence are small, cross-sectional, and based in academic center cohorts. Moreover, they rely on one-time often self-reported measures of adherence failing to capture the dynamic nature of adherence behavior over time. Conflicting results regarding risk factors for nonadherence, and physicians' inability to accurately predict who is likely to nonadhere, make it difficult to know who to target and how to intervene.(9, 10) In addition, most studies to date have included prevalent users of HCQ and therefore conflate potentially different risk factors for nonadherence among patients initiating HCQ and those who have been taking it for years. We therefore aimed to use nationwide data on patients enrolled in Medicaid, the federal-state public health insurance for low-income individuals, to describe

longitudinal patterns and predictors of HCQ adherence among SLE patients newly receiving this medication. To define distinct, dynamic HCQ adherence patterns, we use a well-described but novel method, group-based trajectory models (GBTM). GBTMs have been used in psychology, criminology and sociology to model longitudinal patterns where there are repeated measures available for individuals over time.(11, 12) More recently, they have been applied to clinical research particularly to facilitate causal inference when random assignment to a treatment condition or exposure is not feasible, and to describe disease courses or the evolution of biomarkers over time.(11, 12) In the chronic disease literature, there are a few studies that use GBTM to describe patterns of adherence behavior and the method has been shown to better capture the nuances of adherence over time than standard composite measures such as the proportion of days covered (PDC).(13-16) To our knowledge, GBTMs have not been previously used to describe adherence among patients with SLE. We hypothesized that GBTMs would demonstrate distinct patterns of declining adherence over the first year of use and certain sociodemographic (e.g. young age and black race) and disease-related (e.g. absence of lupus nephritis) characteristics would predict sustained patterns of nonadherence.

Methods

Patient Cohort

We used the Medicaid Analytic eXtract (MAX) from the 29 most populated U.S. states from 2000-2010. HCQ dispensing data were unavailable in MAX for Medicaid beneficiaries living in Ohio and therefore this state was excluded, leaving 28 states in our analysis. MAX includes all billing claims, health care utilization, drug-dispensing data and demographic information for Medicaid beneficiaries. We identified patients aged 18-65 years with $\geq$2

International Classification of Diseases, Ninth Revision (ICD-9) codes for SLE (710.0) from hospital discharge diagnoses of physician visit claims occurring ≥30 days apart, and a dispensing of HCQ within 365 days of an ICD-9 code for SLE. In prior studies using MAX, we required ≥3 ICD-9 codes for SLE however in this study we aimed to increase our ability to capture all patients with new onset SLE who were newly prescribed HCQ and therefore employed ≥2 codes for SLE plus one code for HCQ to accomplish this.(17) This algorithm with ≥2 ICD-9 codes and a related medication has been validated both in the rheumatoid arthritis literature, as well as in electronic health record based analyses among SLE patients with PPVs ranging from 77-89%.(18, 19) In addition, our interest here was HCQ adherence patterns and not SLE-associated outcomes, as it had been for the prior studies.(20, 21) We restricted our cohort to SLE patients with 183 days of continuous enrollment prior to the first dispensing of HCQ (index date) with no use of HCQ during this 183-day period. We then included patients who had ≥365 days of continuous follow-up following the index date. We excluded any individual with no available dispensing data (N=233) and those who were hospitalized for the entire duration of follow-up (N=18). Additionally, we excluded patients who were missing zip code data as median household income was considered a potentially important covariate (N=253).

Adherence Measures

We assessed adherence, our outcome of interest, in two ways. First, we calculated the overall proportion of days covered (PDC) for the 365-day follow-up period beginning at the index date of first HCQ dispensing. We calculated the PDC as the number of days covered divided by 365 days, multiplied by 100. We subtracted hospitalized days from both the numerator and the denominator. In keeping with the prior chronic disease medication adherence literature (22), PDC ≥80% was considered adherent. In addition, we created a 12 -month diary

for each patient where we assigned a binary variable (0 (nonadherent) or 1 (adherent)) for each 30-day period indicating whether that 30-day period had ≥80% coverage (24 of the 30 days) with HCQ. We chose to use 30-day periods because 91% of the new HCQ users in our cohort received a 30-day supply of the medication.

Covariates

We assessed all covariates during the 183-day baseline period prior to and including the index date, unless otherwise specified. Demographic factors included age at the index date, sex, race/ethnicity (White, Black or African American, Hispanic or Latino, Asian (including Native Hawaiian and Pacific Islander), American Indian/Alaska Native, and other), geographic region and state of residence at the index date. We included zip code median household income as a proxy for individual socioeconomic status using American Community Survey data (2006-2010). We assessed comorbidities including venous or pulmonary thromboembolism, pulmonary disease, chronic kidney disease, liver disease, cardiovascular disease, cerebrovascular disease, alcoholism, substance abuse, obesity or cancer/hematologic malignancy using ≥1 ICD-9 codes. For diabetes, we required an ICD-9 code for diabetes or the prescription of a diabetes-related medication. To determine smoking status, we used ≥1 ICD-9 code, CPT code for smoking cessation counseling, or dispensing of smoking cessation-related medications. We used the SLE risk adjustment index, which has been shown to be a better predictor of inpatient mortality among SLE patients than the Charlson comorbidity index, as a measure of SLE-related comorbidities.(23) We determined lupus nephritis using ≥2 ICD-9 hospital discharge diagnosis codes or physician billing claims for nephritis, proteinuria and/or renal failure occurring on or after one SLE diagnosis code.(24) We included antidepressant use as a marker of depression given the low positive predictive value of depression-related claims.(25)

As a marker of disease activity, we included number of laboratory tests for anti-dsDNA, BUN, creatinine, urinalysis and sediment, complement, ESR, and CRP. We included measures of health care utilization (number of emergency department (ED), outpatient visits and hospitalizations, and number hospitalized days), as well as preventive care using CPT codes for influenza and pneumococcal vaccinations and medication codes for pneumocystosis prophylaxis. We assessed the number of other medications filled on the index date of new HCQ use, the dispensing quantity ($\geq$30 days or <30 days), the number of distinct drugs during the baseline period, ever/never use of immunosuppressive medications (methotrexate, sulfasalazine, cyclophosphamide, azathioprine, mycopehnolate mofetil, rituximab, tacrolimus or lefunomide), as well as corticosteroid use (mean daily prednisone-equivalent dose during baseline period), anticoagulant use, nonsteroidal anti-inflammatory medications and selective and non-selective cyclooxygenase-2 inhibitors.

Statistical Methods

We calculated the overall PDC during the 365-day period following the index date. We used our binary indicators of adherence (0, 1) for each 30-day period for the 365 days of follow-up to develop group-based trajectory models (GBTM) in order to classify patients by their HCQ adherence. GBTM has been shown to be the optimal technique for identifying latent longitudinal trajectories.(13, 26) We used "Proc Traj," an add-on package to base SAS (SAS, version 9.4, Cary, NC) to create our GBTMs.

The GBTM estimates multiple regression models at the same time through maximization of a likelihood combining information from all of the models.(13) Multinomial logistic regression with an intercept for each group is used to model the probability of belonging to each potential adherence trajectory as a smooth function of time based on each individual's adherence

pattern over the 365-day period.(13) The GBTM accounts for repeated measures of adherence for each individual and treats them as independent conditional on the trajectory group.(13) Each individual was assigned to the group with the highest probability of membership. GBTM considers missing data to be missing at random and predicts each individual's trajectory membership based on the available information. We assessed linear, quadratic and cubic terms of time to model the probability of being adherent in each group and found that the cubic terms were the best fit for our data.

We estimated trajectory models ranging from 2 to 6 groups. In order to choose the most appropriate model, we considered a number of factors. First we assessed that there were adequate numbers of subjects in each group. We compared model fit using average posterior probability values (>0.8 was considered acceptable) for each group in each model, and compared the overall models using Bayesian information criterion (BIC) with lower BICs being preferable.(27) We aimed for a parsimonious model that balanced model complexity with goodness of fit to best represent our data.

Once we determined the GBTM that best captured our data, we aimed to determine the association between baseline sociodemographic, clinical and health care utilization-related characteristics and the probability of trajectory group membership. To accomplish this, we used multinomial logistic regression models to examine the odds of belonging to a nonadherent trajectory compared to the persistently adherent trajectory for the aforementioned predictors. We included covariates collected during the 183 days prior to the index date, as well as calendar year and state of residence at the index date, in our models.

We conducted additional analyses examining comparisons between two trajectories that started off similar and then diverged approximately 4-5 months after the index date. We updated

baseline covariates to include the period between the original index date of first HCQ dispensing and the fifth month of follow-up and compared characteristics between the groups. We used month 5 as our new index date and we used multivariable logistic regression models to assess predictors of the two trajectories with follow-up beginning at this point through the end of the 365-day period. We also compared healthcare utilization each month between months 4 and month 7 for the two groups.

All analyses were conducted using SAS 9.4 (Cary, NC). Data were obtained from the Centers for Medicare and Medicaid Services (CMS) through a Data Use Agreement and in accordance with CMS policies, all cell sizes <11 are suppressed. The Partners Healthcare Institutional Review Board approved this study.

Results

We identified 10,406 individuals with SLE who were new users of HCQ, had complete HCQ dispensing data, and 365-days of follow-up beginning at the date of HCQ initiation. The mean $\pm$ SD age was 37.8 $\pm$ 11.8 years, 94% were female, 43% were black, 31% white, 19% Hispanic, 4% Asian and 1% American Indian/Alaska Native (**Table 1.1**). During the baseline period, 10% had ICD-9 codes consistent with lupus nephritis, 27% with cardiovascular disease, 29% received an antidepressant medication and 58% received corticosteroids. During the 365-day follow-up period, the overall mean $\pm$ SD PDC was 42% $\pm$ 29; 15% of patients (N=1,575) had a composite PDC $\geq$80%, the cutoff frequently used to characterize adherence. In our cohort, 9% of the patients received >30-day supplies of HCQ.

Table 1.1 Baseline characteristics of new users of HCQ with SLE enrolled in Medicaid	
Baseline characteristics*	**HCQ New Users (N=10,406)**
Age – mean ± SD	37.7 ± 11.8
Age group – N (%)	
18-34 years	4614 (44)
35-50 years	3951 (38)
51-65 years	1841 (18)
Female – N (%)	9800 (94)
Race/ethnicity	
Black	4365 (42)
White	3239 (31)
Hispanic	2047 (19)
Asian	400 (4)
American Indian/Alaska Native	121 (1)
Other	234 (2)
Region	
Northeast	2271 (24)
Midwest	1830 (17)
South	3793 (36)
West	2512 (24)
Median household income^{+} **–** mean ± SD	4.5 ± 1.7
SLE risk adjustment index – mean ± SD	1.0 ± 1.9
Comorbidities- N (%)	
Substance abuse	156 (1)
Alcoholism	57 (1)
Malignancy	236 (2)
Cardiovascular disease	2839 (27)
Cerebrovascular disease	316 (3)
Chronic kidney disease	75 (1)
Diabetes mellitus	990 (9)
Chronic liver disease	345 (3)
Chronic lung disease	1176 (11)
Lupus nephritis	1073 (10)
Obesity	240 (2)
Thromboembolic disease	362 (3)
Smoking	635 (6)
Antidepressant use	3117 (29)
Preventive care – N (%)	
Influenza vaccine	185 (2)
Pneumococcal vaccine	64 (0.6)
Pneumocystosis prophylaxis	937 (9)
Immunosuppressive medication use- N (%)	
Azathioprine	550 (5)
Cyclophosphamide	39 (0.4)
Leflunomide	66 (1)
Methotrexate	618 (6)
Mycophenolate mofetil	385 (4)
Sulfasalazine	88 (1)
Tacrolimus	55 (1)

Table 1.1 (Continued)	
Corticosteroids	
Ever use – N (%)	6138 (58)
Mean daily prednisone-equivalent dose ± SD	2.9 mg ± 17 Median: 0 (0, 3.5)
Mean number of medications – mean ± SD	4.1 ± 3.4
Healthcare utilization	
ED Visits – median (25, 75)	0 (0, 1)
Hospitalizations – Median (25, 75)	0 (0, 1)
Outpatient visits – median (25, 75)	2 (0, 6)
Hospitalized days – mean ± SD	3.9 ± 11
*Determined from the 183 days prior to and including the index date (the date of first HCQ dispensing) +Determined at the zip code level; mean ± SD divided by 10,000	

Group-based Trajectory Model (GBTM)

To understand distinct patterns of nonadherence during the follow-up period, we examined GBTMs with two through six trajectories and found that a four-group model was the best fit for our data (**Figure 1.1**). The posterior probabilities for each of the four trajectories were greater than 0.85, the overall mean ± SD posterior probability was 0.88 ± 0.14, and there was a reasonable sample size in each of the trajectories. The BIC was comparable for this model and the five-group model, however the posterior probabilities and sample size distribution for the trajectories suggested that the four-group model was a better fit.

The four-group model demonstrated four distinct adherence patterns (**Figure 1.1**). Group 1, which includes 38% of the cohort, are persistent nonadherers with few if any refills of HCQ after the initial dispensing. Group 4, which includes 17% of the cohort, are persistent adherers, with, on average, ≥80% of days covered for nearly all months over the course of the year of follow-up with a slightly declining trend from months 10-12. Groups 2 and 3 are intermediate nonadherers and their patterns are more dynamic than groups 1 and 4. The trajectories for Groups 2 and 3 are very similar up until month 5 when their trajectories diverge; Group 3 improves slightly and then reaches a plateau whereas Group 2 becomes nearly completely

nonadherent for the remainder of the follow-up time. With the exception of Group 3, adherence declined by the end of the year of follow-up compared with the first 90-days. For group 1, the overall mean ± SD PDC was 15% ± 10, for group 2, 37% ± 15, for group 3, 57% ± 15, and for group 4, 88% ± 8.

