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Trajectory of adherence behavior in pediatric and adolescent liver transplant recipients – the MALT cohort

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Abstract

Knowledge of the long term trajectory of nonadherence to immunosuppressants can inform decisions regarding organ allocation, adherence monitoring, and intervention efforts. The MALT (Medication Adherence in children who had a Liver Transplant) prospective multi-site study followed 400 pediatric and adolescent liver transplant recipients for 2 years, using the Medication Level Variability Index (MLVI) to monitor adherence. We hypothesized that adherence is an unstable (fluctuating) phenomenon: that patients who are adherent in year one may become nonadherent in year 2, and vice-versa. However, we also hypothesized that a majority (more than 50%) of nonadherent patients remain nonadherent over time. We further hypothesized that the longer nonadherence lasts, the higher the likelihood of adverse events (rejection). Finally, we explored the effect of socioeconomic factors on the evolution of adherence over time. Most (59.7%) of MALT patients who were nonadherent in year 1 remained so in year 2; 18.5% of patients who were adherent in year 1 became nonadherent in year 2. Only 4.4% of patients who were adherent in both year 1 and year 2 had a rejection, compared with 22.9% of patients who were nonadherent during one of the years, and 34.9% of those who were nonadherent in both years ($p < .001$), establishing a “dose dependent” effect of adherence on transplant outcomes. Single-parent households were associated with worsening adherence. Our results suggest that good baseline adherence does not guarantee adherence later on, that nonadherence is likely to persist in

the absence of interventions, and that monitoring of adherence and interventions to improve it should be expected to last for years if transplant outcomes are to be improved.

Keywords

Adherence; Compliance; Liver Transplant; Pediatric

Introduction

Nonadherence to prescribed immunosuppressive medications is associated with most cases of late acute rejection (LAR) in pediatric liver transplant recipients (1, 2). As one of the most important risk factors in transplant care, it is surprising that very few investigations have looked at the relationship between transplant outcomes and variation in medication taking behavior over time. The few studies that have examined this issue (3–8) suggested that adherence is unstable. But it is difficult to draw conclusions because of small sample sizes, selection bias, and usage of variable methods to assess adherence, particularly self-reports or indirect measures. Furthermore, it is not known how variable patterns of adherence influence clinical outcomes (4). As the field still struggles to develop effective strategies to assess and mitigate nonadherence, it is important to understand how variation in adherence behaviors might inform intervention and monitoring strategies.

It is especially important to study variation in adherence behavior in solid organ transplant recipients, because past adherence might influence the decision to relist patients with late liver allograft failure, especially if it turns out that past adherence predicted future adherence. However, if adherence is not stable, such considerations would seem to be misguided. There are also other reasons that it is important to study adherence behavior over time. Knowing whether the average rate of adherence in an entire cohort or clinic changes or not over time might have implications for the allocation of ancillary supports. It might be possible to stratify patients' risk more accurately based on the length of time that they remain nonadherent, if it were the case that a longer period of nonadherence is worse than shorter periods of nonadherence. If fluctuating adherence leads to poor outcomes, then any indication of nonadherence should be pursued aggressively, regardless of the period of time in which it is noted. Lastly, it would be important to look at the effects of age and markers of socioeconomic status (SES) on the trajectory of adherence. It is already known that adolescents have lower rates of adherence than both younger children and adults (9). However, it is unclear if adolescent adherence varies over time more or less than younger children's adherence. Additionally, nonadherence has been shown to correlate with lower SES (9). It is not known, however, whether a lower SES contributes to worsening adherence over time or if it only confers risk at baseline.

We report results from the MALT cohort, in which adherence was measured via the Medication Level Variability Index (MLVI), a validated objective measure of the degree of fluctuation of tacrolimus blood levels over time (10). The MALT prospective, multisite study recruited a nationally representative sample of 400 pediatric liver transplant recipients who were prospectively followed for 2 years each. MALT study results (10) showed that the

MLVI, an objective measure of adherence, predicts rejection outcomes (and also outcomes related to liver injury, such as liver enzyme levels). The former publication demonstrated the validity of the MLVI in predicting poor transplant outcomes. The present manuscript evaluates variance in adherence behavior. The MALT cohort offers a unique opportunity to test these critical and clinically relevant questions since the data set reflects work done under the umbrella of a rigorous clinical trial.

