Pediatric Transplantation
DOI: 10.1111/petr.12480

Longitudinal stability of medication adherence among adolescent solid organ transplant recipients

Loiselle KA, Gutierrez-Colina AM, Eaton CK, Simons LE, Devine KA, Mee LL, Blount RL. (2015) Longitudinal stability of medication adherence among adolescent solid organ transplant recipients. Pediatr Transplant, 00: 1–8. DOI: 10.1111/petr.12480.

Abstract: Solid organ transplantation requires ongoing adherence to immunosuppressants and other medications. Although adolescence is a risk factor for poor medication-taking, little is known about the patterns of adherence within individuals over time. This study aimed to examine the stability of adherence over time using three different assessment techniques. Sixty-six AYA transplant recipients and/or their caregiver completed interviews of adherence at baseline and at least one yr later. Serum immunosuppressant assay levels were collected via medical chart review. Non-adherence percentages based on AYA report, caregiver report, and bioassay did not differ from Time 1 to Time 2. However, correlations for these measures across time were non-significant. Further, the majority of AYAs shifted to a different adherence category from Time 1 to Time 2. Overall, these results demonstrate individual variability in non-adherence over the course of adolescence and young adulthood and highlight the importance of frequent assessment across time for solid organ transplant recipients.

Kristin A. Loiselle[1], Ana M. Gutierrez-Colina[2], Cyd K. Eaton[2], Laura E. Simons[3,4], Katie A. Devine[5], Laura L. Mee[6,7] and Ronald L. Blount[2]

[1]Division of Behavioral Medicine and Clinical Psychology, Center for Adherence and Self-Management, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Department of Psychology, University of Georgia, Athens, GA, USA, [3]Department of Anesthesia, Boston Children's Hospital, Boston, MA, USA, [4]Department of Psychiatry, Harvard Medical School, Boston, MA, USA, [5]Division of Population Sciences, Department of Medicine, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, [6]Transplant Services, Children's Healthcare of Atlanta, Atlanta, GA, USA, [7]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Key words: solid organ transplantation – adolescents – adherence

Kristin A. Loiselle, Division of Behavioral Medicine and Clinical Psychology, 3333 Burnet Avenue, MLC 3015, Cincinnati, OH 45229, USA
Tel.: +1 513 636 8254
Fax: +1 513 803 0415
E-mail: kristin.loiselle@cchmc.org

Accepted for publication 20 March 2015

Medical advances in solid organ transplantation have significantly increased the survival rates for pediatric transplant recipients (1), and successful transplantation is often associated with improved health-related quality of life (2). Despite these positive outcomes, caring for a transplanted organ can be burdensome to both recipients and caregivers. Patients must adhere to complex medical regimens, which include taking a variety of daily medications, including immunosuppressants, to maintain organ graft functioning (3). Failure to adhere to the medical regimen can result in negative health outcomes, including hospitalizations, need for biopsies, and rejection episodes (4).

Adolescence is a particularly vulnerable developmental period for medication non-adherence. Approximately 43% of adolescent transplant recipients are non-adherent to their immunosuppressive regimen and appear to be at higher risk of non-adherence-related graft loss compared to younger children (5). Rejection episodes and other negative medical outcomes are not only life-threatening for patients and stressful for families, but also financially burdensome to the healthcare system. Specifically, a report published in 2007 by the United States Government

Abbreviations: AYA, adolescent and young adult; GA, Genuinely Adherent; GNA, Genuinely Non-adherent; HIPAA, Health Insurance Portability and Accountability Act; MACS, multidimensional adherence classification system; MAM, medical adherence measure; MLM, multilevel modeling.

Accountability Office revealed that Medicare beneficiaries who experienced organ loss cost $50 398 per year to treat, compared to patients who maintained functioning transplants, which only cost $8550 annually (6). Given the multiple negative consequences of non-adherence, research has been conducted to better understand how adherence-related variables, such as perceived barriers to medication adherence, influence AYA patients and their clinical outcomes over time (7).