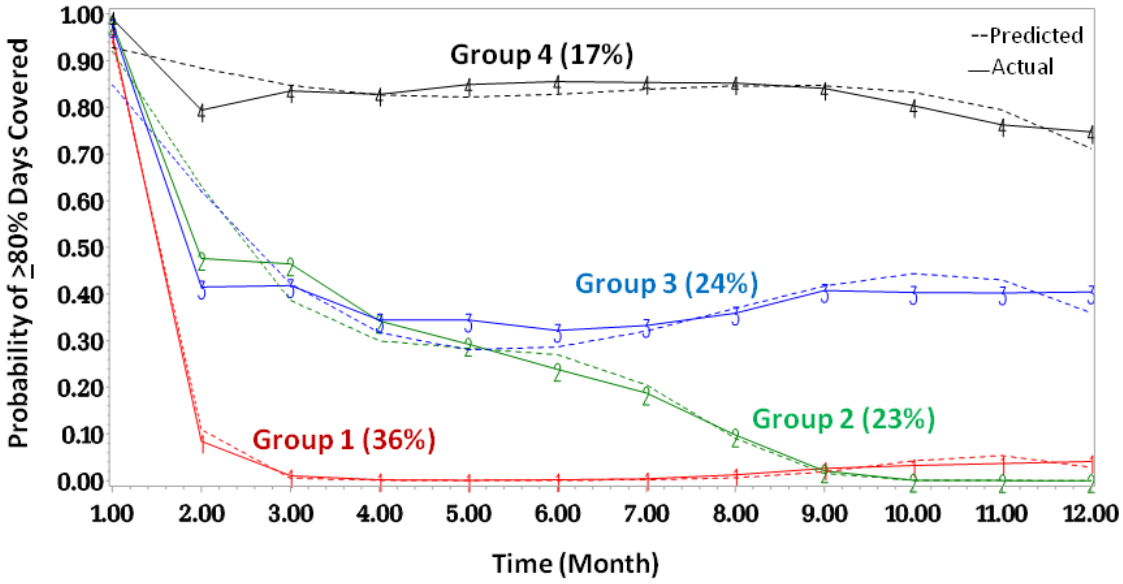

Figure 1.1. Four-group trajectory model of adherence patterns for new HCQ users with SLE; Group 1 are persistent nonadherers, Group 4 are persistent adherers

Baseline characteristics for the four trajectories are presented in **Table 1.2**. The mean age was highest among the persistent adherers (Group 4) and lowest among persistent nonadherers (Group 1) ($p<0.001$). The highest percentage of individuals in Groups 1, 2 and 3 were black compared to Group 4 where the highest percentage of individuals was white. The median household income was similar across groups with slightly higher income among individuals in Group 4 compared to Group 1 ($p=0.01$). The SLE risk adjustment index was highest in Group 4 suggesting a higher burden of SLE-related comorbidities ($p<0.001$). Similarly, the mean number

Table 1.2. Baseline characteristics by trajectory group (N=10,406)

Baseline characteristics	Group 1 (persistent nonadherers)	Group 2 (intermediate nonadherers)	Group 3 (intermediate nonadherers)	Group 4 (persistent adherers)
N (%)	**3772 (36)**	**2431 (23)**	**2481 (24)**	**1722 (17)**
Age – mean ± SD	36.7 ± 11.6	37.1 ± 11.7	37.8 ± 11.8	40.4 ± 12.2
Age group – N (%)				
18-34 years	1808 (48)	1120 (46)	1067 (43)	619 (36)
35-50 years	1388 (37)	923 (38)	975 (39)	665 (39)
51-65 years	576 (15)	388 (16)	439 (18)	438 (25)
Female – N (%)	3568 (95)	2301 (95)	2333 (94)	1598 (93)
Race/ethnicity				
Black	1694 (45)	1069 (44)	1062 (43)	540 (31)
White	1166 (31)	675 (28)	717 (29)	681 (40)
Hispanic	692 (18)	518(21)	513 (21)	324 (19)
Asian	99 (3)	90 (4)	100 (4)	111 (6)
AI/AN	46 (1)	27 (1)	28 (1)	20 (1)
Other	75 (2)	52 (2)	61 (2)	46 (3)
Region				
Northeast	843 (22)	579 (24)	626 (25)	459 (27)
Midwest	627(17)	357 (15)	357 (14)	266 (15)
South	1455 (39)	922 (38)	867 (35)	545 (32)
West	847 (22)	573 (24)	631 (25)	452 (26)
Median household income^{+} – mean ± SD	4.4 ± 1.7	4.5 ± 1.6	4.5 ± 1.7	4.6 ± 1.7
SLE risk adjustment index – mean ± SD	0.9 ± 1.8	1.0 ± 1.8	1.1 ± 2.0	1.3 ± 2.2
Comorbidities- N (%)				
Substance abuse	71 (2)	33 (1)	27 (1)	23 (1)
Alcoholism	23 (1)	11 (0.5)	17 (1)	NR
Malignancy	78 (2)	48 (2)	63 (3)	46 (3)
Cardiovascular disease	942 (25)	658 (27)	709 (29)	509 (30)
Cerebrovascular disease	99 (3)	72 (3)	84 (3)	56 (3)
Chronic kidney disease	27 (1)	15 (1)	20 (8)	11 (1)
Diabetes mellitus	314 (8)	221 (9)	242 (10)	195 (11)
Chronic liver disease	112 (3)	81 (3)	85 (3)	64 (4)

Table 1.2 (Continued)				
Chronic lung disease	402 (11)	299 (12)	269 (11)	197 (11)
Lupus nephritis	366 (10)	244 (10)	252 (10)	197 (11)
Obesity	90 (2)	45 (2)	62 (2)	43 (2)
Thromboembolic disease	109 (3)	84 (3)	84 (3)	82 (5)
Smoking	215 (6)	149 (6)	148 (6)	115 (7)
Antidepressant use	1045 (28)	739 (30)	685 (28)	550 (32)
Preventive care – N (%)				
Influenza vaccine	66 (2)	32 (1)	48 (2)	38 (2)
Pneumococcal vaccine	22 (1)	11 (0.5)	17 (1)	14 (1)
Pneumocystosis prophylaxis	319 (8)	215 (9)	224 (9)	159 (9)
Immunosuppressive medication use- N (%)				
Azathioprine	160 (4)	107 (4)	151 (6)	122 (7)
Cyclophosphamide	11 (0.3)	NR	NR	NR
Leflunomide	20 (0.5)	15 (1)	11 (0.4)	20 (1)
Methotrexate	205 (5)	138 (6)	156 (6)	103 (6)
Mycophenolate mofetil	122 (3)	87 (4)	99 (4)	70 (4)
Sulfasalazine	34 (1)	19 (8)	20 (8)	15 (1)
Tacrolimus	18 (0.5)	13 (1)	NR	15 (1)
Corticosteroids				
Ever use – N (%)	2108 (56)	1475 (61)	1521 (61)	1056 (61)
Mean daily prednisone-equivalent dose ± SD	2.5mg ± 5.8 Median 0 (0, 2.4)	2.9mg ± 6.5 Median 0 (0, 2.9)	2.8mg ± 6.0 Median 0 (0, 3)	4mg ± 40 Median 0 (0, 3.3)
HCQ Prescription ≤30 days- N (%)	3557 (94)	2131 (88)	2270 (91)	1490 (87)
Mean number of medications – mean ± SD	3.7 ± 3.2	4.2 ± 3.4	4.2 ± 3.3	5.3 ± 3.9
Healthcare utilization				
ED Visits – median (25, 75)	0 (0, 1) Mean 0.96 ± 2.4	0 (0, 1) Mean 0.91 ± 2.0	0 (0, 1) Mean 0.82 ± 1.9	0 (0, 1) Mean 0.76 ± 1.9

Table 1.2 (Continued)				
Inpatient – median (25, 75)	0 (0, 1) Mean 0.57 ± 1.1	0 (0, 1) Mean 0.60 ± 1.2	0 (0, 1) Mean 0.60 ± 1.1	0 (0, 1) Mean 0.61 ± 1.2
Outpatient– median (25, 75)	2 (0, 6) Mean 3.9 ± 4.8	2 (0, 6) Mean 3.9 ± 4.9	2 (0, 6) Mean 3.7± 4.8	2 (0,7) Mean 4.0 ± 5.0
Hospitalized days – mean ± SD	3.5 ± 9.5	4.2 ± 12.7	3.9 ± 10.0	4.3 ± 11.0

of medications dispensed ($p<0.001$) and the mean daily prednisone-equivalent dose were both higher in Group 4 compared to Group 1 suggesting a more ill population ($p<0.001$).

Trajectory Predictors

We estimated multinomial logistic regression models to examine predictors of the different trajectories with Group 4 (persistent adherers) as the reference. We found increased odds of belonging to all three nonadherent trajectories for individuals aged 18-34 years and 35-50 years, compared to those 51-65 years **(Table 1.3**). We similarly found increased odds of belonging to Groups 1, 2 or 3 compared to Group 4 associated with black race and Hispanic ethnicity, compared to white. We found reduced odds (OR 0.64, 95% CI 0.47-0.88) of belonging to Group 1 vs. Group 4 (persistent adherers) among Asians compared to whites. We did not find statistically significant associations with median household income (at the ZIP code level) or geographic region.

In terms of comorbidities, we found increased odds of belonging to Group 1 (persistent nonadherers) vs. 4 (persistent adherers) associated with diabetes (OR 1.25, 95% CI 1.01-1.56) and decreased odds for each unit increase in the SLE risk adjustment index (0.95, 95% CI 0.91-0.99). There were reduced odds of belonging to Group 3 vs. 4 associated with lupus nephritis (OR 0.71, 95%CI 0.53-0.96). The odds of belonging to nonadherent Groups 1,2 and 3 vs. Group 4 were inversely related to the total number of medications filled. There was also a reduced odds of belonging to Group 1 vs. 4 associated with corticosteroid use (vs. non-use), OR 0.87, 95% CI 0.76-0.97. There were increased odds of belonging to nonadherent Groups 1 and 2 vs. 4 associated with antidepressant use.

We used multivariable logistic regression to examine predictors of belonging to Group 2 vs. Group 3 beginning at month 5, the point at which the curves diverged and Group 2 became

Table 1.3. Multinomial logistic regression model of the odds of being in the Group 1 (persistent nonadherers), Group 2 or 3 (intermediate nonadherers) trajectories compared with being in the Group 4 trajectory (persistent adherers, reference)

Baseline characteristics N=10,406	**Group 1 (persistent nonadherers) OR (95% CI)**	**Group 2 (intermediate nonadherers) OR (95% CI)**	**Group 3 (intermediate nonadherers) OR (95% CI)**
Age group			
18-34 years	**1.66 (1.39-1.98)**	**1.66 (1.38-2.01)**	**1.41 (1.17-1.71)**
35-50 years	**1.33 (1.13-1.57)**	**1.38 (1.16-1.65)**	**1.32 (1.11-1.57)**
51-65 years	*Ref.*	*Ref.*	*Ref.*
Male (Female = ref)	0.87 (0.68-1.10)	0.85 (0.65-1.11)	0.88 (0.68-1.14)
Race/ethnicity			
White	*Ref.*	*Ref.*	*Ref.*
Black	**1.74 (1.49-2.04)**	**1.95 (1.64-2.31)**	**1.81 (1.53-2.14)**
Hispanic	**1.40 (1.16-1.68)**	**1.66 (1.36-2.02)**	**1.51 (1.24-1.83)**
Asian	**0.64 (0.47-0.88)**	0.92 (0.67-1.27)	0.86 (0.63-1.17)
AI/AN	1.05 (0.60-1.83)	1.15 (0.62-2.12)	1.12 (0.61-2.02)
Median household income	0.99 (0.96-1.03)	1.01 (0.96-1.05)	1.00 (0.96-1.04)
SLE risk adjustment index	**0.95 (0.91-0.99)**	**0.96 (0.92-1.00)**	0.99 (0.95-1.03)
Diabetes mellitus	**1.25 (1.01-1.56)**	1.17 (0.93-1.49)	1.18 (0.94-1.48)
Lupus nephritis	1.06 (0.80-1.41)	0.90 (0.66-1.22)	**0.71 (0.53-0.96)**
Antidepressant use (Never=ref)	**1.18 (1.02-1.36)**	**1.30 (1.12-1.52)**	1.11 (0.95-1.29)
Corticosteroids use (Never=ref) Text	**0.87 (0.76-1.00)**	0.99 (0.86-1.14)	1.07 (0.93-1.23)
Number of medications	**0.90 (0.88-0.91)**	**0.94 (0.92-0.96)**	**0.92 (0.90-0.94)**
Healthcare utilization			
ED Visits	**1.05 (1.01-1.08)**	1.03 (0.99-1.07)	1.02 (0.98-1.06)
Hospitalizations	**1.12 (1.03-1.22)**	1.05 (0.96-1.14)	1.06 (0.97-1.16)
Outpatient visits	1.00 (0.98-1.01)	0.99 (0.97-1.01)	1.00 (0.98-1.01)

Model additionally adjusted for U.S. state, geographic region, calendar year at index date, index date HCQ dispensing amount, laboratory tests, pain medications, preventive care (influenza vaccine, pneumococcal vaccine, pneumocystosis prophylaxis), immunosuppressive medication use, comorbidities (substance abuse, alcoholism, malignancy, cardiovascular disease, cerebrovascular disease, chronic kidney disease, obesity, thromboembolic disease, chronic lung disease, smoking), and mean daily corticosteroid dose. All variables were determined during the 183 days prior to and including the index date. Group 4 (persistent adherers) is there reference.

nearly completely nonadherent while Group 3 plateaued (**Table 1.4**). We included the same baseline variables as above and additionally updated them to include data from months 1-4. We

Table 1.4. Multivariable logistic regression model comparing Group 2 (N=2431, declining adherence) to Group 3 (N=2481, plateaued adherence, reference) at the point of divergence

Predictors*	**Group 2** **Odds Ratio (95% CI)**
Age group	
18-34 years	1.07 (0.89-1.29)
35-50 years	1.03 (0.89-1.22)
51-65 years	*Ref*
Male (Female = ref)	0.93 (0.72-1.20)
Race/ethnicity	
White	*Ref*
Black	1.09 (0.93-1.27)
Hispanic	1.10 (0.91-1.32)
Asian	1.08 (0.78-1.50)
AI/AN	1.14 (0.64-2.02)
Median household income	1.00 (0.96-1.04)
SLE risk adjustment index	0.99 (0.95-1.03)
Diabetes mellitus	1.14 (0.94-1.39)
Lupus nephritis	1.03 (0.85-1.25)
Antidepressant use (Never=ref)	**1.25 (1.10-1.43)**
Corticosteroids use (Never=ref)	0.97 (0.84-1.11)
Number of medications	**0.93 (0.91-0.95)**
Healthcare utilization	
ED Visits	1.01 (0.99-1.03)
Hospitalizations	1.02 (0.92-1.13)
Outpatient visits	1.00 (1.00-1.01)
Number of Laboratory tests	
ESR	1.08 (0.99-1.17)
BUN	**1.15 (1.01-1.32)**
Creatinine	0.96 (0.88-1.06)
Complement (C3 or C4)	0.98 (0.90-1.08)

*Predictors from 6 months prior to first HCQ dispensing and updated through month 4 of follow-up; nonadherence patterns assessed from months 5 through 12.
**Group 3 is the reference. Model is additionally adjusted for U.S. state, geographic region, calendar year at index date, index date HCQ dispensing amount, additional laboratory tests, pain medications, preventive care (influenza vaccine, pneumococcal vaccine, pneumocystosis prophylaxis), immunosuppressive medication use, comorbidities (substance abuse, alcoholism, malignancy, cardiovascular disease, cerebrovascular disease, chronic kidney disease, obesity, thromboembolic disease, chronic lung disease, smoking), and mean daily corticosteroid dose.

found increased odds of belonging to Group 2 associated with the use of antidepressants (OR 1.25, 95% CI 1.10-1.43) and with increased numbers of certain laboratory tests (BUN). We

found a modestly reduced odds of belonging to Group 2 vs. 3 associated with increased number of medications (OR 0.93, 95% CI 0.91-0.95). We did not find statistically significant associations with demographic factors such as age or race/ethnicity, with immunosuppressive use, or with health care utilization. We examined health care utilization separately by month for months 4 through 7 (**Table 1.5**) and found that beginning at month 4, patients in Group 3 had more inpatient visits, and beginning at month 5, longer hospitalizations compared to those in Group 2. We observed a trend towards more outpatient visits for Group 3 compared to Group 2 for months 6 and 7.