We hypothesized that:

1. Adherence is an unstable (fluctuating) phenomenon: that patients who are adherent in year one may become nonadherent in year 2, and vice-versa.
2. A majority (more than 50%) of severely nonadherent patients remain nonadherent over time.
3. The longer nonadherence lasts, the higher the likelihood of adverse events (rejection).

We also explored the effect of socioeconomic factors on the evolution of adherence over time, and the effect of fluctuating adherence on rejection outcomes.

METHODS

Participants

Participants were enrolled in the Medication Adherence in Children Who Had a Liver Transplant (MALT) cohort (10). This multisite prospective trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01154075): NCT 01154075) recruited 400 children or adolescents ages 1–17 years and their families from five pediatric liver transplant centers in the United States (Cincinnati Children's Hospital Medical Center; Mattell Children's Hospital, UCLA; Lurie Children's Hospital, Chicago; Children's Hospital of Pittsburgh of UPMC (CHP); and Mount Sinai Medical Center, New York) and followed each subject for two years. A recruitment diagram and baseline characteristics are available elsewhere (10). We previously reported that the average number of levels used to calculate MLVI in the MALT cohort was 12, and that a higher MLVI was significantly correlated not just with rejections but also with higher liver enzyme levels (10).

Procedures

The study was approved by the respective Institutional Review Boards of all participating institutions and involved parent/caregiver consent and child assent in accordance with each institution's policies. Medical variables and outcomes were followed for a two year period (ending in June 2015). Quarterly chart reviews were conducted during which time all tacrolimus levels were reviewed in order to characterize adherence (as described below). Socioeconomic variables, obtained from the medical chart, included whether or not the child lived in a single-parent household as well as the type of medical insurance that the child (patient) had – private or government sponsored insurance. The MALT cohort enrollment predates the affordable care act, and so “government insurance” refers to other types of coverage. Data were sent via a secure web-based interface to a data-coordinating center (The Emmes Corporation, Rockville, MD).

The Medication Level Variability Index (MLVI)—MLVI (10, 11) is defined as the degree of variation in blood levels of tacrolimus, the primary immunosuppressant used to prevent allograft rejection in liver transplant recipients. Measurement of trough blood levels of tacrolimus is standard practice in participating centers and generally obtained once every three months. MLVI is calculated as the standard deviation (SD) of at least 3 tacrolimus trough blood levels for each patient. A higher MLVI denotes more fluctuation in levels. MLVI can be used as a continuous variable (higher MLVI = more medication level fluctuation = worse adherence) or a dichotomy, where $MLVI > 2.0$ indicates erratic adherence (10). A high MLVI predicts future rejection in pediatric (10) and adult (11) recipients. Further information about the MLVI is presented elsewhere (10, 11).

Central Pathologist-Diagnosed Rejection—The primary outcome measure in the MALT study was LAR, as determined based on independent readings in a central pathology lab, masked to clinical data, using Banff consensus criteria (12). Centers did not perform “protocol” biopsies during the study period; all biopsies were for cause according to clinical indications. All biopsies performed during the study period were reviewed by two central pathologists. If the central pathologists disagreed, the case was adjudicated by the senior study pathologist. For each participant, if there was at least one biopsy-proven episode of rejection during the study period, it was entered as a “positive rejection”.