Clinically, medical providers often consider consistency in patients' medication-taking behavior across encounters. Despite the clinical relevance of consistent adherence, there is limited empirical information about the stability of medication adherence or non-adherence in AYA transplant recipients. A study examining pediatric kidney and liver transplant patients used MLM to demonstrate that, while medication adherence tended to decrease over the course of the study, patients with higher anxiety levels had more stable adherence (8). Of note, patients in this study included both children and adolescents, used only a single method of adherence assessment, and implemented MLM to model adherence trajectories, rather than comparing within-subject adherence rates over time. Additional research is needed to clarify how medication adherence measured via multiple methods may change over time during adolescence and young adulthood for transplant recipients.

In pediatric and young adult patients with type 1 diabetes, relative stability of regimen adherence and glycemic control has been demonstrated over a 12-month period (9). Additionally, a study including children and adolescents with acute lymphoblastic leukemia and lymphoblastic lymphoma found that the majority of patients had consistently "exemplary" or "chronically poor" adherence over the course of one month, with a small subgroup demonstrating "deteriorating" adherence (10). A review of evidence-based self-report and structured interview assessments of pediatric adherence showed, via test–retest reliability data, relative stability from two wk to one yr, further suggesting stability of medication adherence (11). In related research, levels of barriers to adherence in adolescent transplant recipients have demonstrated stability over time (12) and are predictive of poorer medication adherence as well as negative clinical outcomes, including rejection episodes, hospitalizations, and death (7). Considering the well-established relationship between barriers and medication adherence rates, the persistence of barriers over time suggests that adherence problems may also be stable over time.

No study to date, however, has explicitly addressed the central empirical question as to whether non-adherence in AYA transplant recipients is stable over time when measured via multiple methods. For the purposes of this study, stability is defined as non-significant change in adherence behavior or drug levels over time. Stable, as opposed to episodic or random, non-adherence would have important clinical implications, as it would place patients at highest risk of adverse medical outcomes. As such, intervention efforts would ideally be directed toward patients who are consistently non-adherent. Conversely, if non-adherence is an unstable construct in this population, frequent assessments of adherence should be performed.

As a result of the wide variability in how adherence is measured (e.g., self-report questionnaires, structured interviews, electronic monitors, prescription refill histories, drug assays), there may be differences in the stability of non-adherence depending on the measurement tool used. In adolescent transplant recipients, for example, discrepancies in non-adherence rates by measurement method have been reported (13), thus raising the question as to which method is most precise and sensitive. In this population, subjective patient and caregiver self-report questionnaires of patient adherence are clinically feasible and inexpensive, but may be influenced by reporter bias or social desirability (14). Drug assays provide an objective, quantifiable determinant of adherence, but only measure adherence over a short time period, do not offer information about the consistency of medication-taking over the long term, are subject to variability based on individual factors (e.g., age, gender, route of administration), and are not available for all medications (14). To overcome some of these challenges, clinicians and researchers have used standard deviation of drug assay values to provide a more stable measure of adherence over time (15, 16). Despite the methodological rigor of this approach, limitations exist for patients who do not take their medication consistently, who would have low variability, but be consistently non-adherent. Self-report and serum assays are often used with pediatric transplant recipients to measure adherence, but may not correlate with each other (17). Given the potential for discrepancies in the assessment of adherence depending on methodology, it is important to utilize multiple methods to provide a more comprehensive understanding of the longitudinal stability of adherence.

This study aimed to examine the temporal stability of medication non-adherence using three assessment methods (i.e., self-report, serum immunosuppressant level levels, and the MACS (18), an adherence classification system that incorporates a combination of self-report and serum levels) in a sample of AYA solid organ transplant recipients. The goal of this study was to provide empirical data on a fundamental clinical question: "Does medication non-adherence remain stable or change over time?" Based on the review of pediatric literature, it was hypothesized that medication non-adherence would be stable (i.e., no significant statistical differences) over time using each assessment method. Specifically, it was anticipated that (i) there would be no significant changes in the percentage of patients designated as non-adherent from Time 1 to Time 2; (ii) there would be significant positive correlations between individuals' non-adherence between times 1 and 2; and (iii) the proportion of individuals in the four MACS categories would remain stable from Time 1 to Time 2.