Table 1.5. Healthcare utilization for Group 2 (N=2431, declining adherence) and Group 3 (N= 2481, plateaued adherence) in months 4-7

Healthcare utilization	**Month 4**		**Month 5**		**Month 6**		**Month 7**	
	Group 2	Group 3	Group 2	Group 3	Group 2	Group 3	Group 2	Group 3
Outpatient visits- mean ± SD	8.4 ± 7.0	8.4 ± 6.8	9.3 ± 7.6	9.3 ± 7.5	10.1 ±8.2	10.2 ± 8.1	10.9 ± 8.7	11.1 ± 8.7
ED visits- mean ± SD	1.9 ± 3.5	1.8 ± 3.5	2.1 ± 3.7	2.0 ± 3.8	2.3 ± 4.0	2.2 ± 4.0	2.4 ± 4.2	2.4 ± 4.4
Inpatient visits- mean ± SD	**0.25 ±1.0**	**0.29 ± 1.0**	**0.26 ± 1.0**	**0.32 ± 1.1**	**0.28 ± 1.1**	**0.34 ± 1.2**	**0.31 ± 1.1**	**0.37 ± 1.3**
Hospitalized days- mean ± SD	1.6 ± 8.0	1.9 ± 7.8	**1.7 ± 8.3**	**2.1 ± 8.7**	**1.9 ± 8.6**	**2.3 ± 9.9**	**2.1 ± 9.5**	**2.4 ±10.5**
Bolded values indicate statistically significant difference ($p<0.05$) comparing groups 2 and 3 within the month								

Discussion

In this longitudinal study of Medicaid beneficiaries with SLE, we found that adherence among HCQ initiators was poor starting one month after the first dispensing, and for the majority of patients, adherence declined over the first year of use. While prior studies demonstrate that adherence among SLE patients is suboptimal, we have shown in this study as well as in prior work, that adherence among SLE patients enrolled in Medicaid is profoundly poor.(10, 28, 29)

Our model revealed a group of persistent nonadherers, which comprised 36% of our cohort, who had very few HCQ refills after the initial dispensing. We identified a small group of persistent adherers (Group 4, 17%), although even this group experienced a downward trend in adherence beginning at 9-10 months.

In contrast to prior studies, which either measure adherence cross-sectionally or using a composite measure, we were able to explore the nuances of adherence patterns over the first year of use, which was especially relevant for the intermediate nonadherers (Groups 2 and 3). We found that using the PDC, a commonly used composite measure, we would have misclassified 142 patients with nonadherent patterns as adherent and 274 patients with persistently adherent patterns as nonadherent. We found that the 5-month mark represented a critical juncture that may represent a clinical opportunity to intervene before adherence worsens among these "undecided" groups. We found that patients who plateau in terms of their adherence (Group 3) had more and longer hospitalizations suggesting both that they were more seriously ill, and that they likely had more interactions with the healthcare system to have their medications renewed. We also observed a trend towards more outpatient visits in this group suggesting that sustained access to outpatient care may increase the likelihood a patient continues the medication he/she is prescribed. Five months might also be the point at which patients feel that they have adequately trialed the medication if there is no symptomatic improvement, they discontinue. Heightened education at this time about the potential preventive effects of this medication even in the absence of clear tangible effects may be beneficial. (2-4, 6, 7, 30)

Interestingly, we did not find many strong predictors within our available set of covariates that were significantly associated with declining adherence (Group 2) versus plateaued adherence (Group 3) at 5 months. We did not find an association with demographic

factors which suggests that while age and race/ethnicity might contribute initially to who is likely to be a persistent adherer or nonadherent, these factors may not play an important role in determining who continues to be modestly adherent versus who discontinues after an initial period of time. We did find an association with increased antidepressant use among those with declining adherence. Prior studies similarly show depression as a risk factor for poorer adherence and it is possible that among patients with depression the threshold to discontinue a medication that they may not see a tangible benefit after a period of time may be lower.(31)

In order to investigate whether patterns of adherence are distinct by drug, we have separately used group-based trajectory models to examine adherence to azathioprine and mycophenolate mofetil also within the Medicaid SLE population.(32) Interestingly, while we similarly noted poor nonadherence to both drugs, we found that each drug had a distinct pattern of adherence that differed from that of HCQ. While both drugs had subsets of the population who were persistent adherers and persistent nonadherers, the paths of the intermediate nonadherers were distinct. This suggests that while there may be certain patients who will adhere or will not adhere consistently, for those in a more "undecided" category, characteristics of the drug itself, such as side effect profile, may play a role in adherence behavior. In addition, the patients receiving azathioprine and mycophenolate mofetil are likely sicker than those receiving HCQ, and this, as well as ongoing disease activity, may also contribute differently to adherence behavior over time.

Previous studies have highlighted a number of potential predictors for nonadherence including black race, increased comorbidities, low educational attainment, depression and polypharmacy.(31, 33, 34) We found that younger age, Black race, Hispanic ethnicity, and antidepressant medication use increased the odds of nonadherence. However, in our cohort,

corticosteroid use, increased polypharmacy and higher SLE risk adjustment index scores, all associated with increased SLE severity, reduced the odds of persistent nonadherence. Based on the low percentage of patients using other immunosuppressive medications, and the overall low mean SLE risk adjustment index, many of the patients in this cohort have mild to moderate SLE. Our findings suggest that patients who may have more active and severe SLE may be more likely to adhere to their HCQ. It is possible that among patients with milder SLE, while it is the standard of care to continue HCQ in all SLE patients, the patients or physicians may have felt the medication was unnecessary to continue.

There were a number of limitations to this work. First, we used dispensing data to infer adherence however, filling a medication does not guarantee that a medication was taken. While 91% of our cohort received a 30 day or less supply of HCQ, the small subset receiving 60 or 90-day supplies may appear adherent for longer than they were. We did however conduct a sensitivity analyses looking specifically at this group and found similar trajectory patterns but the declines in adherence, as would be expected, started 2-3 month later than in our primary model. The mean $\pm$ SD PDC for the 91% with 30 day or less HCQ prescriptions was 41% $\pm$ 29%, very much the same as our full cohort. We also used a monthly cutoff of $\geq$80% (24 of 30 days covered) to classify a patient as adherent in keeping with prior chronic disease studies. However, this threshold is somewhat arbitrary and it is unclear if there is a difference in clinical outcomes associated with higher or lower levels of adherence. In addition, while we feel that medically indicated discontinuation within the first year of use of HCQ is uncommon, it is certainly possible that patients stopped their medication because they were told to do so by their physician and we cannot distinguish this from nonadherence using claims data alone. Similarly, the claims-based definition we used to identify SLE patients may have identified individuals with "probable

SLE" as well, as these early undifferentiated patients are often prescribed HCQ. However, as HCQ is most often the initial medication prescribed for SLE, we aimed to understand use in that first year. Since HCQ is considered the backbone of care for patients with SLE, and is continued during pregnancy, it is unlikely to be stopped because it is ineffective or contraindicated, however, side effects such as gastrointestinal upset, may preclude its use. In addition, the use of claims data limits our ability to understand SLE disease activity, which may parallel adherence patterns. We did account for predictors that are markers of SLE disease activity and severity such as the SLE risk adjustment index, medication use (corticosteroid dose and immunosuppressive medications), and comorbidities such as lupus nephritis.

The Medicaid population is a high-risk, vulnerable population with a high burden of comorbidities and adverse outcomes. Therefore, while it is an important population to study, findings might not be broadly generalizable as nonadherence is likely higher in this population. It is possible that there may be misclassification, particularly of comorbidities, since primarily ICD-9 codes alone were used for identification. It is also possible that there are important predictors, such as individual-level socioeconomic status, which are not available in Medicaid claims data but may play a significant role in adherence behavior.

This work also has a number of strengths. We included a large non-academic cohort of HCQ initiators with SLE and used a well-established method not previously applied to SLE medication use that enabled us to understand patterns of adherence over the first year of use. Our patient population was racially and ethnically diverse and 28 U.S. states were represented and we adjusted our analyses by state in order to account for potential differences in Medicaid enrollment and drug policies. Adherence was measured longitudinally rather than cross-sectionally as it has been done in most prior SLE-related studies, and therefore was able to

capture the changes in adherence over time. We restricted our cohort to HCQ initiators and therefore did not conflate patterns and risk factors among patients receiving this medication for years with those for whom it was newly prescribed. In addition, rather than using a long-term average measure alone, such as the PDC, as most prior claims-based studies do, we used month-by-month measures which have been shown to better represent the nuances of adherence behaviors.(13) While we found a similar percentage formed the persistently adherent trajectory (17%) as were classified as adherent using the PDC composite measure (15%), we were able to delve into predictors of different patterns of nonadherence. Notably, we were able to understand certain factors that contributed to individuals trending from intermediate to complete nonadherence, which has the potential to inform strategies physicians take to counsel patients and identify the most vulnerable groups.

Overall, our study demonstrated that HCQ adherence is a dynamic behavior that declines over the first year of use. While claims data do not allow us to understand the reasons for nonadherence, it is clear from our findings that the majority of patients prescribed HCQ are not taking the medication as prescribed often beginning the month after first dispensing. Potentially modifiable factors, such as improving sustained access to healthcare not only for those who are more severely ill, might prevent intermediate nonadherers, or “undecided” patients from moving towards increasingly nonadherent pathways. In addition, with the knowledge of the extremely poor adherence among this especially vulnerable patient population, increased counseling and support programs both at the time of first HCQ prescription and throughout the first year of use, are needed to promote more sustained patterns of adherence for all patients.

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Paper 2

Effects of Contextual Factors on Medication Adherence among Patients with Systemic Lupus Erythematosus: A Multilevel Analysis

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Abstract

Background: Adherence to hydroxychloroquine (HCQ) among patients with systemic lupus erythematous (SLE), is suboptimal. Individual-level factors including younger age and non-White race/ethnicity have been implicated however contextual factors have not been explored.

Methods: We identified SLE patients enrolled in Medicaid (2000-2010) from 28 U.S. states who were new users of HCQ (no use in ≥6 months). We required 12 months of continuous enrollment with complete dispensing data and assessed 12-month adherence using the proportion of days covered (PDC). We identified individual-level variables from Medicaid, contextual sociodemographic variables from the American Community Survey and health resources from the Area Health Resources File. We used 4-level hierarchical multivariable logistic regression models to examine the odds (OR (95% Credible Interval)) of adherence (PDC ≥80%) vs. nonadherence.

Results: Among 10,268 new users of HCQ with SLE, 15% were adherent. After adjusting for individual-level characteristics, we observed reduced odds of adherence in zip codes with higher percentages of African Americans (second tertile OR 0.84 (0.73-0.98), third tertile OR 0.81 (0.68-0.96), vs. lowest). This remained consistent after controlling for zip code poverty and education. Odds of adherence were higher in counties with the greatest number of hospitals vs. the fewest (OR 1.32 (1.08-1.60)), and lower in health professional shortage areas (OR 0.86 (0.75-1.00)). There was minimal variation in adherence by area; the greatest was between states (1.4%).

Conclusions: Among Medicaid beneficiaries with SLE, after adjusting for individual-level factors, we observed significant effects of zip code racial composition and certain area health resources on HCQ adherence.

Background

Nonadherence to medications for chronic diseases is a common occurrence and a complex behavior. (1) It is clear from the growing literature to date that identification of those at high risk for nonadherence is frequently unpredictable, and that simple targeted interventions may not be beneficial. One paradigm to understand medication adherence describes the interplay between patient, health provider and health system factors.(1) The majority of adherence-related studies focus on the contribution of patient characteristics including sociodemographic factors, health care utilization, and comorbidities. Fewer studies have additionally examined the influence of interpersonal relationships such as social support and patient-physician relationships.(2) Despite the increased awareness of the central importance of social determinants- social, environmental and economic conditions and neighborhood characteristics - on health behaviors and outcomes, few studies have examined their relationship with medication adherence.(3-5)

We focused our study on the role of contextual factors on adherence among patients with systemic lupus erythematosus (SLE). SLE is a multisystem autoimmune disease that disproportionately affects racial/ethnic minorities and individuals from lower socioeconomic status areas.(6-9) The majority of studies to date demonstrate the highest burden of SLE-related adverse outcomes including end-stage renal disease, cardiovascular disease, and mortality among African American individuals.(10-12) In prior work we demonstrated increased rates of medication nonadherence and associated increased acute care utilization among African American patients with SLE.(13) Most studies to date however do not investigate the potential role that area-level social determinants play on the racial/ethnic and socioeconomic (SES) disparities observed in SLE. One prior study demonstrated an independent effect of

neighborhood poverty on accumulation of SLE-specific damage after accounting for individual-level characteristics.(14) Despite calls in the literature to address this further, the effect of contextual factors on SLE disparities in general, and on medication adherence specifically, remains underexplored.(15) We therefore aimed to investigate the effect of zip code, county and state-level factors including racial composition, area poverty, educational attainment and area health professional resources, on medication adherence after adjusting for patient-level characteristics. We focused on adherence to hydroxychloroquine (HCQ) as it is considered to be the standard of care therapy both for active treatment and for prevention of complications for nearly all patients with SLE, most for the full course of their disease.(16) Medically indicated discontinuation of HCQ for adverse events is rare, particularly in the first year of use.