Statistical Analyses

We specified the following hypotheses prior to data analyses:

1. The average adherence rate (average MLVI) will remain stable over time in the cohort as a whole.
2. Effect of length of time of erratic adherence on rejection outcomes:
 - a. Trend analysis: Over the two years of follow-up, we hypothesized that patients who had good adherence (below-threshold MLVI) in Year 1 and 2 will have the lowest incidence of LAR; patients who were nonadherent in one of those years and adherent in the other will have an intermediate risk; and the highest incidence of LAR will be experienced by patients who were nonadherent in both years (above-threshold MLVI in year 1 and year 2).
 - b. Length of time: When the data are looked at on a rolling basis (adherence calculated for 1 year at a time for different consecutive segments of the 2 year period), patients who were nonadherent in more segments would be more likely to have a rejection, even if the segments were not contiguous.
3. Effect of age: Adolescents will experience deterioration of adherence over time, whereas younger children will display more even adherence over time.
4. Effect of markers of socioeconomic risk: Patients with private health insurance will experience stable adherence over time, whereas patients with public plans will experience deteriorating adherence over time.

To evaluate MLVI on a rolling basis, we calculated MLVIs for one year's set of Tacrolimus levels for each subject, where that year was defined as the year prior to the index quarter. So, per-patient MLVIs were calculated for the periods of 0–12 months, 3–15 months, 6–18 months, 9–21 months, and 12–24 months in the study (Table 1). To calculate the degree of variation between individual patients' MLVI over time, we calculated the SD of each subjects' set of MLVI's (a higher SD = more fluctuation in MLVI levels over time). To look at changes in adherence between the two years of the cohort, we computed MLVI in year 1 (months 0–12) as compared to MLVI in year 2 (months 13–24) per subject. Missing blood level data were not included in the analyses; a thorough evaluation of the effect of missing data on the MLVI's relationship to outcome (no effect) is presented elsewhere (10, 11). Not all patients had at least 3 available tacrolimus levels for each time-frame; we included only those patients for whom at least 3 levels were available. This resulted in somewhat different sample sizes in different analyses.

Statistical analyses were performed using the SAS System for Windows 9.3 (SAS Institute Inc., Cary, NC). Spearman's r correlations were utilized to compare MLVI between the study years. Non parametric Kruskal-Wallis tests were conducted to compare numeric values between groups while McNemar's test was used for group comparisons on dichotomous variables. A Cochran-Armitage Trend Test was used to examine whether there was a trend for increasing rejection rates depending on time with above threshold MLVI.

Finally, as pre-defined in the MALT statistical analysis plan, the sample was divided into pre-adolescent (1–12 years old) and adolescent patients (13–17 years old) because of the known higher prevalence of non-adherence among adolescent transplant recipients.

RESULTS

Table 1 shows MLVI values calculated for the entire MALT cohort on a rolling basis throughout the MALT study period (calculated for 12 months prior to the index quarter, for patients who had at least 3 levels during the reporting period). The differences in number of patients selected for each period reflect differences in number of patients who had at least 3 outpatient blood levels from which to calculate MLVI. There were no differences in the cohort's average adherence readings throughout the two year follow-up period. Similarly, the percentage of nonadherent patients (patients with above threshold MLVI) in the cohort was similar over time; the number of "above threshold" MLVI's was not different between Year 1 and Year 2 in the cohort (McNemar's test, $p=0.15$).

Next, we examined the per-patient association between MLVI's during Year 1 and Year 2. There was a significant correlation between MLVI during Year 1 and Year 2, Spearman $r = 0.45$, $p < 0.001$. Table 2 shows that 18.5% of the patients who were adherent in year 1 became nonadherent in year 2, and 59.7% of the patients who were nonadherent in year 1 remained nonadherent in year 2, establishing both that nonadherent patients tend to remain nonadherent and that adherence in year 1 was not always indicative of continuing adherence in year 2. The findings indicate that substantial variance in MLVI occurred in a subset of the cohort.

Patterns of Adherence and LAR

Table 3 evaluates the relationship between the incidence of LAR and MLVI variance. The frequency of LAR was higher for patients with greater variance in MLVI (Kruskal-Wallis $p < 0.001$). Four distinct subpopulations were identified. Those that were adherent for both the first and second year of observation, those that were non-adherent for both years, those that were adherence and became non-adherent and those that were non-adherent and become adherent (Figure 1). The relationship between LAR and the duration of non-adherence was examined in 3 groups – nonadherent in both years, adherent in both years, and nonadherent in one of the years and adherent in the other year (TABLE 4). For patients who were fully adherent, the rejection rate was just 4.4%. For those with MLVI values above 2 during one of the follow-up years, LAR rate rose to 22.9%. When MLVI was above threshold during both years, the rate of LAR was 34.9% (Table 4); this trend was significant (Table 4), and shows that the longer the patient was nonadherent in the MALT cohort, the higher the risk for LAR.