Methods

Participants

A total of 66 AYAs were represented in this study. Participants were between the ages of 11 and 20 yr (M = 15.8, s.d. = 2.3) at study enrollment. Inclusion criteria were that the AYA received a solid organ transplant at least four months prior to participation, lived with at least one caregiver, spoke English, and was 11 yr of age or older. Seven eligible families declined participation at Time 1 for the following reasons: no time (n = 3), not comfortable with the release of medical records (n = 1), and no reason provided (n = 3). If eligible participants had developmental delay based on caregiver report (n = 5), only caregiver proxy data were collected. See Fig. 1 for details regarding the flow of participants from Time 1 to Time 2. Approximately, 59% (n = 39) of the sample had received a kidney transplant, 25% (n = 16) received a liver transplant, 15% (n = 10) received a heart transplant, and 2% (n = 1) received a double-lung transplant. On average, participating AYAs received their transplanted organ 5.1 yr prior to enrollment in the study (s.d. = 4.7 yr; range = four months–15 yr; median = 3.4 yr). At Time 1, there were immunosuppressant drug levels for tacrolimus (n = 53), cyclosporine (n = 7), and rapamune (n = 23) and 42.2% of participants had drug levels for more than one medication. At Time 2, there were drug levels for tacrolimus (n = 50), cyclosporine (n = 9), and rapamune (n = 21), while 29.5% of participants had levels for more than one immunosuppressant drug. Additional demographic characteristics of the sample are presented in Table 1.

Measures

Caregivers provided all demographic information. AYAs and caregivers completed self-report and caregiver proxy-reported interviews of adherence at baseline (Time 1) and at least one-yr follow-up (Time 2). The mean time between participation was 18 months (s.d. = 1.5 months; range = 12.1–20.1 months). Medical data (i.e., serum immunosuppressant assay levels) were collected via retrospective electronic medical chart review.

Adherence measures

The MAM was used to assess AYA adherence to their medication regimen (19, 20). The MAM uses a semi-structured interview format to elicit responses from adolescents and their caregivers about medication adherence. Participants independently report the number of prescribed medications that the AYA missed, took late, or took on time over the previous seven days. Medication non-adherence is calculated by dividing the number of missed or late doses by the

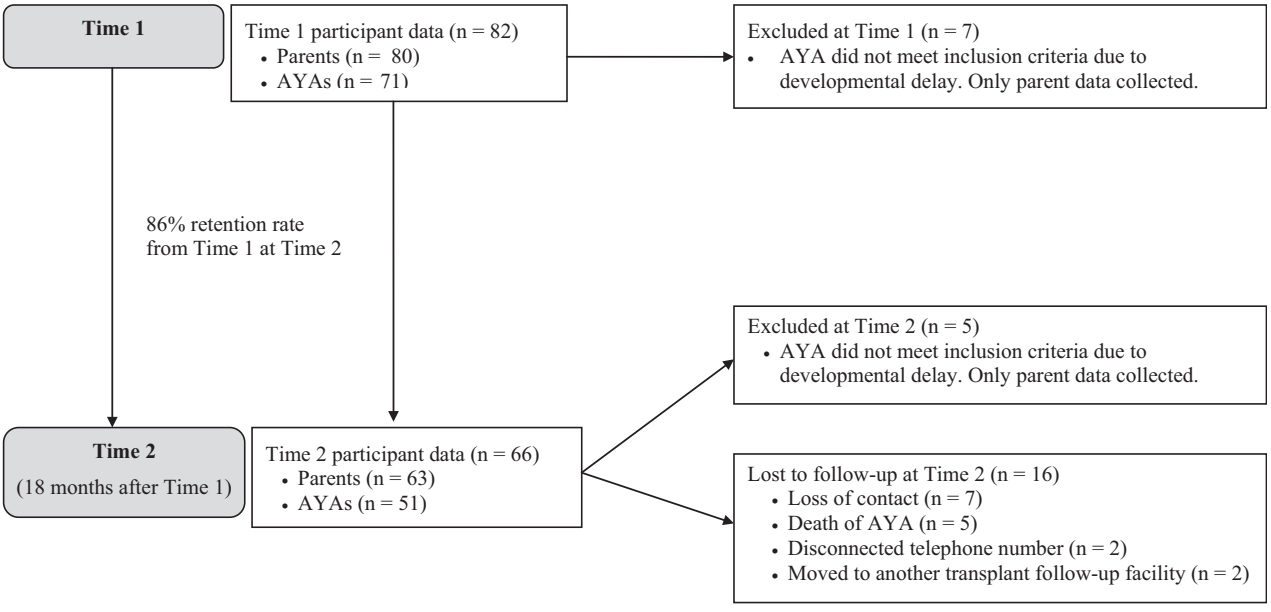

Fig. 1. Flow of participants enrolled from Time 1 to Time 2.