Based on McLeroy's social ecological model, we hypothesized that factors at the individual (intrapersonal), the interpersonal, the community/institutional and the macro level influence HCQ adherence behavior among SLE patients (**Figure 2.1**).(17) We focused our study on SLE patients enrolled in Medicaid, the federal-state public insurance for low-income individuals. While our use of Medicaid administrative data limited our selection of individual and contextual characteristics, we felt that this was a particularly important, vulnerable population to study given the high burden of SLE-related medication nonadherence and adverse outcomes. At the individual patient level, we hypothesized that black race and Hispanic ethnicity, younger age, and antidepressant medication use will be associated with nonadherence. At the community/institutional level, we hypothesized that after adjusting for individual-level factors, neighborhood characteristics including racial composition and concentrated area poverty might lead to poorer adherence through mechanisms such as neighborhood safety limiting access to care and pharmacies or exposure to environmental and social stressors.(18) We felt that higher

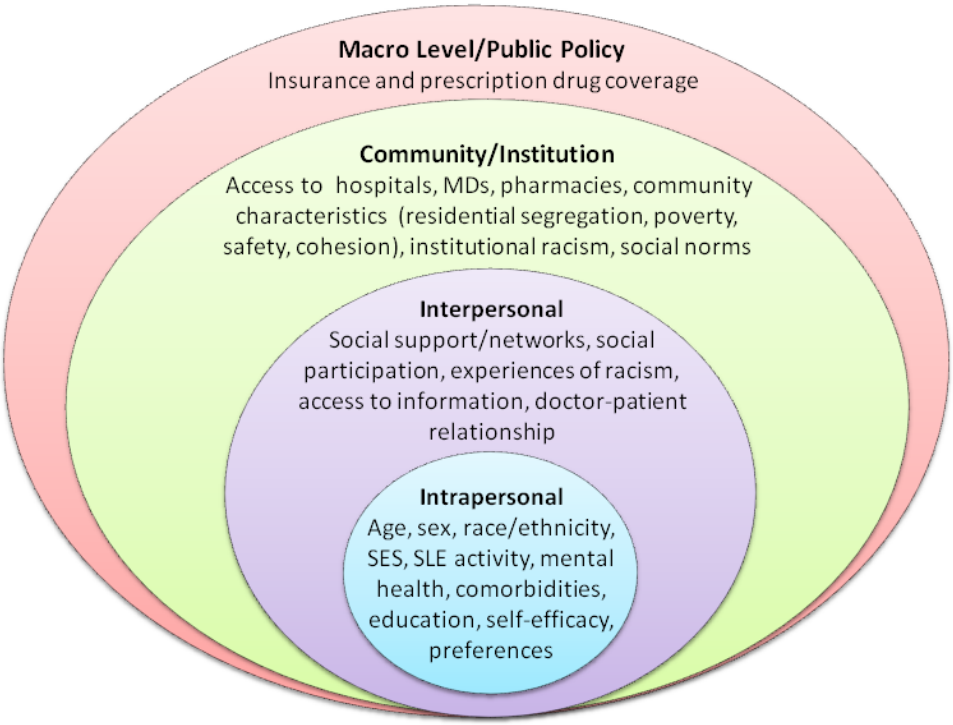

Figure 2.1. Social ecological model adapted to demonstrate potential multilevel contributors to adherence behavior among patients with SLE

area levels of educational attainment might contribute to a more health literate community resulting in healthier behaviors including better adherence. We also hypothesized that fewer area-level health resources would be associated with poorer adherence. At the macro-level, we hypothesized that we would observe between state variability in adherence due to differences in Medicaid eligibility across states. While we suspected that interpersonal factors such as stronger patient-physician relationships and increased social support might be associated with higher rates of adherence, we did not have access to these measures.

Methods

Patient Population

We used data from the Medicaid Analytic eXtract (MAX) for the 29 most populated U.S. states from 2000-2010 with pharmacy drug dispensing data, billing claims and health care utilization for all Medicaid beneficiaries. We identified patients aged 18-65 years with prevalent SLE, defined as ≥2 International Classification of Diseases, Ninth Revision (ICD-9) codes for SLE (710.0) from hospital discharge diagnoses of physician visit claims occurring ≥30 days apart, and dispensing of HCQ within 365 days of a SLE ICD-9 code. We restricted our cohort to new users of HCQ, which we defined as 183 days of continuous enrollment prior to the first dispensing of HCQ (index date) with no use of HCQ during this time. We then required ≥365 days of continuous enrollment in Medicaid following the index date to assess adherence after HCQ initiation. We excluded patients if dispensing data were either partially (N=92) or entirely (N= 241) missing during the follow-up period. Ohio did not contribute dispensing data to MAX during this time period and therefore we excluded all patients from this state (N=388). We also excluded patients who were hospitalized for the entire 365-day period following the index date (N=18), those without zip codes reported (N=253), and those with zip codes that were discordant with their states of residence (N=46).

Outcome: Adherence

We defined adherence using the proportion of days covered (PDC) for the 365-day period beginning at the index date of first HCQ dispensing. The PDC was determined from drug dispensing data in MAX and calculated as the number of days covered divided by 365 days, multiplied by 100. We subtracted hospitalized days from both the numerator and the denominator. We used a PDC threshold of ≥80% to define adherence (19) and our outcome for all of our models compared adherence (PDC ≥80%) to nonadherence (PDC <80%, referent group).

Individual-Level Covariates

We used MAX data to identify all individual-level covariates in the 183-day period prior to and including the index date of first HCQ dispensing. We included age (18-34 years, 35-50 years and 51-65 years) sex (male, female) and race/ethnicity (White, Black or African American, Hispanic or Latino, Asian (including Native Hawaiian and Pacific Islander), American Indian/Alaska Native (AI/AN), and other). We included SLE-related comorbidities using the SLE risk adjustment index, which has been shown to be a better predictor of mortality among SLE patients than the Charlson comorbidity index.(20) We separately assed lupus nephritis using ≥2 ICD-9 hospital discharge diagnosis codes or physician billing claims for nephritis, proteinuria and/or renal failure occurring on or after one SLE diagnosis code. (21) We included diabetes using an ICD-9 code for diabetes or the prescription of a diabetes-related medication, because we found this to significantly contribute to adherence behavior among Medicaid beneficiaries our prior work.(22) We included antidepressant use as a marker of depression given the low positive predictive value of depression-related claims.(23) We tested other comorbidities as well (cardiovascular disease, liver disease, pulmonary disease, cerebrovascular disease, cancer) and did not find significant associations with adherence, or meaningful differences in our other point estimates and therefore we did not include these in our final models.

We assessed preventive care using CPT codes for influenza and pneumococcal vaccinations and medication (NDC) codes for pneumocystosis prophylaxis. We additionally assessed obesity with ≥1 ICD-9 code and smoking status using ≥1 ICD-9 code, CPT code for smoking cessation counseling or dispensing of smoking cessation-related medications, as markers of health status and behaviors that might be associated with adherence. As markers of SLE disease activity and also healthcare utilization, we assessed number of laboratory tests for

anti-dsDNA, renal function, urinalysis and sediment, complement (C3 and C4), and inflammation (ESR and CRP). We also measured healthcare utilization during the baseline period using number of ED visits, hospitalizations and outpatient visits, as well as the number of hospitalized days. We included number of overall medications, as well as use of corticosteroids and other immunosuppressive medications (azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, sulfasalzine, tacrolimus). Individual-level socioeconomic status measures (e.g. income, education, occupation) are not available in MAX.

Contextual Covariates

We determined zip code, county and state of residence for each individual from MAX. MAX data are de-identified and as such, zip code is the smallest geographic area available; individual addresses are not available. Using American Community Survey (ACS) data (2006-2010), we determined zip code, county and state-level percent of the population in each area with incomes below the federal poverty level (FPL) and the percent black.(24, 25) We also assessed educational attainment at the zip code and county level. Due to very small numbers of individuals within each area who were not high school graduates, our three composite categories were high school graduate or less, some college, and college graduate and above. We also used the ACS data to determine the state-level Gini coefficient, a marker of income inequality ranging from 0-1, where 1 represents the greatest inequality. We used the mean of US Census data from 2000 and 2010 to determine percent urban for each county.

To determine zip and county level concentrations of health services and health professionals, we used the Area Health Resources Files (ARHF) from 2000 and 2010.(26, 27) The total number of physicians and total number of medicine subspecialists were derived from the American Medical Association files, divided by each county's population size, per 1,000

individuals. The total number of hospitals, similarly divided by county population size per 1,000 individuals, was from the Health Resources and Services Administration (HRSA). We compared the means for each variable from 2000 and 2010 and they were similar and we chose to use the overall mean of the 2000 and 2010 data for our analyses. We determined the total number of licensed pharmacists, divided by county population size per 1,000 individuals from the mean of 2000 and 2009 data available from the National Center for the Analysis of Healthcare Data (NCAHD) within the ARHF.(27) These data were obtained by NCAHD from the state licensure boards and include pharmacists with a current license residing within the state of licensure. There were 52 counties (4%) without reported pharmacist data. We also obtained the primary care provider Health Professional Shortage Area (HPSA) designation of none, partial and whole for each county from HRSA.(28) These HPSA designations are characterized by shortages of providers that may be geographic (the entire county), for a population group (i.e. for low-income individuals within the county), or of facilities that lack health providers (medical or mental health or correctional) within an area.(28) We obtained number of rheumatologists per state from the American College of Rheumatology for 2000, and divided this by each state's population size determined from the US Census (2000), per 10,000 individuals. With the exception of the HPSA and educational attainment, which were already in three groups, we opted to examine our contextual variables in tertiles with the lowest tertile as the reference, to facilitate interpretability and to be consistent across levels.

Statistical Analyses

We constructed hierarchical four-level multivariable random intercepts logistic regression models with individuals (level 1) nested in zip codes (level 2), nested in counties (level 3), nested in states (level 4) to examine the odds of HCQ adherence (PDC $\geq$80) vs. nonadherence (PDC

<80). We examined the fixed effects of the aforementioned individual-level and contextual variables, and accounted for random effects at the zip code, county and state levels. We examined variance partitioning at the zip code, county and state levels for each of our models, beginning with our null model, to understand the level at which most between-area variability was occurring and the degree to which our fixed effects could account for this (See **Supplemental Material** for sample equations). We additionally adjusted all of our multivariable models by index year of first HCQ dispensing. For our sociodemographic aggregate fixed effects (percent below FPL, percent black and educational attainment), we explored separate models at the zip code, county and state levels, while accounting for the random effects at each level. For our models examining county and state-level health services/health professional characteristics, we chose the model including individual and zip code fixed effects with the smallest deviance information criteria (DIC) statistic. In addition to exploring the association between these factors and adherence, we aimed to see whether inclusion of county-level health services variables would attenuate the effects of individual and zip code level factors.

We used SAS 9.4 (Cary, NC) to organize our variables and MLwiN 2.36 (Center for Multilevel Modeling, Bristol University, London, UK) to conduct our multilevel analyses. All multilevel analyses used Markov Chain Monte Carlo (MCMC) procedures (burn-in length 500, monitoring chain length 5000, thinning 1) using a Metropolis-Hasting algorithm. This is a Bayesian approach, which can be described as sequential learning, whereby prior information is accounted for in the estimates and the distributional assumptions of maximum likelihood methods are not required.(29) For our fixed parameter estimates, we present the MCMC estimates with 95% credible intervals. Unlike 95% confidence intervals, credible intervals do not have to be normally distributed and instead provide the potential range of values following the

MCMC simulation of many model runs. For random effects parameters, we present level-specific residual variance estimates with 95% credible intervals, as well as the percent of variance partitioned at each level.

MAX data were obtained through a Data Use Agreement from the Centers of Medicare and Medicaid Services and findings are reported in accordance with their specifications (cell sizes <11 are suppressed). This study was approved by the Brigham and Women's Hospital Institutional Review Board.

Results

Individual and Area-Level Characteristics

We identified 10,268 Medicaid beneficiaries residing within 4,930 zip codes, in 1,414 counties, in 28 states, with prevalent SLE who HCQ initiators. On average, there were 2.1 ± 2.8 (range 1-29) individuals per zip code, 7.3 ± 28.7 (range 1-739) individuals per county, and 366.7 ± 416.9 (range 84-1960) individuals per state. There were, on average, 3.5 ±7.5 (range 1-190) zip codes per county and 50.5 ± 24.9 (range 13-120) counties per state.

The mean age of our cohort was 37.7 ± 11.8 years and 94% were female (**Table 2.1**). The racial composition of the cohort included 42% Black or African American, 31% White, 20% Hispanic, 4% Asian, 1% American Indian/Alaska Native, and 2% other. On average, the mean ± SD SLE risk adjustment index was low (1.0 ± 1.9), 11% of patients received an immunosuppressive medication and 60% received corticosteroids during the baseline period. The mean ± SD number of overall medications was 4.2 ± 3.4 and 29% received an antidepressant medication. Overall, the mean PDC was 42.3% ± 28.7 and 1567 individuals (15.3%) were adherent (PDC ≥80%) to HCQ during the 365-day follow-up period after first dispensing.

Table 2.1. Individual-level baseline characteristics of new HCQ users enrolled in Medicaid	
Baseline characteristics*	**N=10, 268**
Age- mean ± SD	37.7 ± 11.8
Age group (years)- N(%)	
18-34	4542 (44.2)
35-50	3902 (38.0)
50-65	1824 (17.8)
Sex- N (%)	
Female	9669 (94.2)
Male	599 (5.8)
Race/ethnicity-N(%)	
Black	4289 (41.8)
White	3194 (31.1)
Hispanic	2036 (19.8)
Asian	397 (3.9)
American Indian/Alaska Native	121 (1.2)
Other	231 (2.3)
SLE risk adjustment index – mean ± SD	1.0 ± 1.9
Lupus nephritis- N (%)	1049 (10.2)
Diabetes mellitus- N(%)	964 (9.4)
Smoking – N (%)	616 (6.0)
Obesity – N (%)	240 (2.3)
Antidepressant use – N (%)	2976 (29)
Preventive care – N (%)	
Influenza vaccine	178 (1.7)
Pneumococcal vaccine	58 (0.6)
Pneumocystosis prophylaxis	903 (8.8)
Immunosuppressive medication use** **- N (%)**	1127 (11)
Number of laboratory tests+- mean ± SD	1.6 ± 2.8
Corticosteroids	
Ever use – N (%)	6112 (59.5)
Mean number of medications – mean ± SD	4.2 ± 3.4
Healthcare utilization	
ED Visits – median (25, 75)	0 (0, 1)
Hospitalizations – median (25, 75)	0 (0, 1)
Outpatient visits – median (25, 75)	2 (0, 6)
Hospitalized days – mean ± SD	3.9 ± 10.6; Median 0 (25^{th} 0, 75^{th} 4)
*Baseline characteristics determined from the 183 days prior to and including the index date of first dispensing of HCQ **Includes use of azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus +Includes BUN, creatinine, urinalysis, complement (C3, C4), ESR, CRP, anti-dsDNA	

In terms of area-level characteristics, the mean ± SD percent with income below the FPL was 14.1% ± 9 at the zip code level, 16.5% ± 6.5 at the county level and 14 ± 3.2 at the state level (**Table 2.2**). The mean percent black was 18.3% ± 23.2 at the zip code level, 13.9% ± 16.9

at the county level and 14.3% ±10 at the state level. The majority of individuals in the zip codes and counties assessed were in the high school graduate or less category for educational attainment. The mean percent urban was 51.2% ± 29.8 and the mean Gini coefficient for the 28 states included was 0.46 ± 0.02. County-level health resources per capita are presented in **Table 2.2**. Of the counties included, 39.8% were whole Health Professional Shortage Areas. The mean number of rheumatologists per 10,000 individuals per state was 0.13 ± 0.03.