Effects of Age and SES

Table 5 shows the demographic characteristics of patients with below-threshold MLVI (adherent patients) depending on their adherence status in Year 2. Patients with government-issued insurance or no insurance, patients whose parents did not have a college degree and patients who lived with only one parent were significantly more likely to become nonadherent in year 2. Table 6 shows the characteristics of patients who were nonadherent in year 1. Patients from single-parent households were significantly more likely to remain nonadherent in year 2. Taken together, both tables show that single parent households denoted increased risk, as did indices of low SES, in general. As shown in Table 6, in contrast to our initial hypothesis, age did not differentially impact MLVI stability. However (Figure 2), SES did impact the progression of above-threshold MLVI when calculated quarterly, with patients on private insurance remaining stable while patients with other insurance (lower SES) showing a deterioration over time

DISCUSSION

Whether adherence is a stable behavior or not among transplant recipients has largely been considered subjectively or in studies with limited generalizability (8); very few studies have looked at outcomes associated with fluctuations in adherence (4), and the methods by which adherence was measured were quite imperfect. For example, one study that attempted to look at adherence behavior over time (7) showed that patients who self-reported good adherence experienced as many rejections as patients with self-reported non-adherence, and were, in addition, significantly more likely to die. Those results suggest that the adherence measure in that study was flawed (an alternative interpretation of those data could also be that good adherence to medical recommendations in that cohort indeed lead to significantly poorer outcomes as compared with patients who did not follow the medical recommendations, who did significantly better; but we believe that this is an unlikely scenario, unless that cohort was highly unusual).

The present study was able to examine trajectories of adherence over time and their influence on outcomes using a large, multi-site sample of pediatric transplant recipients, employing an objective measure of adherence. We found that the cohort's average adherence rate remained stable over time, with no significant differences in rates of adherence in the sample as a whole between Year 1 and Year 2. But (Figure 2, Table 2) 18.5% of the patients who were adherent in Year 1 became nonadherent in Year 2. Therefore, previously good adherence is not always an indication of good adherence later on. This finding suggests that regular monitoring of adherence should be considered for all patients, including those who appear to be managing their medications well at baseline. Overall, we found that about 61% of patients remained adherent over the 2 year period, 15% remained non-adherent, and 24% show fluctuating adherence.

The fact that almost 60% of patients who were nonadherent in Year 1 remained nonadherent in Year 2 is concerning. We did not change standard practices in MALT, therefore it is possible that some of those patients were targeted for clinical intervention or support at the site. All MALT centers have a dedicated transplant social worker and a nurse coordinator, and most have a dedicated psychologist. However, we do not know the extent to which those, or other, services were mobilized for any particular patient; those important details, which could have implications to staffing decisions in transplant centers, could be a focus of a separate study. On one hand, the current standard of practice and putative psychosocial supports might have been a positive factor in that most patients in the cohort showed good adherence in both year 1 and year 2, and 40% of patients who were nonadherent in Year 1 became adherent in Year 2. On the other hand, the fact that of those who were nonadherent in year 1, almost 60% remained nonadherent strongly suggests that current practices are insufficient and a dedicated adherence monitoring and intervention program is indicated. In aggregate, our results suggest that adherence should be monitored continuously and addressed when it reaches a "risk" threshold (such as, MLVI>2.0) rather than considered to be a static risk.