Table 1. Demographic information (n = 66)

	Patient			Caregiver	
Factor	Mean	s.d.	Median	Mean	s.d.
Age (yr)	15.8	2.3	16.0	44.5	7.8
Time since transplant (yr)	5.1	4.7	3.4		
	n	%		n	%
Sex					
Female	30	45.5		64	97.0
Race					
White	41	62.1		42	63.6
Black	19	28.8		19	28.8
Asian	1	1.5		1	1.5
Other	5	7.6		4	6.1
Relationship to child					
Biological parent				59	89.4
Adoptive/foster parent				7	10.6
Family income					
Less than $10 000				10	15.2
$10 000–24 999				10	15.2
$25 000–49 999				15	22.7
$50 000–74 999				9	13.6
$75 000–99 999				6	9.1
$100 000–149 999				7	10.6
$150 000+				7	10.6
Caregiver marital status					
Married/partnered				41	62.1
Single				10	15.2
Divorced/separated				13	19.7
Widowed				2	3.0

total number of prescribed doses that week. Those values are then multiplied by 100 to obtain the percentage of medications missed that week and the percentage of medications taken late that week. Participants who missed or were late in taking 10% or more of their prescribed doses in the past week were classified as "non-adherent," based on cutoffs used in previous adherence research (21). Significant associations between MAM-reported non-adherence, clinical outcomes, and barriers to adherence have been reported in the literature, indicating that the MAM has adequate validity (5, 20).

Data on serum immunosuppressant drug blood levels were obtained for up to 12 months prior to the initial interview and 12 months prior to the follow-up interview at least one yr later. Outpatient immunosuppressant drugs were examined, including cyclosporine, tacrolimus, and sirolimus. Drug levels collected during inpatient hospitalizations (if applicable) were excluded from analyses. Previous research (22–24) has identified specific ranges for out-of-target immunosuppressant levels that are associated with poor adherence (i.e., <150 or >400 for cyclosporine, <5 or >10 for sirolimus, <5 or >17 for tacrolimus, >3 s.d. for tacrolimus). The literature describes different out-of-target ranges for each drug because specific therapeutic levels vary depending on the type of immunosuppressant medication. In other words, therapeutically indicated levels for a drug, such as cyclosporine, will be different than those for another drug, such as sirolimus. As a result, they cannot be compared using the same range of values. Based on these empirically derived out-of-target ranges, participants were coded as "non-adherent" if they had at least one serum level that fell out of the target ranges (high or low level for cyclosporine, sirolimus, tacrolimus, or >3 s.d. for tacrolimus) and "adherent" if all levels were within the specified ranges. Additionally, previous literature showed that patients with tacrolimus s.d.s greater than three have significantly more rejection episodes than individuals with s.d.s less than three (25). The presence of atypical medical factors (e.g., recent changes in medication, aggressive treatments due to infection or organ rejection, inpatient hospitalization) that may have influenced immunosuppressant levels was determined by a transplant coordinator familiar with each patient enrolled in the study. For AYAs experiencing significant influential factors, drug assays during those events were not included to minimize biased data.

Adherence classification system

The MACS was developed to classify adherence in pediatric solid organ transplant recipients by combining objective (e.g., immunosuppressant drug assay levels, standard deviation of tacrolimus) and subjective (e.g., self-report and proxy report) measures of adherence (18). This multidimensional approach retains the strengths of both types of measures and categorizes patients based on a combination of patient and caregiver self-report and immunosuppressant drug levels. MACS categories include the following: (i) those who report good adherence and have adequate drug levels (GA), (ii) those who report good adherence but have drug levels out of the target range (Deniers/Medically Complicated), (iii) those who report non-adherence and have adequate drug levels (Disclosers/Medically Stable), and (iv) those who report non-adherence and have drug levels out of the target range (GNA). The MACS has adequate validity, with GNA AYA transplant recipients being more likely to experience rejection episodes and hospitalizations in the past six months. Additionally, five of the 82 patients died within one yr after baseline, all of who were from the GNA category. Additionally, patients classified as GA had the fewest adverse medical events (18).