Table 2.2. Zip code, county and state-level demographic and health services characteristics

Area-level Characteristics	Zip Code (N= 4,930)	County (N= 1,414)	State (N=28)
Percent with income below the federal poverty level[+]- mean ± SD	14.1 ± 9.1	16.5 ± 6.5	14.0 ± 3.2
Tertile 1- mean ± SD, range	5.4 ± 2.2 (0-8.9)	1.0 ± 1.0 (0-2.5)	10.5± 1.4 (8.1-12.1)
Tertile 2- mean ± SD, range	12.4 ± 2.1 (8.9-16.3)	6.9 ± 3.4 (2.5-14.3)	13.8 ± 0.8 (12.4-15.1)
Tertile 3- mean ± SD, range	34.5 ±7.3 (16.3-70.7)	33.8 ± 15.3 (14.3-84.6)	17.7 ±1.6 (15.8-21.4)
Percent black[+] – mean ± SD	18.3 ± 23.2	13.9 ± 16.9	14.3 ± 10
Tertile 1- mean ± SD, range	1.1± 1.0, (0- 3.2)	9.9 ± 2.4 (2.9-13.2)	4.6 ±1.9 (1.7-7.3)
Tertile 2- mean ± SD, range	8.9 ± 4.2 (3.2-17.8)	15.8 ±1.4 (13.2-18.5)	12.2 ±2.8 (7.5-15.5)
Tertile 3- mean ± SD, range	45.1 ± 22.1 (17.8-100)	23.7 ± 4.8 (18.5-43.4)	26.4 ± 6.7 (15.6-37.0)
Educational attainment[+]- N (%)			
HS or less	3904 (79.2)	1285 (90.9)	--
Some college	288 (5.8)	26 (1.8)	--
College graduate and beyond	738 (15)	103 (7.3)	--
Number of rheumatologists*- mean ± SD	--	--	0.13 ± 0.04
Tertile 1- mean ± SD, range	--	--	0.09 ±0.01 (0.07-0.11)
Tertile 2- mean ± SD, range	--	--	0.12 ±0.01 (0.11-0.14)
Tertile 3- mean ± SD, range	--	--	0.17 ±0.04 (0.14-0.26)
Total number of Total MDs-** mean ± SD	--	1.53 ± 1.75	--
Tertile 1- mean ± SD, range	--	0.43±0.18 (0-0.72)	--
Tertile 2- mean ± SD, range	--	1.09 ±0.25 (0.72-1.56)	--
Tertile 3- mean ± SD, range	--	3.06 ± 2.3 (1.56-25.3)	--
Total number of hospitals-** mean ± SD	--	0.03 ± 0.03	

Table 2.2 (Continued)			
Tertile 1- mean ± SD, range	--	0.01±0.01 (0-0.02)	--
Tertile 2- mean ± SD, range	--	0.03 ± 0.01 (0.02-0.04)	--
Tertile 3- mean ± SD, range	--	0.07 ±0.04 (0.04-0.59)	--
Total number of medicine subspecialists-** mean ± SD	--	0.46 ± 0.64	--
Tertile 1- mean ± SD, range	--	0.08 ± 0.05 (0-0.16)	--
Tertile 2- mean ± SD, range	--	0.30 ± 0.09 (0.16-0.47)	--
Tertile 3- mean ± SD, range	--	1 ± 0.87 (0.4-10.5)	--
Total number of pharmacists-** mean ± SD	--	0.54 ± 0.33	--
Tertile 1- mean ± SD, range	--	0.23 ± 0.07 (0-0.34)	--
Tertile 2- mean ± SD, range	--	0.45 ± 0.07 (0.34-0.60)	--
Tertile 3- mean ± SD, range	--	0.90 ± 0.30 (0.60-2.73)	--
Health Professional Shortage Areas[#]- N (%)			
None	--	236 (16.7)	--
Partial	--	615 (43.5)	--
Whole	--	563 (39.8)	--
Percent Urban[++] – mean ± SD		51.2 ± 29.8	
Tertile 1- mean ± SD, range	--	17.0 ± 12.8 (0-36.8)	--
Tertile 2- mean ± SD, range	--	51.5 ± 8.6 (36.9-67.3)	--
Tertile 3- mean ± SD, range	--	85.2 ± 10.2 (67.3-100)	--
Gini Coefficient – mean ± SD[+]	--	--	0.46 ± 0.02
Tertile 1- mean ± SD, range	--	--	0.44 ±0.01 (0.43-0.45)
Tertile 2- mean ± SD, range	--	--	0.46 ±0.003 (0.46-0.47)
Tertile 3- mean ± SD, range	--	--	0.47 ± 0.01 (0.47-0.50)

[+]From the American Community Survey (2000-2006)
*From the American College of Rheumatology (2000), per 10,000 state population in 2000 (US Census)
**Per capita, per 1,000 individuals in the county, mean from the Area Health Resources Files 2000 and 2010; MD data from the American Medical Association, hospital data from HRSA; For pharmacists, N=1362, 52 counties (4%) do not report pharmacist data
[#]HPSAs as defined and reported by HRSA, 2010
[++]From the Area Health Resources Files 2000 and 2010 (mean)

Individual-Level Fixed Effects

In our four-level random intercepts logistic regression model, accounting for zip code, county, and state random effects, we identified a number of factors associated with adherence (**Table 2.3,** Model 3). We found lower odds of adherence (vs. nonadherence) associated with younger age groups (vs. older age groups), with black race and Hispanic ethnicity (vs. white), with antidepressant medication use (vs. nonuse) and with more emergency department visits. We found higher odds of adherence associated with a higher SLE risk adjustment score, more laboratory tests and more baseline medications, in line with our prior work in the Medicaid population.(22)

Area-Level Fixed Effects

After accounting for individual-level fixed effects, and random effects at each level, we found lower odds of adherence vs. nonadherence in zip codes with higher percent black. Comparing tertile 2 to 1 (lowest percent black), the OR was 0.84 (95% CI 0.72-0.98) and comparing tertile 3 to 1, the OR was 0.81 (95% CI 0.68-0.96) (**Table 2.3**, Model 3). After adjusting for zip code percent black, the odds of adherence associated with individual-level black race was slightly less pronounced (OR 0.67, 95% CI 0.57-0.79 after adjustment, OR 0.61, 95% CI 0.53-0.70 before). When we further adjusted our model by zip code level percent below FPL (Model 4) and educational attainment (Model 5), the effect of zip code percent black remained significant and we observed a more pronounced decreased odds of adherence for tertile 3 vs.

Table 2.3. Individual and zip code-level models* examining the odds of HCQ adherence (PDC ≥80%) vs. nonadherence (PDC <80%) with 95% credible intervals (CI)

	Model 1	Model 2	Model 3	Model 4	Model 5
Individual Level Fixed Effect Covariates					
Male (ref=female)		1.22 (0.98-1.51)	1.21 (0.98-1.50)	1.22 (0.98-1.52)	1.21 (0.96-1.50)
Age (ref = 51-65 years)					

Table 2.3 (Continued)				
18-34 years	**0.61 (0.52-0.71)**	**0.60 (0.52-0.71)**	**0.61 (0.53-0.71)**	**0.60 (0.51-0.69)**
35-50 years	**0.71 (0.61-0.83)**	**0.70 (0.61-0.81)**	**0.71 (0.61-0.82)**	**0.70 (0.61-0.80)**
Race/ethnicity (ref=White)				
Black	**0.61 (0.53-0.70)**	**0.67 (0.57-0.79)**	**0.67 (0.56-0.79)**	**0.66 (0.57-0.78)**
Hispanic	**0.71 (0.60-0.83)**	**0.72 (0.61-0.85)**	**0.71 (0.59-0.84)**	**0.71 (0.59-0.85)**
Asian	**1.53 (1.19-1.97)**	**1.53 (1.18-1.98)**	**1.52 (1.19-1.94)**	**1.52 (1.16-1.98)**
AI/AN	0.78 (0.44-1.29)	0.79 (0.45-1.33)	0.77 (0.42-1.29)	0.77 (0.43-1.30)
Other	0.86 (0.59-1.24)	0.88 (0.62-1.28)	0.89 (0.61-1.25)	0.89 (0.59-1.27)
SLE risk adjustment index	**1.04 (1.00-1.07)**	**1.04 (1.00-1.07)**	**1.04 (1.01-1.07)**	**1.03 (1.00-1.07)**
Lupus nephritis	1.13 (0.92-1.38)	1.14 (0.92-1.38)	1.14 (0.93-1.39)	1.14 (0.93-1.39)
Diabetes mellitus	0.83 (0.68-1.00)	**0.82 (0.67-0.99)**	0.82 (0.67-1.01)	0.83 (0.68-1.02)
Antidepressant use	**0.87 (0.76-0.99)**	**0.86 (0.75-0.98)**	**0.86 (0.76-0.98)**	**0.86 (0.76-0.99)**
Corticosteroid use	1.04 (0.92-1.17)	1.05 (0.94-1.19)	1.05 (0.94-1.22)	1.05 (0.93-1.19)
Number of lab tests	**1.03 (1.00-1.05)**	**1.03 (1.00-1.05)**	**1.02 (1.00-1.05)**	**1.02 (1.00-1.05)**
Number of medications	**1.09 (1.08-1.11)**	**1.10 (1.08-1.12)**	**1.09 (1.07-1.11)**	**1.10 (1.08-1.12)**
Use of immunosuppressive medications	0.90 (0.75-1.07)	0.90 (0.76-1.07)	0.91 (0.76-1.08)	0.90 (0.76-1.08)
Healthcare Utilization				
# ED visits	**0.96 (0.93-0.99)**	**0.96 (0.93-1.00)**	**0.96 (0.93-0.99)**	**0.96 (0.93-0.99)**
# outpatient visits	1.00 (0.99-1.02)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
# hospitalizations	0.94 (0.87-1.02)	0.94 (0.88-1.02)	0.95 (0.88-1.02)	0.94 (0.88-1.02)
Zip Code Level Fixed Effect Covariates				
Percent Black (ref=lowest tertile)				
Tertile 2		**0.84 (0.73-0.98)**	**0.85 (0.73-0.97)**	**0.85 (0.73-0.99)**
Tertile 3		**0.81 (0.68-0.96)**	**0.79 (0.66-0.94)**	**0.79 (0.66-0.95)**

Table 2.3 (Continued)					
Percent below FPL (ref=lowest tertile)					
Tertile 2				1.02 (0.87-1.19)	1.02 (0.86-1.22)
Tertile 3				1.09 (0.93-1.28)	1.10 (0.93-1.32)
Educational attainment (ref=HS or less)					
Some college					1.13 (0.85-1.49)
College graduate+					1.02 (0.84-1.24)
Random Effects					
Between state					
σ^2 (95% CI)	0.048 (-0.001-0.097)	0.033 (-0.008-0.075)	0.038 (-0.002-0.077)	0.038 (-0.004-0.079)	0.041 (-0.002-0.083)
Variance attributable	1.4%	1.0%	1.1%	1.1%	1.2%
Between county					
σ^2 (95% CI)	0.003 (-0.001-0.007)	0.013 (-0.007-0.032)	0.001 (0.000-0.002)	0.002 (-0.001-0.004)	0.001 (0.000-0.001)
Variance attributable	0.09%	0.4%	0.02%	0.06%	0.03%
Between zip code					
σ^2 (95% CI)	0.003 (-0.000-0.006)	0.001 (0-0.003)	0.008 (-0.007-0.023)	0.002 (0.001-0.002)	0.001 (0.000-0.002)
Variance attributable	0.09%	0.03%	0.2%	0.06%	0.03%
DIC	8742.1	8400.6	**8397.4**	8400.4	8403.3

All models are 4-level (individual, zip code, county, state) random intercepts multivariable logistic regression models.
Model 1: Null model
Model 2: Individual-level variables
Model 3: Model 2 + Zip code level percent black
Model 4: Model 3 + Zip code level percent below federal poverty level (FPL)
Model 5: Model 4 + Zip code level percent educational attainment
*Models all additionally adjusted for calendar year of index date, obesity, smoking, number of hospitalized days, and preventive care (influenza or pneumonia vaccines, PCP prophylaxis)

tertile 1. Neither zip code percent below FPL or educational attainment were significantly associated with adherence. We additionally examined these aggregate fixed effects in separate models at the county and state levels (**Table 2.4**). We did not observe statistically significant associations with county-level percent black or percent below FPL, or with the state-level Gini

coefficient and adherence. We also examined the relationship of tertiles of the Gini coefficient, adjusting for individual level factors and for zip code percent black. We did not find a significant association with either tertile of the Gini coefficient but the effect of percent black at the second and third tertiles remained unchanged and significant.