The MALT cohort was comprised of patients who were recruited at various points posttransplant. Therefore, our findings reflect the general evolution of adherence in recipients, but are not necessarily reflective of a linear posttransplant trajectory. It is possible that nonadherence during certain specific periods, for example, immediately after transplant, evolves differently. In MALT, the longer the patient was nonadherent, whether consecutively or not, the risk for rejection increased. This finding suggests that nonadherence should be addressed as soon as it is identified. In addition, we found that variance in adherence also increased risk for LAR. This suggests that interventions to improve adherence should follow patients for a long period of time, as transient improvements in adherence might not have a lasting effect on outcomes if the patient lapses back into nonadherence at the end of the intervention. Like many other risk factors for poor transplant outcomes (such as hypertension), addressing nonadherence should be considered within the context of a lifetime regimen of monitoring, coupled with intervention whenever a concern rises, again and again.

An intriguing finding was that patients who had private health insurance had stable adherence over time, whereas patients with other, largely public, health insurance had

worsening adherence over time. This may have nothing to do with the insurance per se but rather may reflect variable risk in participants in those different insurance pools. Others have reported an association between insurance type and transplant outcomes (13), and we have previously addressed the general association between demographic factors in the MALT cohort (10). But adherence in those other studies was evaluated as a static risk rather than as an evolving one, whereas our results suggest that adherence is an evolving risk, at least in some patients. Looking at the evolution of risk over time (as opposed to cumulative risk), we believe, offers us a unique opportunity to evaluate whether the risk is potentially amenable to interventions or not. Even more impressive was the association between one-parent households and progressively poor adherence, whereas two-parent households were associated with improved adherence over time. This could be related to less supervision in single parent households, but a cautionary note is indicated: those are associations, and we cannot infer a causal relationship. Our data are limited to a two-year period; it is possible that the trajectory that we report for the two years was not present in other years. If so, our findings may mean that there is less fluctuation in adherence patterns in single parent households. Patients who come from single parent households should probably be monitored more closely with regards to transplant function and adherence, but our data cannot be taken to mean that the fact that only one parent is involved is in itself the reason for the increased risk: it could be that the risk is related to other associated factors, such as low SES. We note that the fact that those SES – related risks evolved (got worse) over time strongly suggests that the risk might be ameliorated, perhaps through increased attention to those vulnerable patients and a lower threshold for intervention efforts. This evolving, rather than static, risk suggests that interventions might be beneficial, especially, in low SES patients, as it may be possible to reverse or halt the worsening of adherence over time.

On the other hand, we found that adolescence, a time when pediatric transplant recipients generally assume primary responsibility for their own care (2, 14), confers a “stable” risk of nonadherence, with no improvement or deterioration over time, suggesting that the age of transition to self-care is a robust “baseline” risk. Our results highlight the importance of finding more effective ways to assess and support transition to self-managed care (15).

There are several limitations to this study. A limitation of our study design is that all values were obtained clinically and not according to a predetermined protocol (this increases the generalizability of the findings but introduces some bias in the way that data were obtained). The fact that some patients had less than 3 levels at a relevant monitoring period is a limitation, related again to the fact that we did not obtain blood tests for study purposes. It is reassuring that, as we previously described (10), the number of tacrolimus levels that were obtained during the course of the study was not significantly different between adherent versus nonadherent patients. Although age at diagnosis, time from liver transplantation to study period, indication for liver transplantation, and concomitantly prescribed medications were reviewed in the MALT cohort (10), we did not look at other constructs such as previous episodes of rejection and medical comorbidities such as renal impairment. Those can impact the likelihood of rejection, although they may not necessarily alter the degree of relationship between nonadherence and poor outcomes. While we were able to ascertain which insurance type the patients had, we cannot tell what kind of access they had to insurance options, which might be a more precise indicator of socioeconomic status. Finally, a significant

limitation is the fact that the clinical utility of MLVI monitoring is still unknown – only a robust intervention study can determine the best way that this marker, or any other marker, can be used.