Procedures

This longitudinal study included participants from a larger investigation examining health behaviors, quality of life, and perceived barriers to medication adherence in adolescent transplant recipients (7, 18). All study procedures were in full compliance with HIPAA regulations and approved by participating institutional review boards. Eligible families were called or approached during their regular clinic visit by a trained research assistant who invited them to participate in the study. Informed consent, assent, and HIPAA release were obtained from all participating families during their clinic visit or via mail. Self-report and proxy-reported adherence interviews were independently administered to participants by trained interviewers. Data were collected via telephone or during a clinic visit at baseline (Time 1) and at the at least one-yr follow-up (Time 2). Twenty-dollar gift cards were provided on each measurement occasion as compensation for participants' time and effort.

Data analyses

All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, Armonk, NY, USA). Descriptive statistics were calculated for all sociodemographic and adherence variables. Nonparametric statistical methods were used to assess stability of adherence across time using caregiver proxy- and AYA self-report and serum immunosuppressant levels. First,

McNemar's chi-square tests were used to assess changes in adherence group (i.e., adherent vs. non-adherent based on self-report and serum immunosuppressant levels) from Time 1 to Time 2. McNemar's chi-square test is used for dependent-samples data that are dichotomous (e.g., adherent vs. non-adherent) (26). Second, phi coefficients were calculated to examine the correlation among self-report and serum immunosuppressant non-adherence categories between times 1 and 2 to assess stability at the individual patient level. Finally, the McNemar–Bowker test (27) was used to examine the proportion of individuals in the four MACS categories at Time 1 and Time 2. The McNemar–Bowker test is also used to compare dependent-samples data; however, it is appropriate when the variable has more than two categories. Cramer's V was used as a measure of effect size for the MACS results.

Results

Non-adherence across Time

Stability of caregiver proxy- and AYA-reported non-adherence across time

According to AYAs, 18.2% reported missed and/or late medication-taking at Time 1 and 33.3% reported non-adherence at Time 2; however, this difference did not reach statistical significance. Similarly, there was no significant difference across time for caregiver proxy report of non-adherence (27.3% at Time 1 vs. 30.3% at Time 2). There were non-significant and weak effect sizes for the correlation between Times 1 and 2 non-adherence per AYA and caregiver proxy report (Table 2).

Stability of immunosuppressant drug assay levels across time

At Time 1, 66.7% of AYAs had at least one out-of-range drug level, while this decreased to 56.1% at Time 2. There was no significant difference between serum immunosuppressant indicators of non-adherence across the two time points. There were non-significant and weak effect sizes for the correlations between Times 1 and 2 non-adherence based on drug assay levels.

MACS Classification

As shown in Table 3, the highest percentage of AYAs fell into the Disclosers/Medically Stable category at both Time 1 (39.4%) and Time 2 (33.3%). Additionally, 57.1% of GNA patients at Time 1 remained in that category at Time 2, which represented the largest percentage remaining in their initial classification. AYAs who were classified as GA or Deniers/Medically Stable at Time 1 were the least likely to remain in these categories at Time 2 (35.3% and 33.3%, respectively). At the group level, the overall proportion of AYAs in each MACS category was similar at times 1 and 2 according to the McNemar–Bowker test ($\chi^2 = 5.067$, $p = 0.535$). There was a small effect for this relationship (Cramer's $V = 0.270$, $p = 0.109$). Examination of data at the individual level revealed that 57.6% of AYAs shifted from their original (Time 1) MACS

Table 2. Non-adherence from Time 1 to Time 2

Adherence measure	Time 1%	Time 2%	% Difference	χ^2	p	Phi
Reported non-adherence						
AYA report, missed or late*	18.2	33.3	15.1	2.250	0.134	0.054
Caregiver report, missed or late†	27.3	30.3	3.0	0.000	1.000	0.138
Serum assay levels						
Non-adherent‡	66.7	56.1	−10.6	1.087	0.297	0.089

For AYA report and caregiver proxy report, percentages reported are >10% missed or late. For serum assay levels, the value reported is the percentage of participants with at least one out-of-range drug level; *n for Time 1 = 56, n for Time 2 = 49; †n for Time 1 = 64, n for Time 2 = 61; ‡n for Time 1 = 62, n for Time 2 = 61.