Table 2.4. Multilevel models examining odds of adherence (PDC ≥80%) vs. nonadherence for county and state level sociodemographic characteristics, adjusting for individual-level characteristics and for zip code, county and state random effects

	Model A	Model B	Model C	Model D	Model E	Model F
County-level fixed effects						
Percent Black (ref=lowest tertile)						
Tertile 2	0.99 (0.83-1.18)	0.98 (0.82-1.19)	0.97 (0.79-1.17)			
Tertile 3	0.89 (0.73-1.08)	0.85 (0.69-1.05)	0.84 (0.67-1.03)			
Percent below FPL (ref=lowest tertile)						
Tertile 2		1.08 (0.93-1.25)	1.09 (0.94-1.26)			
Tertile 3		1.15 (0.97-1.37)	1.14 (0.95-1.36)			
Educational attainment (ref=HS or less)						
Some college			0.75 (0.42-1.31)			
College graduate+			1.02 (0.85-1.23)			
State-level fixed effects						
Percent Black (ref=tertile 1)						
Tertile 2				1.01 (0.81-1.29)	1.03 (0.81-1.38)	1.01 (0.74-1.28)
Tertile 3				0.95 (0.75-1.20)	0.97 (0.75-1.27)	0.94 (0.68-1.24)
Percent below FPL (ref=tertile 1)						
Tertile 2					1.07 (0.84-1.33)	1.02 (0.78-1.37)
Tertile 3					0.98 (0.75-1.29)	0.89 (0.66-1.24)

Table 2.4 (Continued)						
Gini coefficient (ref=tertile 1)						
Tertile 2						1.15 (0.83-1.53)
Tertile 3						1.19 (0.87-1.67)
Random Effects						
Between state						
σ^2 (95% CI)	0.04 (-0.003-0.083)	0.043 (-0.003-0.09)	0.035 (-0.007-0.077)	0.033 (-0.008-0.075)	0.044 (-0.005-0.093)	0.047 (-0.012-0.105)
Variance attributable	1.2%	1.3%	1.1%	1.0%	1.3%	1.4%
Between county						
σ^2 (95% CI)	0.001 (0-0.002)	0.001 (0-0.003)	0.006 (0-0.023)	0.054 (-0.001-0.11)	0.004 (-0.002-0.01)	0.002 (0-0.003)
Variance attributable	0.03%	0.03%	0.2%	1.6%	0.1%	0.1%
Between zip code						
σ^2 (95% CI)	0.002 (0-0.005)	0.001 (0-0.001)	0.001 (0-0.002)	0.000 (0.000-0.000)	0.001 (0-0.001)	0 (0-0.001)
Variance attributable	0.06%	0.03%	0.03%	0%	0.03%	0%
DIC	8401.8	8401.0	8404.5	8403.5	8404.7	8406.1

All models are 4-level (individual, zip code, county, state) random intercepts multivariable logistic regression models.
Model A: Individual level fixed effects (Model 2) + county percent black
Model B: Model A + county percent below FPL
Model C: Model B + county educational attainment
Model D: Individual level fixed effects (Model 2) + state level county percent black
Model E: Model D + state level percent below FPL
Model F: Model E + state level Gini coefficient

We built our subsequent models starting with Model 3 (**Table 2.3**) both because it had the lowest DIC and because we aimed to test whether concentration of health resources and urbanicity accounted for the effect of zip code percent black on adherence (**Table 2.5**). We found higher odds of adherence vs. nonadherence comparing the county-level highest number of hospitals per capita compared to the lowest (OR 1.32, 95% CI 1.08-1.60). We found lower odds of adherence vs. nonadherence associated with residing in a whole HPSA (OR 0.86, 95%CI 0.75-1.00). We did not find statistically significant associations with number of physicians,

medicine subspecialists, or pharmacists per capita and adherence. At the state level, we observed a trend towards greater odds of adherence in states with more rheumatologists per capita, but this was not statistically significant (Model 12). We also explored the relationship between urbanicity and adherence and did not find a significant relationship (Model 11). The effect of percent black comparing tertile 3 vs. 1 remained significant in each of these models, and the effect of tertile 2 vs. 1 remained significant in most models as well.

Table 2.5 Models examining the odds and 95% credible intervals of adherence (PDC ≥80%) vs. nonadherence (PDC <80%) by county-level and state-level healthcare resources and county-level percent urban, adjusting for individual and zip code-level factors

	Model 6	Model 7	Model 8	Model 9	Model 10	Model 11	Model 12
Zip code-level fixed effects							
Percent Black (ref=lowest tertile)							
Tertile 2	0.87 (0.75-1.01)	**0.85 (0.74-0.99)**	0.87 (0.74-1.02)	**0.84 (0.72-0.97)**	**0.86 (0.74-1.00)**	**0.86 (0.74-0.99)**	**0.85 (0.74-0.98)**
Tertile 3	**0.83 (0.69-0.99)**	**0.82 (0.69-0.99)**	**0.83 (0.69-1.00)**	**0.80 (0.67-0.95)**	**0.81 (0.68-0.98)**	**0.82 (0.70-0.98)**	**0.82 (0.70-0.96)**
County-level fixed effects							
Total MDs per capita (ref=lowest tertile)							
Tertile 2	0.89 (0.70-1.11)						
Tertile 3	0.88 (0.70-1.08)						
Total subspecialists per capita (lowest tertile)							
Tertile 2		0.93 (0.76-1.16)					
Tertile 3		0.84 (0.69-1.03)					

Table 2.5 (Continued)							
Number of hospitals per capita (lowest tertile)							
Tertile 2			1.14 (0.99-1.31)				
Tertile 3			**1.32 (1.08-1.60)**				
HPSA (ref=none)							
Partial				0.82 (0.64-1.03)			
Whole				**0.86 (0.75-1.00)**			
Number of pharmacists per capita (lowest tertile)					0.92 (0.77-1.13)		
Tertile 2					0.90 (0.75-1.08)		
Tertile 3							
Percent urban (lowest tertile)							
Tertile 2						0.92 (0.73-1.16)	
Tertile 3						0.83 (0.69-1.02)	
State-level fixed effects							
Number of rheumatologists per capita (lowest tertile)							
Tertile 2							1.22 (0.91-1.60)
Tertile 3							1.15 (0.87-1.47)
Random Effects							
Between state							
σ^2 (95% CI)	0.041 (-0.003-	0.042 (-0.004-	0.054 (0.002-	0.029 (-0.01-	0.036 (-0.009-	0.03 (-0.012-	0.041 (-0.004-

Table 2.5 (Continued)	0.085)	0.087)	0.106)	0.069)	0.08)	0.072)	0.085)
Variance attributable	1.2%	1.3%	1.6%	0.87%	1.1%	0.90%	1.2%
Between county							
σ^2 (95% CI)	0.005 (-0.006-0.017)	0.004 (-0.001-0.016)	0.002 (-0.003-0.008)	0.002 (0.001-0.003)	0.001 (0-0.003)	0.027 (-0.007-0.61)	0.007 (-0.004-0.019)
Variance attributable	0.15%	0.12%	0.06%	0.06%	0.03%	1.7%	0.21%
Between zip code							
σ^2 (95% CI)	0.001 (0.001-0.002)	0.001 (0-0.001)	0.001 (0-0.002)	0.002 (0-0.003)	0.001 (0.001-0.003)	0.001 (0-0.002)	0.001 (0-0.002)
Variance attributable	0.03%	0.03%	0.03%	0.06%	0.03%	0.03%	0.03%
DIC	8400.5	8396.2	8391.9	8397.8	8400.3	8397.9	8397.8

All models include all individual and zip-code level fixed effect covariates from Model 3 (chosen because it has the lowest DIC). Models 6-10 add each of the below variables separately due to collinearity. All models are 4-level (individual, zip code, county, state) random intercepts multivariable logistic regression models.
Model 6: Model 3 + county-level number of total MDs per capita
Model 7: Model 3 + county-level number of total medicine subspecialists per capita
Model 8: Model 3 + county-level number of total hospitals per capita
Model 9: Model 3 + county-level Health Professional Shortage Areas (Primary care)
Model 10: Model 3 + county-level number of pharmacists per capita
Model 11: Model 3 + county-level percent urban
Model 12: Model 3 + state-level number of rheumatologists per capita

Random Effects

We observed minimal between state, between county and between zip code level variation and in our null model (**Table 2.3**, Model 1) none of these effects were statistically significant. Of the little variance we detected, most was attributable to between states (1.4%). We observed minor residual variations in random effects between models but overall effects were very small and most were either not statistically significant, or of borderline significance.

Discussion

In this population of high-risk, chronically ill, low SES individuals with SLE where only 15% were adherent to HCQ over the first year of use, we observed significant relationships between certain individual and contextual factors and adherence. In line with prior studies among SLE patients, younger age, Black race, Hispanic ethnicity and antidepressant use were associated with poorer adherence whereas more active SLE was associated with better adherence.(13, 30-32) At the area level, we found a dose-response relationship between higher zip code level percent black and reduced odds of adherence and this remained true after adjusting for individual level factors including race, as well as for area-level poverty, educational attainment, urbanicity, and healthcare resources. Living in counties designated health professional shortage areas was associated with lower odds of adherence, whereas living in areas with more hospitals was associated with greater odds.

While significant racial, ethnic and SES disparities exist in SLE prevalence and disease-related outcomes, there are few studies to date that explore the contribution of area-level factors to these disparities. Persistent neighborhood poverty, after accounting for individual-level poverty, has been associated with increased SLE-related damage, and Medicaid patients with SLE have been shown to travel further to see a rheumatologist. (14, 33) Multiple prior studies demonstrate poorer medication adherence among African American patients with lupus as well as poorer outcomes overall. (10, 13, 30-32, 34) As HCQ is the backbone of care for SLE and has been associated with fewer disease flares, a reduction in risk of thromboembolic disease, cardiovascular disease, end-stage renal disease and mortality, it is plausible that differences in HCQ adherence by race/ethnicity may contribute to disparities in outcomes.(10, 34-40)

August and Billimek proposed a theoretical model among low SES individuals with chronic diseases that links neighborhood deprivation to increased likelihood of nonadherence.(18) The authors hypothesize that living in a disadvantaged neighborhood results in increased exposure to stressors (e.g. disorder, crime) and reduces an individual's capacity to engage in healthy behaviors such as adherence. In keeping with behavioral economics theory, individuals have present-biased preferences, meaning that disproportionate weight is placed on present relative to future costs and benefits.(41, 42) In settings with increased stress and poverty, this may be even more pronounced and adherence to chronic disease medications for potential future benefit (e.g. prevention of asymptomatic complications) may be outweighed by more immediate needs and concerns. In addition, the environment may contribute to social norms within a community that do not prioritize adherence.(43-45) Together, the authors posit that these factors result in unfavorable beliefs about adherence which may result in nonadherent behavior.(18)

There are a few studies in the chronic disease literature that explore these relationships. Among individuals with multiple chronic diseases, medication adherence was highest among patients living in areas with higher education rates and higher income.(5) Among patients with diabetes, neighborhood factors including food insecurity, social cohesion and neighborhood esthetics were associated with glycemic control, which may be tied in part to hyperglycemic medication adherence.(3) Among African American patients with asthma, poorer adherence to inhaled corticosteroids was associated with increased area crime even after adjusting for other area-level measures of SES.(4)

In our study we found a significant relationship between increased zip code level percent black and poorer adherence to HCQ. This remained true after adjusting for area poverty and

educational attainment, as well as for individual-level race. While zip code is an imperfect proxy for neighborhood (46), this observation at the zip code level but not at the county or state levels suggests a potential effect on HCQ adherence by more proximal racial composition, possibly in part due to racial residential segregation. Residential segregation describes both the composition and the spatial distribution of an area and a number of measures of dissimilarity, isolation, concentration, centralization and clustering have been proposed.(47, 48) Our lack of addresses did not allow us to geocode our data to accurately examine the differential distribution of individuals of different races across smaller residential units (e.g. census blocks or tracts) within larger geographic areas, or to look at spatial relationships to explore this in further depth.(47, 48) However we hypothesize that similar mechanisms proposed to explain the relationship between segregation and health behaviors may contribute to the association we observed. Within these areas, there may be reduced access to high quality healthcare and pharmacy services, to transportation, and to safe, low crime areas to walk.(48, 49) There may be increased stress and depression from exposure to and perceptions of racial discrimination which may to contribute to nonadherence.(49, 50) Community social trust might also contribute to adherence behavior.(51) It is also plausible that there may be reverse causation as individuals who are less likely to engage in healthy behaviors overall may also be less likely or able to move out of racially segregated areas. This may in part be related to the known racial differences in the educational, occupational and economic opportunities afforded to individuals who live in segregated neighborhoods.(49)

It is also possible that social and cultural norms within neighborhoods influence adherence behavior. Racial bias experienced in healthcare is one plausible mechanism for this.(49) Prior studies among SLE patients suggest differences between African American and

white patients in their willingness to accept certain SLE-related medications, in their beliefs about medication effectiveness, and in their trust in health providers.(52) In addition, in one study, more than 50 percent of African American patients with SLE reported experiencing racial discrimination in healthcare and this was linked to increased depression.(50) Similar patterns have been described among African American patients with hypertension where racial discrimination has been specifically associated with medication nonadherence.(53) Living in close proximity to individuals with negative healthcare experiences related to racism may contribute to a social norm of nonadherence.

Interestingly, in our analyses we did not observe an independent effect from area percent below FPL, or from state-level income inequality (Gini coefficient). There was a moderate correlation between zip code percent below FPL and percent black ($r=0.46$, $p<0.0001$) suggesting that areas with increased percent black overlap with those with increased concentrations of poverty. However, the effect of zip code percent black on adherence persisted after adjusting for both zip code percent below FPL and state Gini coefficient, suggesting that other mechanisms beyond area socioeconomic deprivation and income inequality contribute. We hypothesize that we may not see an independent area-level effect of poverty because of the dominant individual-level effect as our population was selected on the basis of having low enough income to qualify for Medicaid. Possibly, once enrolled in Medicaid, small differences in income that may contribute to certain aspects of nonadherence (i.e. copayments), become less relevant.

We additionally investigated area health resources and adjusting for these did not significantly attenuate the relationship between area level percent black and adherence. It is important to note however, that we could only assess the number of health professionals and

facilities and not the quality of services provided. Increased number of health providers available in an area has been previously associated with improved health outcomes.(54) While we did find an association with greater numbers of hospitals and increased odds of adherence, we did not find a parallel association with more physicians, subspecialists or pharmacists. It is possible that among this Medicaid population, hospital-based clinics provide the majority of care to complex patients with SLE, whereas private practice physicians may not accept Medicaid, or more high-risk, complicated patients. Adherence behavior in this vulnerable SLE population may also be more related to the quality of care received, and the interactions between patients and providers, rather than the concentration of services available to the population at large.(55) Alternatively, there might be more physicians that come to practice in areas with high concentrations of medically complex patients and therefore adherence may be poorer overall in these areas to begin with. Overall however, we did find that living in a health professional shortage area, whether it was related to physicians or facilities, was associated with poorer adherence. The lack of an association between number of pharmacists and adherence may be harder to tease apart because inclusion in this study required one filling of HCQ implying that patients had at least some access to a pharmacy. We did not have data on actual pharmacies by area and number of licensed pharmacists might not correlate with pharmacies where Medicaid beneficiaries fill their prescriptions. In addition, we did have a small percentage (4%) of counties with missing pharmacist data, which could have influenced our findings to some degree.