In conclusion, our results, which show a high level of nonadherence in the cohort (about 40% of patients were either nonadherent the entire period or showed fluctuating adherence), support the need for continuous monitoring of adherence, the timely provision of targeted interventions to improve adherence, and the continuous provision of such interventions over a long period of time. We found that the MLVI is able to stratify risk according to the length of time in which a high MLVI is present. Since nonadherent patients are likely to remain so without an intervention, we believe that our data suggest that targeted interventions would be crucial in order to reverse this trajectory. This conclusion is tempered, however, by the fact that to date, we are not aware of even one well-powered randomized controlled trial that has conclusively shown that a specific adherence intervention can improve transplant outcomes such as rejection rates or graft survival (although quite a few showed improvement in adherence rates without improvements in transplant outcomes). Our results suggest that markers of low SES, as well as single-parent households, should be considered a risk factor for progressively worse adherence. Since our previous analyses (10) found that adolescents are a vulnerable group of patients with a heightened risk for organ rejection related to nonadherence, our results reinforce the need for continuous monitoring of adherence during the time that transition to self-managed care happens in this age group. When used in clinical practice, it is important to note that the MLVI, reflecting the nature of the behavior of nonadherence, fluctuates over time. Therefore, in clinical use, we suggest that the MLVI be computed anew every time a blood level is obtained, from blood levels recorded in the 12 months period leading to the time in which this new level was recorded.

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ABBREVIATIONS

LAR	Late Acute Rejection
MALT	Medication Adherence in children who had a Liver Transplant
MLVI	Medication Level Variability Index
SD	Standard Deviation
SES	Socioeconomic Status

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Figure 1. scatterplot of the relationship between adherence in years 1 or 2 and rejection

Cross = a subject who had a rejection during follow up/Circle = a subject who did not have a rejection.

MLVI = Medication Level Variability Index.

Quartiles:

a = fully adherent patients (MLVI ≤ 2.0 in years 1 and 2)

b = partially adherent – patients who were nonadherent in year 1 and became adherent in year 2 (MLVI > 2.0 in year 1 and MLVI ≤ 2.0 in year 2)

c = partially adherent – patients who were adherent in year 1 and became nonadherent in year 2 (MLVI ≤ 2.0 in year 1 and MLVI > 2.0 in year 2)

d = patients who were nonadherent (MLVI > 2.0) in both years 1 and 2.

Figure 2.
Proportion of MLVI > 2.0 by insurance type over two year follow-up

Table 1

Distribution of MLVI Calculated for One Year Period on a Three Months Rolling Basis

	N	Mean	SD	Median	Min	Max
MLVI 0-12 Months	364	1.6	1.2	1.2	0.1	13.0
MLVI 3-15 Months	339	1.6	1.4	1.2	0.0	13.5
MLVI 6-18 Months	329	1.6	1.3	1.2	0.0	11.5
MLVI 9-21 Months	320	1.6	1.4	1.2	0.0	12.8
MLVI 12-24 Months	305	1.7	1.5	1.2	0.0	12.1

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Table 2

Relationship Between MLVI > 2.0 in Year 1 and Year 2

	Total		MLVI > 2.0 in Year 2			
			No		Yes	
	N	%	N	%	N	%
Total	294	100.0	210	100.0	84	100.0
MLVI > 2.0 in Year 1						
No	222	75.5	181	81.5	41	18.5
Yes	72	24.5	29	40.3	43	59.7

Table 3
Relationship Between Rejection and Degree of Fluctuation of MLVI, Calculated Quarterly for One Year Period.

	SD of MLVI Calculated for One Year Period on Three Months Rolling Basis						Kruskal-Wallis Test
	N	Mean	SD	Median	Min	Max	
Total	358	0.5	0.6	0.3	0.0	4.8	
Rejections							
No	316	0.4	0.5	0.3	0.0	4.0	<0.001
Yes	42	0.8	0.9	0.5	0.1	4.8	

Relationship Between Rejection and the Amount of Time a Patient Had MLVI >2.0 (None, Year 1 or Year 2, Both Year 1 and Year 2).