Table 3. Percentage of stability and change in MACS categorization from Time 1 to Time 2

	Time 2				
	GA (n = 14)	Deniers (n = 12)	Disclosers (n = 22)	GNA (n = 18)	Total (%)
Time 1					
GA (n = 17)	n = 6, 35.3%	n = 4, 23.5%	n = 4, 23.5%	n = 3, 17.6%	100
Deniers (n = 9)	n = 2, 22.2%	n = 3, 33.3%	n = 2, 22.2%	n = 2, 22.2%	100
Disclosers (n = 26)	n = 6, 23.1%	n = 4, 15.4%	n = 11, 42.3%	n = 5, 19.2%	100
GNA (n = 14)	n = 0, 0%	n = 1, 7.1%	n = 5, 35.7%	n = 8, 57.1%	100

The number and percentage of patients who remained stable at Time 2 within their original Time 1 MACS category are indicated in the shaded diagonal. Patients who shifted from their Time 1 MACS category to a different category at Time 2 are represented in one of the other three categories to which they moved within the non-shaded sections of each row. At Time 1, 25.8% were GA, 13.6% were Deniers, 39.4% were Disclosers, and 21.2% were GNA. At Time 2, 21.1% were GA, 18.2% were Deniers, 33.3% were Disclosers, and 27.3% were GNA. Deniers = Deniers/Medically Stable; Disclosers = Disclosers/Medically Stable.

adherence category to one of the other three adherence categories at Time 2.

Discussion

The current study examined the stability of medication non-adherence across two time points in a sample of AYA solid organ transplant recipients using three methods: AYA- and caregiver proxy-reported adherence, serum immunosuppressant levels, and a method that combines both approaches. Hypotheses regarding the stability of adherence across time were partially supported. Results indicate that at a group level, the percentage of non-adherence based on AYA report, caregiver proxy report, and bioassay did not differ from Time 1 to Time 2. However, when using correlational methods, which assess the stability of non-adherence more at the individual level, there were no significant correlations from Time 1 to Time 2. Further, additional results showed that the majority of AYAs shifted to a different MACS adherence category across time. Taken together, these data suggest that non-adherence appears to be stable when examined at a group level. However, non-significant and weak effect size correlations among adherence measures between Time 1 and Time 2 reveal that individuals experience shifts in their medication-taking behavior, with some reporting improvements and others reporting decreases in non-adherence. This highlights the importance of frequent assessment over the course of adolescence and young adulthood for solid organ transplant recipients given that barriers to medication-taking may change over time. Research aimed at understanding adherence patterns in adolescents in vital given the increased risk of morbidity and mortality, as well as healthcare expenditures associated with problematic medication-taking.

Although a statistically significant difference was not detected in MACS classification across time, it is notable that the largest number of participants (57.1%) remaining in the same category at Times 1 and 2 were those that were GNA. Additionally, there were no participants who moved from being GNA to GA at the follow-up time point. This suggests that non-adherence documented by both self-report and out-of-range serum immunosuppressant levels may be particularly difficult to change over time as compared to participants who fall into the other three MACS classifications, which are more likely to vary.

Past research examining adherence among AYAs with other chronic medical conditions has shown a negative relationship between adherence and time since diagnosis, such that adherence declines the further out a patient is from diagnosis (28). However, there has been limited research on the trajectory of adherence as it relates to time since pediatric solid organ transplantation. One study found that time since transplantation was not related to adherence among a sample of kidney transplant recipients (29). The mean time since transplant in the current sample was approximately five yr before initial enrollment in the study, indicating that patients and families had been managing their medication regimen for a long period of time when they were enrolled in the study. This suggests that patterns of medication-taking can change through adolescence and young adulthood. Given that some participants reported improvement, while others reported a decline in adherence for AYAs over time, it will be important to identify medical and psychosocial predictors of change.