Notably, we did not find significant between-area variation in adherence and the minimal variation we observed was between states. We expected to see significantly more between-state variation as a result of differences in Medicaid eligibility criteria by state. However it is possible that the poorest individuals may not be enrolled in Medicaid and the difference in adherence by

variations in poverty level eligibility among overall poor individuals may not be that significant. It is also possible that we did not see significant differences because once enrolled, HCQ copayments and days supplied requirements between the 28 states included are similar. At the zip code and county level, it is possible that the lack of between-area variation observed was a result of a significant proportion of areas with few SLE patients, and the high prevalence of overall nonadherence in this population.

This study had a number of strengths. The majority of studies that examine the relationship between contextual factors and health behaviors and outcomes do not use multilevel designs.(56) We were able to examine the relationship between area-level sociodemographic and health services characteristics and adherence while accounting for individual-level characteristics, as well as for potential clustering by geographic area. To our knowledge, this is the first study to examine the role of contextual factors beyond area-level poverty on adherence behavior in a high-risk patient population. Among patients with SLE, previous researchers highlight the need for a better understanding of the contribution of social determinants to racial/ethnic disparities in health outcomes however few studies to date examine this.(15) While we were unable to explore the question of neighborhood-level racial residential segregation in depth due to the lack of geographic data more granular than zip code, the finding of poorer adherence in zip codes with higher percent black is hypothesis-generating and paves the way for further studies to examine this potential relationship. Similarly, our mixed findings on the significance of the availability of area health resources on adherence in this population should lead to additional studies examining potential differences in the quality of care provided in more deprived neighborhoods.

Our study also has limitations. While low income is part of the criteria for Medicaid eligibility, we did not have other individual-level measures of SES (e.g. occupation, education). In addition, we lacked geographic area data other than zip code, county and state of residence and therefore we were unable to assess direct neighborhood effects or to geocode our data to examine measures of residential segregation. Our use of administrative data also did not enable us to control for SLE disease activity, however markers such as healthcare utilization, number of SLE-related laboratory tests and the SLE risk adjustment index, were used to approximate this. We measured adherence using the PDC, calculated using dispensing data, and used a cutoff of $\geq$80% as is accepted in the chronic disease literature. However, medication dispensing may not entirely correlate with actual adherence and the need for adherence of $\geq$80% to HCQ to yield clinically meaningful outcomes has not been explored. We were unable to examine cross-level interactions between individual race/ethnicity and percent black or percent below FPL due to small cell sizes. We chose not to collapse non-white race/ethnicity into one comparator group because of the significantly different effects we observed by specific race/ethnicities. For the contextual variables we explored, while we propose that the associations found represent the contribution of these factors to HCQ adherence, it is possible that there is reverse causation. Lack of engagement in healthy behaviors may contribute to either movement to certain areas, or the inability to leave more underserved areas.

In this study of low-income Medicaid beneficiaries with SLE, adherence to HCQ was poor. In addition to reaffirming the role of certain individual-level sociodemographic and disease-related factors to adherence behavior, we propose that contextual influences contribute as well. In light of the known racial/ethnic disparities we observe in SLE disease prevalence and outcomes, our findings related to zip code percent black and area health resource concentration

should pave the way for further work examining the importance of social determinants, including segregation and discrimination, as well as neighborhood-specific healthcare quality, on health behaviors and outcomes in this vulnerable population.

Paper 2 Bibliography

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Paper 3

Can Patient Navigators Improve Adherence to Disease-Modifying Antirheumatic Drugs? Quantitative Findings from the Med Assist Pilot Study

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Abstract

Background: Non-adherence to DMARDs is common, worsens during the treatment course, and results in adverse outcomes. We studied whether patient navigators – laypersons trained in care coordination, motivational interviewing, basic pharmacology and disease management-improved oral DMARD adherence.

Methods: We enrolled 107 patients aged ≥18 years with systemic rheumatic diseases who initiated an oral DMARD within 6 months. Navigators interacted with patients up to 2-4 times per weeks for 6 months. Patients completed validated surveys (Morisky Medication Adherence Scale (MMAS-8), Mental Health Inventory (MHI-5), Beliefs about Medicines Questionnaire and Brief Illness Perception Questionnaire) at baseline and 6 months. We used paired t-tests to compare baseline and 6-month outcomes. We examined the association of age, race/ethnicity, insurance and MHI-5 with change in MMAS-8 score using multivariable linear regression.

Results: Among 107 patients enrolled, 69 (64%) completed baseline and 6-month MMAS-8 surveys. Mean age was 55 ±16 years; 93% were female. The mean baseline MMAS-8 score was 6.7 ±1.3 (borderline adherence), and the mean MHI-5 was 60.8 ± 9.1(<68 suggests any depressive symptoms). After 6 months, there were no significant changes in MMAS-8 (p=0.09) or MHI-5 (p=0.83). Patients described fewer medication concerns (p=0.03), but a more threatening perception of illness (p=0.01). Our multivariable model demonstrated a small change in MMAS-8 for each 5-year increase in age (β=0.14, p=0.02).

Conclusion: Our intervention resulted in no significant change in adherence from baseline. A randomized controlled trial is needed to determine whether patient navigators are effective in maintaining adherence to DMARDs over time.

Background

Medication adherence among patients with systemic rheumatic diseases is known to be suboptimal.(1) Non-adherence to disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) may result in increased disability, failure to reach remission, escalation of costly therapy, and increased adverse events.(2) In systemic lupus erythematosus (SLE), non-adherence is associated with increased acute care utilization and significant organ damage.(3) The majority of prior interventions using education and group support to improve adherence among rheumatology patients have not demonstrated a beneficial effect, whereas individually-tailored strategies and those delivered by health care providers have been more successful.(4) Patient navigators, or non-healthcare professionals, trained in advocacy, care coordination and basic disease-related management, have been used to improve disease monitoring among patients with other chronic diseases but not previously for patients with rheumatic diseases.(5) We designed and implemented a 6-month single arm pilot intervention, "Med Assist," to test whether a rheumatology-specific patient navigator improves short-term adherence to oral DMARDs.

The framework for this intervention stems from the Health Belief Model (HBM), and incorporates aspects of Social Cognitive Theory (SCT) (6, 7). As demonstrated in **Figure 3.1**, perceived susceptibility is defined as a patient's belief about his/her risk of rheumatic disease progression. In order to be willing to take a DMARD, a patient must have an understanding of his/her risk of developing organ damage or disability. Perceived severity, a patient's belief in the degree of illness, damage and disability, combined with susceptibility, comprise the perceived threat from the rheumatic disease. We designed the navigator's role in part to educate patients about this threat based on the patient's baseline level of understanding. Perceived benefits include the patient's understanding of the short and long-term efficacy of DMARDs to reduce

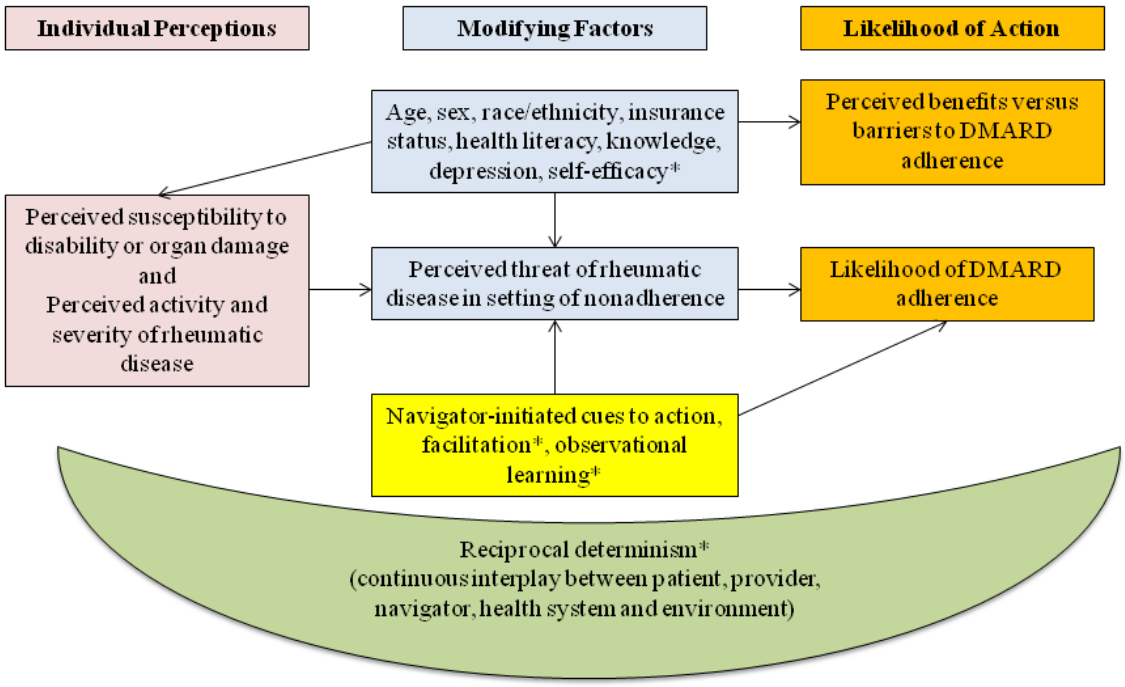

Figure 3.1. Modified Health Belief Model incorporating elements of Social Cognitive Theory (marked with an asterisk) as the logic model for the design and evaluation of the patient navigator intervention

pain and damage. This construct is countered by perceived barriers to medication adherence and concerns about the medications, and the balance between benefits and barriers creates the likelihood of adherence. The navigator's objective was to understand these barriers to DMARD adherence and to develop individually-tailored strategies to address them. The navigator provided the cues to action; the strategies to activate readiness to adhere. We also incorporated elements of SCT in the design of the intervention, notably an understanding by the navigators of the patient's self-efficacy or belief in his/her ability to adhere.(7) Other SCT constructs including observational learning (exposure to peer modeling of adherence strategies) and facilitation (providing tools, resources and health delivery modifications to make adherence easier) guided the navigators' actions. A central tenet of SCT, reciprocal determinism, or the interaction between people and their environments, is highlighted by adherence behavior, which

results from the continuous interplay of individual, provider and health system factors. One of the navigators' goals was to better understand these interactions and address barriers encountered. We presented qualitative findings previously (8) and here describe quantitative findings among participants who completed validated adherence-related surveys stemming from these constructs, at baseline and after 6-months of the navigator intervention.

Materials and Methods

Patient Identification

We identified individuals aged ≥18 years receiving care at the Brigham and Women's Hospital Arthritis Center. We included patients who were diagnosed with any systemic rheumatic disease who initiated an oral DMARD in the prior 6 months. Patients were identified by chart review or by direct rheumatologist referral. No additional exclusion criteria were applied. Rheumatologists were informed of the nature of the intervention and therefore may have preferentially referred patients who they felt might benefit.

Navigator Intervention

We identified two college educated non-health professionals, one bilingual in Spanish and English, and provided training in motivational interviewing, care coordination, advocacy, basic pharmacology and rheumatic disease management. The details of the navigators' training are described in a prior manuscript (8). Navigators contacted patients once every 2-4 weeks for 6 months. The navigators assessed specific needs and barriers related to the patient's underlying rheumatic disease and DMARD use and designed individually-tailored strategies to assist each patient. Several authors (CHF, AC, AW, DHS) independently categorized and counted the types

of actions performed by the navigators by reviewing all patient interaction reports and any conflicts were adjudicated by the group.

Survey Instruments

We collected demographic information at baseline and administered surveys at baseline and after the 6-month intervention. We used the constructs of the HBM and SCT to guide our choice of validated survey instruments (**Figure 3.1**) and to guide navigator actions. We assessed self-efficacy qualitatively and not quantitatively.(8) We measured adherence using the Morisky Medication Adherence Scale (MMAS-8), previously validated among patients with related chronic diseases.(9) The scale ranges from 0 to 8, <6 is poor adherence, 6-<8 is borderline and 8 is high. We used the Mental Health Inventory (MHI-5), which ranges from 0-100, to measure any depressive symptoms (scores <68) and severe symptoms (<52).(10) We used the Beliefs about Medicines Questionnaire (Concerns Scale) which ranges from 5-25, with higher scores representing the most concerns, to understand medication-related barriers to adherence, which contributes to the likelihood of action.(11) To measure the perceived level of threat associated with a patient's rheumatic disease, we used the Brief Illness Perception Questionnaire, ranging from 0-80, with 80 representing the most severe view of the illness.(12) To assess individual perceptions of disease activity, we used the Rheumatoid Arthritis Disease Activity Index (RADAI), ranging from 0-48 for RA patients (13) and the Systemic Lupus Activity Questionnaire (SLAQ) for SLE patients (14), ranging from 0-47, both validated, self-reported measures with higher scores indicating increased disease activity**.**

Statistical Analyses

We used parametric and non-parametric tests based on variable distribution to compare baseline characteristics by adherence category. We used paired t-tests to compare baseline and 6-

month survey scores. We compared adherence at baseline and at 6-months among all participants, and restricted to those with poor or borderline adherence at baseline. We used multivariable linear regression to estimate the relationship between age, race/ethnicity and insurance status and change in MMAS-8. We compared differences in changes in adherence by the tasks that the navigator performed to determine whether addressing certain concerns had more or less impact on MMAS-8 score. All analyses were conducted in SAS 9.4 (Cary, NC). The BWH Institutional Review Board approved this study.

Results

The Med Assist patient navigator pilot intervention enrolled 107 patients with systemic rheumatic diseases receiving care at the BWH Arthritis Center. Among these patients who engaged with a navigator, 69 (64%) completed the baseline and 6-month MMAS-8 adherence surveys. The mean ± SD age was 54.5 ± 16.3, 93% were female, 73% were white, and 16% were Hispanic (**Table 3.1**). All of the patients were insured, 55% with private insurance, 15% with Medicaid and 32% with Medicare. The majority (87%) were diagnosed with RA and received methotrexate (57%) and/or hydroxychloroquine (41%).

At baseline, the mean ± SD MMAS-8 score for the 69 patients was 6.7 ± 1.3; 15 (22%) were poor adherers (MMAS-8 <6), 38 (55%) were borderline adherers (MMAS-8 6-<8), and 16 (23%) were high adherers (MMAS-8=8) **(Table 3.1**). High adherers were, on average, older ($p<0.01$). We did not observe other statistically significant differences by demographic factors and baseline adherence category. At baseline, the mean MHI-5 score was 60.8 ± 9.1, which suggests that the majority of the population had some degree of depressive symptoms (MHI-5 <68). Seven patients (15%) had severe symptoms (MHI-5<52).