Table 4

	MLVI in Year 1 and Year 2										Cochran-Armitage Trend Test		
	Total		MLVI<2.0 in Year 1 AND Year 2				MLVI<2.0 in Year 1 AND >2.0 in Year 2 or vice versa					MLVI>=2.0 in Year 1 AND Year 2	
			N	%	N	%	N	%	N	%		N	%
Total	294	100.0	181	100.0	70	100.0	43	100.0					
Rejections													
No	255	86.7	173	95.6	54	77.1	28	65.1				<0.001	
Yes	39	13.3	8	4.4	16	22.9	15	34.9					

Table 5

Demographic Characteristics of Participants Who Were Adherent in Year 1 (MLVI≤2.0)

	MLVI>2.0 in Year 2			
	Yes N=41	No N=181	Total	P Value ^I
Age at Baseline				
0<13.0	29 (70.7%)	135 (74.6%)	164 (73.9%)	0.69
>= 13.0	12 (29.3%)	46 (25.4%)	58 (26.1%)	
Gender				
Male	14 (34.1%)	91 (50.3%)	105 (47.3%)	0.08
Female	27 (65.9%)	90 (49.7%)	117 (52.7%)	
Insurance				
Private insurance	11 (26.8%)	94 (51.9%)	105 (47.3%)	0.01
Other	30 (73.2%)	87 (48.1%)	117 (52.7%)	
Parent College Degree				
Missing	1 (2.4%)	13 (7.2%)	14 (6.3%)	0.02
No	29 (70.7%)	87 (48.1%)	116 (52.3%)	
Yes	11 (26.8%)	81 (44.8%)	92 (41.4%)	
Household Status				
Missing	0	2 (1.1%)	2 (0.9%)	0.02
Single-parent household	13 (31.7%)	29 (16.0%)	42 (18.9%)	
Two-parent household	28 (68.3%)	150 (82.9%)	178 (80.2%)	

¹Fishers Exact test performed to determine differences in proportions between MLVI>2.0 and MLVI≤2.0 in year2 for various demographic characteristics.

Table 6

Demographic Characteristics of Participants Who Were Nonadherent in Year 1 (MLVI>2.0)

	MLVI>2.0 in Year 2			
	Yes/N=43	No/N=29	Total	P Value ^I
Age at Baseline				
0<13	25 (58.1%)	22 (75.9%)	47 (65.3%)	0.14
>= 13	18 (41.9%)	7 (24.1%)	25 (34.7%)	
Gender				
Male	15 (34.9%)	16 (55.2%)	31 (43.1%)	0.10
Female	28 (65.1%)	13 (44.8%)	41 (56.9%)	
Insurance				
Private insurance	20 (46.5%)	15 (51.7%)	35 (48.6%)	0.81
Other	23 (53.5%)	14 (48.3%)	37 (51.4%)	
College Degree				
Missing	3 (7.0%)	0	3 (4.2%)	>0.99
No	28 (65.1%)	20 (69.0%)	48 (66.7%)	
Yes	12 (27.9%)	9 (31.0%)	21 (29.2%)	
Household Status				
Single-parent household	13 (30.2%)	0	13 (18.1%)	0.001
Two-parent household	30 (69.8%)	29 (100.0%)	59 (81.9%)	

^I Fishers Exact test performed to determine differences in proportions between MLVI>2.0 and MLVI≤2.0 in year2 for various demographic characteristics.

Distribution of MLVI Calculated for One Year Period (Three Months Rolling Basis) by Age

Table 7

	Age at Baseline (years)											
	<13.0						≥ 13.0					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
MLVI 0-12 Months	265	1.5	1.0	1.2	0.1	7.1	99	1.7	1.7	1.1	0.2	13.0
MLVI 3-15 Months	246	1.5	1.3	1.1	0.0	13.5	93	1.8	1.7	1.3	0.1	12.0
MLVI 6-18 Months	240	1.5	1.2	1.2	0.0	7.6	89	1.7	1.7	1.3	0.1	11.5
MLVI 9-21 Months	233	1.5	1.2	1.1	0.1	7.5	87	1.8	1.8	1.3	0.0	12.8
MLVI 12-24 Months	220	1.6	1.3	1.2	0.1	8.6	85	1.8	1.7	1.4	0.0	12.1