Despite the novel findings of this study, there are several limitations to consider. First, although this is one of the few studies to examine adherence over time, there were only two data points, which were an average of 18 months apart. Additionally, there were different time frames for determining adherence from the self-report (past seven days) and immunosuppressant drug levels (past year). Future research should consider more frequent and additional assessments to obtain a better sense of the trajectory of adherence. Obtaining more frequent assessments may permit the use of sophisticated statistical tests (e.g., trend analysis) to examine adherence over time. Second, most transplant recipients in this study were over five yr from their transplant and results may not generalize to AYAs with newly received transplants. Third, approximately 20% of the patients represented in this study received their transplant within one yr of Time 1 participation. Adherence rates may have been affected by the medication and dosing changes that typically occur within this time frame. Fourth, our study may have lacked sufficient power to detect changes in MACS categories across the two time points, suggesting that our failure to find significant differences could have been an artifact of low power. As a result, these analyses should be replicated in larger samples. Fifth, there are limitations associated with all forms of adherence assessment. Although we used more than one validated approach, which has been recommended in the literature (11, 30), criticisms exist including biased recall (self-report) and variability in drug metabolism (bioassays) that may have impacted adherence rates. Sixth, non-adherent patients may have been underrepresented in the study due to death

(related to non-adherence) or attrition since Time 1. Finally, our sample size did not permit examination of effects by organ group. While there are many similarities across organ groups, there may be some issues relevant only to certain groups (e.g., regimen complexity) that would affect the stability of adherence over time which were not measured in this study.

Future research is needed to improve our understanding of the stability of adherence by examining the utility of new technologies. For example, mobile phones can be used to assess adherence on a daily basis as well as capture information that may be related to adherence, such as location, presence of friends or family who may support or hinder medication-taking, self-reported mood, and perceived barriers to adherence (31, 32). Such detailed information could lead to tailored interventions to improve adherence and prevent non-adherence-related medical complications. Additionally, it is crucial that future research examining adherence behaviors over time incorporates clinical outcome measures (e.g., graft functioning, hospitalizations). Evaluation of the relationship between patterns of medication-taking and these outcomes may help clarify the impact of changes in non-adherence over time.

Overall, the results of this study point to a number of potential clinical implications for professionals providing clinical care to AYA solid organ transplant recipients. It is important for healthcare providers to regularly assess adherence with their AYA patients, as individual AYAs may demonstrate different patterns of medication-taking over time. Additionally, providers should assess adherence using more than one method (e.g., self-report, serum drug levels), as AYAs' adherence classification can differ between types of measurement.

Acknowledgment

This study was funded by Transplant Services Research Fund at Children's Healthcare of Atlanta.

Authors' contributions

Kristin A. Loiselle: Participated in concept/design, statistical analysis, data analysis/interpretation, drafting the article, critical revision of article, and approval of article; Ana M. Gutierrez-Colina: Participated in concept/design, data analysis/interpretation, drafting the article, critical revision of article, and approval of article; Cyd K. Eaton: Participated in concept/design, data analysis/interpretation, drafting the article, critical revision of article, and approval of article; Laura E. Simons: Participated in data collection, concept/design, data analysis/interpretation, drafting the article, critical revision of article, and approval of article; Katie A. Devine: Participated in data collection, concept/design, data analysis/interpretation, drafting the article, critical revision of article, and approval of article; Laura L. Mee: Participated in data collection, concept/design, critical revision of article, and approval of article; Ronald L. Blount: Participated in securing funding, concept/design, data analysis/interpretation, drafting the article, critical revision of article, and approval of article.