Table 3.1. Baseline characteristics overall and by Morisky Medication Adherence Scale (MMAS-8) category*

Characteristics	Overall (N=69)	Poor Adherence (N=15)	Borderline Adherence (N=38)	High Adherence (N=16)	p-value**
Age (years) – mean ± SD	54.5 ± 16.3	42.4 ± 12.3	55.4 ± 15.9	63.7 ± 14.4	**<0.01**
Sex – N (%)					
Female	64 (92.8)	14 (93.3)	36 (94.7)	14 (87.5)	0.82
Male	5 (7.3)	1 (6.7)	2 (5.3)	2 (12.5)	
Race – N (%)					
White	50 (72.5)	8 (53.3)	27 (71.1)	15 (93.8)	0.09
Non-White	6 (8.7)	2 (13.3)	3 (7.9)	1 (6.3)	
Unknown	13 (18.8)	5 (33.3)	8 (21.1)	--	
Ethnicity – N (%)					
Hispanic	11 (15.9)	5 (33.3)	7 (18.4)	--	0.11
Non-Hispanic	54 (78.3)	10 (66.7)	30 (78.9)	14 (87.5)	
Unknown	4 (5.8)	1 (6.7)	1 (2.6)	2 (12.5)	
Educational Attainment- N (%)	5 (7.2)	3 (20)	2 (5.3)	--	
Less than high school degree	20 (29)	5 (33.3)	10 (26.3)	5 (31.3)	0.28
High School & some college	37 (53.6)	5 (33.3)	21 (55.3)	11 (68.8)	
College graduate/graduate school	7 (10.1)	2 (13.3)	5 (13.2)	--	
Unknown					
Insurance – N (%)					
Medicaid	10 (14.5)	4 (26.7)	4 (10.5)	2 (12.5)	0.24
Medicare	22 (31.9)	4 (26.7)	10 (26.3)	8 (50)	
Private	37 (53.6)	7 (46.7)	24 (63.6)	6 (37.5)	
Disease – N (%)					
RA	60 (87)	11 (73.3)	35 (92.1)	14 (87.5)	0.19
SLE	4 (5.8)	2 (13.3)	1 (2.6)	1 (6.3)	
MCTD/Other	5 (7.2)	2 (13.3)	2 (5.3)	1 (6.3)	
Medication Use+ – N (%)	39 (56.5)	8 (53.3)	19 (50)	12 (75)	
Methotrexate	28 (40.6)	8 (53.3)	16 (42.1)	4 (25)	0.23
Hydroxychloroquine	9 (13)	2 (13.3)	5 (13.2)	2 (12.5)	
Sulfasalazine	5 (7.3)	1 (6.7)	3 (7.9)	1 (6.3)	
Tofacitinib					

*MMAS-8 of <6 is poor adherence, 6-<8 is borderline adherence and 8 is high adherence; +Patients could have received more than one DMARD; **p-values determined using parametric and non-parametric tests based on distribution; Percentages are by column

We examined baseline characteristics and MMAS-8 scores for the 38 patients enrolled who did not complete the 6-month intervention (**Table 3.2**). The mean age was 55 ± 17.6, the

majority were female (94.7%) and white (65.8%). The mean MHI-5 score was slightly higher than those who completed the intervention (62.2 ± 11.7) indicating fewer depressive symptoms, the mean illness perception score was slightly lower 41.7 ± 8.6, and the mean MMAS-8 score was modestly lower (6.3 ± 1.9).

Table 3.2. Baseline characteristics of 38 patients who enrolled but did not complete the intervention

Baseline Characteristics	N=38
Age (years) – mean ± SD	55 ± 17.6
Sex – N (%)	
Female	36 (94.7)
Male	2 (5.3)
Race – N (%)	
White	25 (65.8)
Non-White	2 (5.3)
Unknown	11 (28.9)
Ethnicity – N (%)	
Hispanic	8 (21.1)
Non-Hispanic	29 (76.3)
Unknown	1 (2.6)
Educational Attainment- N (%)	
Less than high school degree	2 (5.3)
High School & some college	22 (57.9)
College graduate/graduate school	13 (34.2)
Unknown	1 (2.6)
Insurance – N (%)	
Medicaid	4 (10.5)
Medicare	13 (34.2)
Private	20 (52.6)
Other	1 (2.6)
Disease – N (%)	
RA	27 (71.1)
SLE	3 (7.9)
MCTD/Other	8 (21.1)
Medication Use^{+} – N (%)- [N=33]	
Methotrexate	17 (51.5)
Hydroxychloroquine	12 (36.4)
Sulfasalazine	2 (6.1)
Tofacitinib	2 (6.1)

The navigators documented over 360 conversations with enrolled patients. Qualitative analyses demonstrated that the navigators uncovered a number of medication-related side effects, financial issues and doctor-patient communication barriers which influenced their adherence (8).

For the 69 patients who completed the MMAS-8 surveys, the navigators facilitated patient-doctor communication (for 27% of the patients), provided education about a DMARD or about the patient's rheumatic disease (22%), developed and implemented personalized strategies such as automatic refills, refrigerator magnet reminders, or text message alerts to improve the likelihood of adherence (14%), assisted with care coordination (13%), addressed financial and insurance issues (11%), provided social and emotional support (9%) and facilitated expedited mental health referrals (3%).

We compared survey scores at baseline with those after the 6-month intervention (**Table 3.3**). We found no significant difference in adherence with a slightly lower mean MMAS-8 score of 6.4 ± 1.6 at 6 months (p=0.09). Similarly, we did not observe an improvement in depressive symptoms (p=0.83), with the same 15% with MHI-5 scores <52. There was no change in disease activity (RADAI and SLAQ). We did find a statistically significant decrease in concerns related to medications (Beliefs about Medicines, Concerns Scale, p=0.03), as well as an increase in the perceived threat associated with the patients' rheumatic disease (Brief Illness Perception, p=0.01). A sensitivity analysis excluding the 16 patients with baseline high adherence scores (MMAS-8=8) similarly did not demonstrate a statistically significant difference in pre- and post-MMAS-8 scores (p=0.15) or in depressive symptoms (p=0.53). We also did not find statistically significant changes in MMAS-8 score when examined separately for each action performed by the navigators. In our multivariable linear regression model estimating the relationship between age, race/ethnicity and insurance status and change in MMAS-8, we found an association between 5-year increase in age and change in MMAS-8 score (β=0.14, p=0.02), but no significant relationship with the other variables examined.

Table 3.3. Baseline and 6-month post intervention mean ± SD survey scores

Survey Instrument*	N	Baseline (Pre-Intervention)	6-month (Post-Intervention)	p-value**
Morisky Medication Adherence Scale (MMAS-8)	69	6.7 ± 1.3	6.4 ± 1.6	0.09
Mental Health Inventory (MHI-5)	48	60.8 ± 9.1	60.5 ± 8.9	0.83
Beliefs about Medicines, Concerns Scale	48	11.8 ± 4.7	11.6 ± 4.9	**0.03**
Brief Illness Perception Questionnaire	47	45.7 ± 9.8	47.1 ± 8.0	**0.01**
RA Disease Activity Index (RADAI)	46	13.5 ± 9.3	12.3 ± 7.9	0.21
SLE Activity Questionnaire (SLAQ)	4	38.0 ± 6.0	39.5 ± 5.8	0.26

*MMAS-8 range 0-8, MHI-5 range 0-100, Beliefs about Medicines range 5-25, Brief Illness Perception range 0-80, RADAI range 0-48, SLAQ range 0-47
**p-values determined using paired t-tests

Discussion

In this Med Assist pilot study, two navigators worked with patients with rheumatic diseases to understand barriers to DMARD adherence and to develop individually tailored strategies to address these barriers. During this 6-month pilot intervention, the navigators performed a number of services for the patients enrolled but we did not observe an improvement in adherence as measured by the MMAS-8. We did demonstrate a small but statistically significant reduction in medication-related concerns, as well as an increase in patients' threat perceptions associated with their rheumatic disease. In line with the HBM framework, an understanding of the threat and severity associated with a rheumatic disease, and a reduction in fears associated with medication use may increase the likelihood of adherence.

There are a number of plausible explanations for the lack of observed improvement in MMAS-8. One explanation is that modifying patients' perceptions about the threat of illness (or conversely, benefit of treatment) does not necessarily result in altered behavior, i.e. people's intentions do not always align with their actions. This may be because adherence behavior is

complex and rooted in factors that are not directly modifiable by a person in the navigator role, even when concrete strategies are tailored to each patient's needs. An alternate explanation is that the "dose" of intervention was insufficient to influence behavior change – e.g. the navigator was not able to form a close enough relationship with patients over the 6-month intervention period using primarily phone calls to truly monitor, understand and alter behavior. The lack of improvement in disease activity also suggests that this patient population may have more complex or difficult to manage disease and therefore follow-up beyond 6 months may have been necessary to test the intervention's efficacy. It is also possible that self-reported adherence using the MMAS-8 may not accurately represent adherence behavior. Additionally, the many roles performed by the navigator may have been more related to rheumatologic care in general than directly to adherence behavior and therefore may not have been captured by this scale. It is also possible that our study was underpowered to detect a clinically meaningful change in adherence. We had estimated that 70 patients were needed to determine a difference in MMAS-8 of 0.35 ($1-\beta=0.81$, $\alpha=0.05$).

Alternatively, one could interpret the lack of significant change in MMAS-8 (i.e. maintenance of adherence over the 6-month period) as a potential benefit of the navigator intervention. Prior studies of continued adherence to DMARDs ("persistence") among RA patients suggest that declines are typically observed over time for nearly all medications.(15) We did not have a control group in this pilot study however one could hypothesize that if the natural course of adherence is a decline over time, the stable adherence observed may represent a beneficial effect of the navigator. A randomized controlled trial is needed to investigate whether this is the case by determining the trend in adherence among those without navigator involvement.

Our study had a number of strengths. We enrolled a relatively diverse cohort of patients, including those who were Spanish-speaking, and nearly two-thirds of those enrolled remained engaged with the navigator over a 6-month period. We trained patient navigators to deal with rheumatology-specific issues and medications and were the first to translate an intervention that showed promise in other chronic disease management to improve adherence among patients with rheumatic diseases. Our patients had varied levels of adherence at baseline with the majority with either poor or borderline adherence suggesting potential for improvement. Our navigators were able to communicate regularly with these patients and perform a number of tasks to reduce personal and healthcare-related barriers faced. Additionally, they facilitated patient-physician communication and provided education about medications and about the patients' rheumatic diseases. Finally, we utilized previously validated survey instruments grounded in a well-established theoretical framework, to evaluate our intervention.

There were limitations to this work. This was a pilot study and not a randomized controlled trial and therefore we are unable to draw conclusions regarding the possible incremental benefit of this intervention compared to current standard of care. We did not directly measure intentional versus unintentional adherence or self-efficacy using surveys, however the navigators assessed these factors qualitatively.(8) There are also limits to the generalizability of this study. The majority of participants were female, and many were well-educated. All enrollees received care at a single academic center and the majority had rheumatoid arthritis. In addition there may be selection bias in terms of who is willing to enroll in a patient navigator intervention, as well as the possibility of differential attrition. We did investigate this further by examining the 38 patients who initially enrolled but did not complete

follow-up surveys. We did not find significant differences in demographic factors or in baseline adherence between these patients and the 69 with completed MMAS-8 surveys.

Overall, our Med Assist study demonstrates the feasibility of a rheumatology-specific patient navigator intervention, and the potential for individually-tailored techniques to reduce concerns about medications and increase awareness regarding the importance of receiving treatment for systemic rheumatic diseases. While we did not find a significant change in adherence pre- and post-intervention, the lack of a control group, and the 6-month duration of this pilot study do not permit us to make causal inferences regarding the efficacy of this intervention to improve adherence. Further studies are needed to determine the longer-term efficacy of using a patient navigator to improve DMARD adherence.

Paper 3 Bibliography

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Supplemental Materia1

I. Example Equations for Multilevel Models (Paper 2)

Models are the log odds of adherence vs. nonadherence for the i[th] individual (level 1) in the j[th] zip code (level 2) in the k[th] county (level 3) in the l[th] state (level 4).

$u_{2jkl} = zip\ code\ random\ effect;\ u_{3kl} = county\ random\ effect;\ u_{4l}$= *state random effect*

Null Model

$$logit\ (\pi_{ijkl}) = B_0 + u_{2jkl} + u_{3kl} + u_{4l}$$

Individual-level fixed effects added

$$logit\ (\pi_{ijkl}) = B_0 + \Sigma BX(individual\ factors)_{ijkl} + u_{2jkl} + u_{3kl} + u_{4l}$$

Zip code-level fixed effects added

$$logit\ (\pi_{ijkl}) = B_0 + \Sigma BX(individual\ factors)_{ijkl} + \Sigma BX(zip\ code\ factors)_{jkl} + u_{2jkl} + u_{3kl} + u_{4l}$$

County-level fixed effect added

$$logit\ (\pi_{ijkl}) = B_0 + \Sigma BX(individual\ factors)_{ijkl} + \Sigma BX(zip\ code\ factors)_{jkl} + B1(county\ per\ capita\ number\ of\ MDs)_{kl} + u_{2jkl} + u_{3kl} + u_{4l}$$

State-level fixed effect added (to individual/zip model)

$$logit\ (\pi_{ijkl}) = B_0 + \Sigma BX(individual\ factors)_{ijkl} + \Sigma BX(zip\ code\ factors)_{jkl} + B1(state\ rheumatologists)_{l} + u_{2jkl} + u_{3kl} + u_{4l}$$

II. Variance Partitioning Equations for Random Intercepts Models:

σ_l^2 = between-state variation (level 4)
σ_{kl}^2 = between-county variation (level 3)
σ_{jkl}^2 = between-zip code variation (level 2)

Proportion of variance attributable to level 4: $\frac{\sigma_l^2}{\sigma_l^2+\sigma_{kl}^2+\sigma_{jkl}^2+3.29}$

Proportion of variance attributable to level 3: $\frac{\sigma_{kl}^2}{\sigma_l^2+\sigma_{kl}^2+\sigma_{jkl}^2+3.29}$

Proportion of variance attributable to level 2: $\frac{\sigma_{jkl}^2}{\sigma_l^2+\sigma_{kl}^2+\sigma_{jkl}^2+3.29}$