References

1. Magee JC, Krishnan SM, Benfield MR, Hsu DT, Shneider BL. Pediatric transplantation in the United States, 1997–2006. Am J Transplant 2008: 8: 935–945.
2. Larosa C, Baluarte HJ, Meyers KE. Outcomes in pediatric solid-organ transplantation. Pediatr Transplant 2011: 15: 128–141.
3. Agarwal A, Pescovitz MD. Immunosuppression in pediatric solid organ transplantation. Semin Pediatr Surg 2006: 15: 142–152.
4. Fredericks EM, Lopez MJ, Magee JC, Shieck V, Opipari-Arrigan L. Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. Am J Transplant 2007: 7: 1974–1983.
5. Dobbels F, Ruppar T, de Geest S, Decorte A, Damme-Lombaerts V, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: A systematic review. Pediatr Transplant 2010: 14: 603–613.
6. United States Government Accountability Office. End-Stage Renal Disease: Characteristics of Kidney Transplant Recipients, Frequency of Transplant Failures, and Cost to Medicare, [online], 2007. Available at: http://www.gao.gov/new.items/d071117.pdf (accessed May 3, 2014).
7. Simons LE, McCormick ML, Devine K, Blount RL. Medication barriers predict adolescent transplant recipients' adherence and clinical outcomes at 18-month follow-up. J Pediatr Psychol 2010: 35: 1038–1048.
8. Wu YP, Aylward BS, Steele RG. Associations between internalizing symptoms and trajectories of medication adherence among pediatric renal and liver transplant recipients. J Pediatr Psychol 2010: 35: 1016–1027.
9. Stewart SM, Lee PWH, Waller D, et al. A follow-up study of adherence and glycemic control among Hong Kong youths with diabetes. J Pediatr Psychol 2003: 28: 67–79.
10. Rohan J, Drotar D, McNally K, et al. Adherence to pediatric asthma treatment in economically disadvantaged African-American children and adolescents: An application of growth curve analysis. J Pediatr Psychol 2010: 35: 394–404.
11. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based assessment of adherence to medical treatments in pediatric psychology. J Pediatr Psychol 2008: 33: 916–936.
12. Lee JL, Eaton CK, Gutierrez-Colina AM, et al. Longitudinal stability of individual barriers to medication adherence. J Pediatr Psychol 2014: 39: 667–676.
13. Dobbels F, Damme-Lombaert RV, Vanhaecke J, de Geest SD. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant 2005: 9: 381–390.
14. Rapoff MA. Adherence to Pediatric Medical Regimens. New York: Springer, 2010.
15. Annunziato RA, Emre S, Shneider BL, et al. Transitioning health care responsibility from caregivers to patient: A pilot study aiming to facilitate medication adherence during this process. Pediatr Transplant 1998: 12: 309–315.
16. Shemesh E, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating

non-adherence to medications in transplant recipients? Pediatr Transplant 2010: 14: 940–943.
17. Simons LE, Blount RL. Identifying barriers to medication adherence in adolescent transplant recipients. J Pediatr Psychol 2007: 32: 831–844.
18. Simons LE, Gilleland J, Blount RL, Amaral S, Berg A, Mee LL. Multidimensional Adherence Classification System (MACS): Initial development with adolescent transplant recipients. Pediatr Transplant 2009: 13: 590–598.
19. Zelikovsky N, Schast AP. Eliciting accurate reports of adherence in a clinical interview: Development of the Medical Adherence Measure. Pediatr Nurs 2008: 34: 141–146.
20. Zelikovsky N, Schast AP, Palmer J, Meyers KE. Perceived barriers to adherence among adolescent renal transplant candidates. Pediatr Transplant 2008: 12: 300–308.
21. Marhefka SL, Farley JJ, Rodrigue JR, Sandrik LL, Sleasman JW, Tepper VJ. Clinical assessment of medication adherence among HIV-infected children: Examination of the Treatment Interview Protocol (TIP). AIDS Care 2004: 16: 323–337.
22. Chisholm MA. Issues of adherence to immunosuppressant therapy after solid-organ transplantation. Drugs 2002: 62: 567–575.
23. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther 2002: 24: 330–350.
24. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in pediatric and adolescent liver transplant recipients. Pediatrics 2004: 113: 825–832.
25. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. Pediatr Transplant 2008: 12: 67–72.
26. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947: 12: 153–157.
27. Bowker AH. A test for symmetry in contingency tables. J Am Stat Assoc 1948: 43: 572–574.
28. Reed-Knight B, Lewis JD, Blount RL. Association of disease, adolescent, and family factors with medication adherence in pediatric inflammatory bowel disease. J Pediatr Psychol 2011: 36: 308–317.
29. Penkower L, Dew MA, Ellis D, Sereika S, Kitutu JMM, Shapiro R. Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. Am J Transplant 2003: 3: 1418–1425.
30. Hommel KA, Davis CM, Baldassano RN. Objective versus subjective assessment of oral medication adherence in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2009: 15: 589–593.
31. Marciel KK, Saiman L, Quittell LM, Dawkins K, Quittner AL. Cell phone intervention to improve adherence: Cystic fibrosis care team, patient, and parent perspectives. Pediatr Pulmonol 2010: 45: 157–164.
32. Puccio JA, Belzer M, Olson J, et al. The use of cell phone reminder calls for assisting HIV-infected adolescents and young adults to adhere to highly active antiretroviral therapy: A pilot study. AIDS Patient Care STDS 2006: 20: 438–444.